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Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Title: Maternally controlled length of the neurogenic period determines the number of produced neocortical neurons

Authors: *B. K. STEPIEN[1], S. VAID[2], R. NAUMANN[2], A. HOLTZ[2], W. B. HUTTNER[2]
[1]Max Planck Inst. of Mol. Cell Biol. and, Dresden, Germany; [2]Max Planck Inst. of Mol. Cell Biol. and Genet., Dresden, Germany

Abstract: Mammalian species exhibit an enormous variability in the size of their neocortex and the number of neurons therein, which are generated during a relatively short developmental window. The number of neurons produced in a given species is determined by the pool sizes of the various neural stem and progenitor cells, their proliferative capacity and the various progenitor lineages, as well as by the length of the neurogenic period. Mathematical modelling has suggested that distinct classes of mammals can be distinguished that differ in their progenitor lineages and modes of progenitor cell division (Lewitus et al., 2014 PLoS Biology 12, e1002000). Remarkably, within each of these classes, the final neuronal output was found to be directly correlated to the length of the neurogenic period.
In the present study we have explored, in a mouse model system, the previously proposed link between the neurogenic period and gestation length on the one hand and neuron production on the other hand, and have aimed at the identification of cell-extrinsic and/or maternal factors that link these two parameters. We have used mouse inbred strains with genetically determined, different gestation lengths to determine the number of neocortical pyramidal neurons produced in relation to the length of the neurogenic period. Given the difference between gestation lengths of up to 10% between the strains with shortest and longest gestation, we observe that the long-gestation strain produces more upper-layer, but not deep-layer, neurons than the short-gestation strain. Moreover, the onset of gliogenesis, which in mouse follows neurogenesis, appears later in the long-gestation strain, consistent with a lengthening of the neurogenic period. The increased neuron production upon lengthening of the neurogenic period depends on the maternal environment as embryo transfer between the short- and long-gestation strains results in a neuron production that is consistent with maternal phenotype.
Taken together our results point to a common developmental mechanism synchronizing gestation with neurogenic period and suggest an important role of maternally-derived factors in determining neocortex size. Our data open the door for further investigation of the maternal-fetal communication and its effect on organ growth.

Disclosures: B.K. Stepien: None. **S. Vaid:** None. **R. Naumann:** None. **A. Holtz:** None. **W.B. Huttner:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: King's College London Graduate School Funding

Title: The effects of apolipoprotein E (APOE) polymorphism on human hippocampal neurogenesis

Authors: *H. LEE[1], S. THURET[2]
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Abstract: Apolipoprotein E (APOE) polymorphism is the most common genetic risk factor for Alzheimer's disease (AD), the ε4 allele of which is known to both increase the overall onset of the disease and also decrease the age of onset. Growing body of evidence suggests that APOE polymorphism may differentially affect adult hippocampal neurogenesis in the dentate gyrus, which has been implicated in AD progression in its own right. However, the impact of APOE isoforms on hippocampal neurogenesis at a cellular/molecular level is yet to be fully understood. We have performed a time-course characterization for neurogenic properties in isogenic human induced pluripotent stem cell lines that differ only in APOE genotype by differentiating them into hippocampal neural progenitor cells (NPC) and then dentate gyrus granule cell (DGC)-like neurons. We found that APOE4/4 cells showed significantly different patterns of expression for hippocampal NPC markers and PROX1, the marker for mature DGCs, compared to APOE3/3 cells. The gene expression pattern of APOE and immunolabeling of MAP2 and DCX did not significantly differ between APOE3/3 and APOE4/4 cells. The isogenic lines exhibited differential phenotypes in the expression of Ki-67, a marker for cell proliferation, during DGC differentiation. Taken together, our findings suggest that APOE genotype can impact the course of hippocampal neurogenesis, and that sustaining normal levels/pattern of hippocampal neurogenesis can be a potential target for early intervention against AD for APOE4-carriers. We are now aiming to investigate whether APOE genotype interacts with environmental factors to either exacerbate or ameliorate the phenotypes we have characterized thus far in our model system.

Disclosures: H. Lee: None. **S. Thuret:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: Grant 15H04268
Grant 17K07126
Grant 15K14337

Title: Role of Meis1 in the cerebellar development

Authors: *T. OWA
Natl. Inst. of Neurosci., Tokyo, Japan

Abstract: Cerebellar granule cell precursors (GCPs) and granule cells (GCs) represent good models to study neuronal development. Here, we report that the transcription factor myeloid ectopic viral integration site 1 homolog (Meis1) plays pivotal roles in the regulation of mouse GC development. We found that Meis1 is expressed in GC lineage cells and astrocytes in the cerebellum during development. Targeted disruption of the Meis1 gene specifically in the GC lineage resulted in smaller cerebella with disorganized lobules. Knock-down/knock-out (KO) experiments for Meis1 and *in vitro* assays showed that Meis1 binds to an upstream sequence of Pax6 to enhance its transcription in GCPs/GCs and also suggested that the Meis1-Pax6 cascade regulates morphology of GCPs/GCs during development. In the conditional KO (cKO) cerebella, many Atoh1-positive GCPs were observed ectopically in the inner external granule layer (EGL) and a similar phenomenon was observed in cultured cerebellar slices treated with a bone morphogenic protein (BMP) inhibitor. Furthermore, expression of Smad proteins and Smad phosphorylation were severely reduced in the cKO cerebella and Meis1-knock-down GCPs cerebella. Reduction of phosphorylated Smad was also observed in cerebellar slices electroporated with a Pax6 knock-down vector. Because it is known that BMP signaling induces Atoh1 degradation in GCPs, these findings suggest that the Meis1-Pax6 pathway increases the expression of Smad proteins to upregulate BMP signaling, leading to degradation of Atoh1 in the inner EGL, which contributes to differentiation from GCPs to GCs. Therefore, this work reveals crucial functions of Meis1 in GC development and gives insights into the general understanding of the molecular machinery underlying neural differentiation from neural progenitors.

Disclosures: T. Owa: None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: FONDECYT 1161374

Title: The protein tyrosine phosphatase receptor delta PTPRD regulates embryonic neurogenesis during cortical development

Authors: *G. I. CANCINO[1,2], H. TOMITA[2], C. L. WOODARD[2], C. C. RIOSECO[2], B. G. NEEL[3], D. R. KAPLAN[2,4], F. D. MILLER[2,5]
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Abstract: Neurodevelopmental disorders are due to an abnormal brain development commonly associated to cognitive impairment, motor disorders and communication problems. Recent work suggests that neural precursor cells (NPCs) are important cellular substrates for neurodevelopmental disorders, since disruption of genes associated to neurodevelopmental disorders in NPCs perturb the numbers and types of neurons that are generated. We have focused on PTPRD, a protein tyrosine phosphatase receptor that is genetically associated with neurodevelopmental disorders such as autism spectrum disorder, restless leg syndrome, and ADHD. Here, we asked whether PTPRD mutations cause aberrant neural development by perturbing neurogenesis, focusing on the embryonic murine cortex. Using embryonic cortical precursors from E12.5 $Ptprd^{-/-}$ mice, we evaluated whether PTPRD regulates NPCs *in vitro*. Furthermore, we used embryonic brains at different embryonic ages from $Ptprd^{-/-}$ mice to evaluate the role of PTPRD in self-renewal, proliferation, and differentiation of NPCs during embryonic neurogenesis. Here, we show that loss of one or both alleles of PTPRD caused decreased proliferation and self-renewal of cortical neural precursor cells and aberrantly increased neurogenesis. These effects were intrinsic to neural precursor cells since acute PTPRD in vitro and in vivo knockdown caused similar perturbations. PTPRD mediated these effects by dephosphorylating receptor tyrosine kinases since it interacted with TrkB and PDGFRβ, and loss of PTPRD caused hyperactivation of TrkB, PDGFRβ and the downstream MEK-ERK signaling pathway in neural precursor cells. Moreover, inhibition of aberrant MEK activation by Trametinib and PD98059 MEK inhibitors rescued the increased neurogenesis caused by knockdown or homozygous loss of PTPRD in cortical precursor cells in culture. These results

suggest that PTPRD regulates receptor tyrosine kinases to ensure appropriate developmental neurogenesis, providing a mechanism for its genetic association with neurodevelopmental disorders.

Disclosures: G.I. Cancino: None. **H. Tomita:** None. **C.L. Woodard:** None. **C.C. Rioseco:** None. **B.G. Neel:** None. **D.R. Kaplan:** None. **F.D. Miller:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Title: Synergistic effects of a plasma fraction and exercise on neurogenesis

Authors: *I. D. GALLAGER, R. ALCANTARA-LEE, M. CASTRO, R. ESTRADA, S. P. BRAITHWAITE, V. KHEIFETS
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Abstract: Exercise has long been considered the gold standard for increasing neurogenesis in animal models of aging. It is widely promoted clinically as a method to stave off the deleterious effects of increased inflammation, decreased neurogenesis and cognitive deficits observed in age-related disorders. We have identified a human plasma fraction that has beneficial effects on neurogenesis and cognition and explored whether it acts through similar pathways to exercise. The plasma fraction or vehicle was delivered intravenously to aged immunodeficient, NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}/SzJ (NSG), mice. Following administration, a subset of mice were provided home-cage running wheels for 6 weeks to assess the effects of voluntary exercise. Significant increases in terminal histological measures of cell survival (BrdU) and neurogenesis (doublecortin, DCX) within the dentate gyrus of the hippocampus were confirmed for both the animals treated with the bioactive plasma fraction and those exposed only to exercise. Unexpectedly, animals provided with both a home-cage running wheel and treated with the plasma fraction showed dramatic synergy in stimulating neurogenesis through both markers of new neurons (DCX) and cell proliferation (Ki67). This synergy was observed in both young (3 month old) and middle-aged (6 month old) mice. We also demonstrate that cellular proliferation is directed towards neuronal cell fate. This finding suggests that orthogonal biological processes are involved in the neuroregenerative mechanisms of the plasma fraction and those induced by voluntary exercise. The therapeutic application of plasma fractions together with exercise may provide synergistic benefit to aging populations with cognitive disorders.

Disclosures: I.D. Gallager: A. Employment/Salary (full or part-time):; Alkahest Inc. **R. Alcantara-Lee:** A. Employment/Salary (full or part-time):; Alkahest Inc. **M. Castro:** A.

Employment/Salary (full or part-time):; Alkahest Inc. **R. Estrada:** A. Employment/Salary (full or part-time):; Alkahest Inc. **S.P. Braithwaite:** A. Employment/Salary (full or part-time):; Alkahest Inc. **V. Kheifets:** A. Employment/Salary (full or part-time):; Alkahest Inc..

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: KAKENHI 16H05364
KAKENHI 15K15405
KAKENHI 16K19674

Title: Administration of maternal leukemia inhibitory factor induces Nkx.2.1 in the ventral cerebrum of fetal mice

Authors: *H. SAKAGAMI[1], T. TSUKADA[2,3], H. SAKATA-HAGA[2], H. SHIMADA[2,4], K. MIURA[1], H. WANG[2], T. ARIKAWA[5], S. TAKATA[3], H. SHOJI[5], T. HATTA[2]
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Abstract: Leukemia inhibitory factor (LIF) from fetal erythroblasts promotes the proliferation of cortical neural progenitors in the fetal brain (Hatta, T., et al., 2002); however, the exact mechanism of its contribution to cerebral cortex development remains unclear. To identify the molecular mechanism underlying this phenomenon, we examined the effects of maternal LIF administration on fetal gene expression using DNA microarray analysis and qPCR. Our findings demonstrate that maternal LIF induces the expression of placental ACTH, which subsequently induces LIF expression in fetal erythroblasts (Shimamura et al., 2010). This LIF-ACTH-LIF signal relay plays a vital role in proper cerebral cortex development in mice. Pregnant mice (C57BL/6J) received an intraperitoneal injection of LIF (5μg/kg) at 13.5 days post coitum. After 30 min or 3 h of LIF administration, the placenta, and fetal cerebrum, choroid plexus, liver, and blood cells were collected, and RNA was purified from each tissue. DNA microarray analysis revealed that maternal LIF administration increased the expression of genes associated with proliferation and differentiation of interneurons, including *Dlx-1*, *Dlx-2*, *Nkx2.1*, *Lhx6*, and *Gad2*—in the fetal cerebral cortex 3 h after LIF administration. In addition, an increase in the expression of these genes were quantitatively determined by qPCR. Maternal LIF administration increased the expression of *Nkx2.1* in the fetal ventral cerebrum, including the medial ganglionic eminences (MGE), 3 h after LIF administration. In MGE, *Nkx2.1* induces *Lhx6*, which is involved in the differentiation and migration of cortical GABAergic interneurons. Considering

the sequential expression of GABAergic neuron-associated genes, our results suggest that the differentiation and migration of interneurons in the cerebral cortex may be promoted by maternal LIF administration via induction of *Nkx2.1* expression.

Disclosures: H. Sakagami: None. **T. Tsukada:** None. **H. Sakata-Haga:** None. **H. Shimada:** None. **K. Miura:** None. **H. Wang:** None. **T. Arikawa:** None. **S. Takata:** None. **H. Shoji:** None. **T. Hatta:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant
1R01NS083947-01

Title: GSK3 beta inhibition restores impaired neurogenesis in premature infants with intraventricular hemorrhage

Authors: *P. BALLABH[1], P. DOHARE[2]
[1]Pediatrics and Neurosci., [2]Albert Einstein Col. of Med., Bronx, NY

Abstract: Intraventricular hemorrhage (IVH) is a common complication of extreme prematurity in infants born at 23-28 weeks of gestational age. Survivors exhibit impaired growth of the cerebral cortex and suffer from cognitive deficits, intellectual disabilities, and neurobehavioral disorders. However, the underlying mechanism(s) are obscure. Previously, we have shown that neocortical neurogenesis continues until at least 28 gestational weeks. This renders the extremely prematurely born infants vulnerable to impaired neurogenesis. Here, we hypothesized that IVH would disrupt neurogenesis in the dorsal telencephalon and thus, might reduce the neuronal populations in the upper cortical layers. We also postulated that signaling through GSK3β, a critical intracellular kinase regulated by Wnt and other pathways, would mediate this effect. These hypotheses were tested observationally in autopsy specimens from premature infants, and experimentally in a premature rabbit IVH model. Significantly, in premature infants with IVH, the number of neurogenic $Tbr2^+$ cortical progenitor cells was reduced compared to infants without IVH, indicating acutely decreased neurogenesis. Accordingly, in rabbits with IVH, total and cycling $Tbr2^+$ progenitor cells and $Sox2^+$ radial glia were reduced in the dorsal ventricular and subventricular zone. The occurrence of IVH in rabbit kits also diminished the density of $Cux1^+$ and $Satb2^+$ neurons in the upper cortical layers after longer survival. Additionally, Pax6 expression and phosphorylation of retinoblastoma protein were elevated in rabbits with IVH, suggesting inhibition of the G1-to-S phase transition. Both the acute reduction of $Tbr2^+$ and

$Sox2^+$ neurogenic progenitors, and the subsequent decrease of $Cux1^+$ upper layer neurons, were reversed by treatment with AR-A014418, a specific inhibitor of GSK3β. These results indicate that IVH impairs late stages of cortical neurogenesis, and suggest that treatment with GSK3β inhibitors may enhance neurodevelopment in premature infants with IVH.

Disclosures: P. Dohare: None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Title: GATA cofactor Fog1 is reguired for the development of dorsal raphe serotonergic neurons and inactivation of Fog1 causes anxiety

Authors: *L. TIKKER[1], P. CASAROTTO[2], C. BIOJONE[2], N. M. ESTARTÚS[1], J. PARTANEN[1]
[1]Mol. and Integrative Biosci. Res. Programme, [2]Neurosci. Ctr., Univ. of Helsinki, Helsinki, Finland

Abstract: Dysfunction of serotonergic neurons in the dorsal raphe nucleus can cause several psychiatric disorders, including anxiety disorders. Therefore, the correct development of dorsal raphe neurons is essential. Previously, it has been shown that GATA-family transcription factors, Gata2 and Gata3 are required for the development of the dorsal raphe neurons. These transcription factors also have multiple co-regulators with whom they form a regulatory complex to modulate the gene expression by which they influence differentiation and cell fate in several tissues. We hypothesized that these regulators also have a role in the development of serotonergic neurons in the dorsal raphe. Here we have studied one of these regulators, the GATA cofactor Fog1 (Friend of GATA-1) that is also expressed in the developing serotonergic neurons. We show, how inactivation of Fog1 does not prevent early serotonergic neuron differentiation, but leads to a loss of one of its subgroups, the lateral wing serotonergic neurons of the dorsal raphe. Interestingly, these neurons have been implicated in panic disorder. Analyses of the behaviour of the Fog1 mutant mice showed neophobia and increased anxiety. Our results demonstrate that the GATA cofactor Fog1 is required for the development of serotonergic neuron diversity and differentiation of a functionally important serotonergic neuron subgroup in the dorsal raphe.

Disclosures: L. Tikker: None. **P. Casarotto:** None. **C. Biojone:** None. **N.M. Estartús:** None. **J. Partanen:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: Swiss National Science Foundation
Fondation Carigest

Title: Large-scale parallel tracing of cell-type specific transcriptional trajectories in the developing mouse neocortex

Authors: *D. JABAUDON[1], L. TELLEY[2], G. AGIRMAN[1], J. PRADOS[1], P. OBERST[1], L. NGUYEN[3], A. DAYER[1]
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Abstract: The cerebral cortex is a cellularly heterogeneous structure, whose circuits underlie our high-order cognitive and sensorimotor abilities. During development, distinct subtypes of glutamatergic neurons are sequentially born and differentiate from dynamic populations of progenitors located below the cortex, in the ventricular zone. The aggregate competence state of these progenitors progresses as corticogenesis proceeds; likewise, newborn neurons transit through sequential transcriptional states as they differentiate. Little is known on the orthogonal molecular mechanisms driving on the one hand the developmental progression of progenitors through competence states, and on the other hand the differentiation of newborn neurons through cell-type specific differentiation states. To address these questions, we used FlashTag (Telley et al., Science 2016) to trace the developmental trajectories of successive waves of isochronic neurons and progenitors throughout corticogenesis and performed a large-scale, parallel single cell transcriptional profiling of these time-locked populations. Our results identify chronotopic transcriptional maps defining the type-specific organization of transitions through cellular states, and highlight principles allowing emergence and consolidation of type-specific neuronal identities in the developing cerebral cortex.

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Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01MH094653
NIH Grant R01MH111267

Title: An Evf2 lncRNA-dependent enhancer-gene superloop links the mevalonate pathway with serotonin receptor gene regulation in developing interneurons

Authors: *J. D. KOHTZ[1], I. C. CAJIGAS, 60614[1], K. S. SWYTER, 60614[1], A. C. CHAKRABORTY, 92037[2], F. A. AY, 92037[3], E. MORRIS[1]
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Abstract: GABAergic interneuron subtype identities are established early in the developing embryo (day 13.5 in mice) in ganglionic eminences (GEs). Gene networks that contribute to interneuron identity are fundamentally based on enhancer-mediated selective regulation of genes during this time. Here, we show that the *Evf2* lncRNA is a master regulator of interneuron subtype genes in E13.5GEs, acting through both antisense *Dlx6* repression and selective targeting of enhancer-gene superloops (at distances greater than 2Mb). *Evf2* is required for *Dlx5/6* ultraconserved enhancer (UCE) interaction with the repressed target gene aldo-ketoreductase 1b8 (*Akr1b8*), at a 27Mb distance. Genetic and gain-of-function experiments support that *Evf2* loss increases *Akr1b8*, a repressor of *5Htr3a* in caudal GE, and activator of *5Htr3a* in medial GE. *Akr1b8* spatial dependence is explained by *Akr1b8* regulated enhancers (*AkrRE1* and *AkrRE2*) located ~63kb downstream of *5Htr3a*, in the *5'*-end of the *Zbtbt16* gene. Metabolites of the mevalonate pathway differentially regulate *AkrRE1/2*, linking epigenetic and lipid mechanisms with serotonin receptor regulation. These studies support a role for an lncRNA-dependent enhancer-gene superloop that contributes to interneuron development, identifying a novel mechanism of serotonin receptor regulation in developing mouse brain.

Disclosures: J.D. Kohtz: None. **I.C. Cajigas:** None. **K.S. Swyter:** None. **A.C. Chakraborty:** None. **F.A. Ay:** None. **E. Morris:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: Becario Conacyt No.339239
Conacyt CB-2015-1-25484
INPer: 3230-21202-01-2015

Title: Systemic administration of antihistamines in pregnant rats impairs offspring motor cortical cytoarchitecture and pyramidal intrinsic electrophysiological properties

Authors: *R. VALLE-BAUTISTA[1], E. GRIEGO-MELO[2], G. HERRERA-LÓPEZ[2], E. GALVÁN[2], N. DÍAZ[3], J. ARIAS-MONTAÑO[1], A. MOLINA-HERNÁNDEZ[3]
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Abstract: In rat cortical neuroepithelium, histamine H_1-receptor (H_1R) is expressed at embryo day (E) 12, when deep cortical layer neuron differentiation begins. Interestingly, *in vitro* through H_1-receptor activation histamine (HA) promotes neuron differentiation of cortical neural stem cells to deep layer forkhead box protein 2-positive neurons ($FOXP2^+$). And, the *in utero* administration of chlorpheniramine (H_1R antagonist/inverse agonist) at E12 decreases the number of microtubule associated protein 2-positive ($MAP2^+$) and $FOXP2^+$ neurons at E14. The above suggests that early treatment with chlorpheniramine decreases cortical neuron differentiation, event that could lead to postnatal changes on cortical lamination and function.The aim of this study was to evaluate the pharmacological effect of two antihistamines drugs during deep cortical layer development and its implications in the motor cortex. To achieve this goal, pregnant rats were daily injected (ip) from E12 to E14 with chlorpheniramine, mepyramine or vehicle (control), and their offspring was sacrificed at postnatal days (P) 0, 5 and 21. We determined HA level (ELISA, P0 and P21), H_1R density (binding assay), expression and layer position of H_1R and FOXP2 (qRT-PCR and immunofluorescence, respectively), cortical cytoarchitecture (Golgi-Cox stain) and the intrinsic electrophysiological properties of pyramidal neurons in primary motor cortex from P21 control and treated litters. Our results showed a significant increase in H_1R density and a decrease in both dendritic tree arborization, as well as orientation changes, and in the amplitude of the action potential evoked by current injection at P21 in the chlorpheniramine group as compared with the other groups. These data suggest that only chlorpheniramine treatment during the establishment of the deep cortical layers affects postnatal motor cortex cytoarchitecture and suggests alterations in the intrinsic electrophysiological properties of pyramidal neurons in pregnant rats offspring; insult that could

have consequences in both early and late postnatal cortical processes. As chlorpheniramine is a drug classified into B category for pregnancy by the FDA, is important to perform more studies and begin to reconsider the use of this specific drug during pregnancy.

Disclosures: R. Valle-Bautista: None. **E. Griego-Melo:** None. **G. Herrera-López:** None. **E. Galván:** None. **N. Díaz:** None. **J. Arias-Montaño:** None. **A. Molina-Hernández:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS092466
NSFC Grant 81471306
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15IRTSTHN022
2016GH15

Title: Pannexin1 plays a prominent role in promoting axonal growth during neuroblastoma cell differentiation

Authors: Q. XING[1], P. DOHARE[1], Q. LI[1,3], F. GUAN[3], *D. C. SPRAY[2]
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Abstract: Pannexin1 (Panx1) is a protein found in vertebrates that is related to invertebrate gap junction proteins. Rather than forming gap junction channels between cells, Panx1 forms large conductance pores that allow exchange of moderately large signaling molecules such as ATP from inside to outside the cell. Functions of Panx1 channels include signaling through purinergic receptors that are activated by released ATP and likely play major roles in such processes as neuronal myelination and maturation. We have performed studies on a neuroblastoma cell line (Neuro2a) to determine mechanisms underlying this phenomenon. For this, we knocked out Panx1 in Neuro2a cells using CRISPR/Cas9, obtaining modified Neuro2a cell lines that were Panx1 deficient and did not exhibit compensatory upregulation of Panx2, Panx3 or other proteins forming large conductance channels (Cx36, Cx43, CAHLM).To determine the extent to which neurite extension was affected by Panx1 deletion, we compared fraction of neurite bearing WT and Panx1 null Neuro2a cells up to day 5 after plating in medium alone or with supplementation by two agents known to stimulate neuronal outgrowth [40μM retinoic acid (RA), 50ng/ml nerve growth factor (NGF), 5% FBS as control]. The results show that the percentage of neurite bearing WT Neuro2a cells increased at day 3, day 4 and day 5 after RA induction, compared

with the control group (P<0.001); similar extent of differentiation was seen with NGF at day 3 (P<0.05) and day 4 (P<0.001). In contrast, neurite outgrowth in Neuro2a cells lacking Panx1 was markedly suppressed at day 3-5 after treatment both with RA and NGF (P<0.05). Our findings that Panx1 deletion decreases the differentiation of Neuro2a cells and diminishes the maturational effects of NGF and RA provides evidence that Panx1 plays a major role in controlling axonal growth in the peripheral nervous system.

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Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

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Topic: A.01. Neurogenesis and Gliogenesis

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NIH U54HD090257 District of Columbia Intellectual Developmental Disabilities Research Center
Children's Research Institute Children's National Health System,
Fetal Medicine Institute, Children's National Health System

Title: Impaired interneuron density in the human preterm prefrontal cortex

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Abstract: Preterm birth is a significant risk factor for neuropsychiatric disease development, particularly schizophrenia and autism spectrum disorder. A common feature of these disorders is an imbalance between neuronal excitation and inhibition in the prefrontal cortex (PFC), mediated by developmental alterations of Gamma-Aminobutyric Acid (GABA) interneurons. Specifically, alterations in Brodmann area 9 (BA9), a region involved in working memory and social cognition, may account for some of the characteristic cognitive deficits of these disorders. Histological evidence of decreased GABA levels has been seen in rodent models and humans with major psychiatric disorders. Similarly, in preterm birth survivors, a decrease is also seen in right frontal GABA concentration and connectivity, suggesting similar deficits. To elucidate the cellular changes underlying these alterations, we have investigated GABA interneurons in human PFC from both preterm and term infants. Interneurons continue to be generated through late

pregnancy (35 weeks) and keep migrating and integrating into the frontal lobe during infancy, leaving them highly susceptible to perinatal insults. We examined interneuron numbers and subtypes in BA9, from 7 term (> 37 weeks of gestation) and 6 preterm (< 29 weeks of gestation) infants who survived until ~4 months of age (NIH Neurobiobank University of Maryland, Baltimore, MD; ID #709). Sex, gestational age and cause of death varied, but were not attributed to CNS abnormalities. Tissues were sectioned and stained for four interneuron markers. Positive cells were counted in two bins of equal width corresponding to the upper and lower layers of the frontal cortex. A significant decrease was observed in the number of somatostatin and calretinin positive interneurons in the upper but not the lower section of the cortex of preterm infants. However, no change was observed in the number of calbindin or neuropeptide Y expressing cells. To further investigate the effect of preterm birth on human interneuron maturation, the density, and the position of interneurons in the cortical layers is being assessed by total GABA expression and co-staining with interneuron subtype markers to determine whether there is a maturational delay and whether the cell loss is specific to a ganglionic eminence. Taken together, these data will lead to a better understanding of the impact of preterm birth on interneuron development; and will potentially lead to new avenues for treatment to reduce offspring's neuropsychiatric risk after compromised pregnancies.

Disclosures: H. Lacaille: None. **C.M. Vacher:** None. **D. Bakalar:** None. **J.J. O'Reilly:** None. **J. Salzbank:** None. **A.A. Penn:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.14/A14

Topic: A.01. Neurogenesis and Gliogenesis

Support: Siriraj Research Developmental Fund

Title: Expression of NCAM, PSA-NCAM, GFAP, and S100 in subgranular zone of dentate in developing hippocampus

Authors: *S. CHOMPOOPONG[1], C. TURBPAIBOON[1], B. TASSANEETRITHEP[2], W. WIRIYARAT[3], P. NIMNOI[1], W. SIRIPAN[1]
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Abstract: In mammals, neurogenesis presents in the subgranular zone (SGZ) of dentate in hippocampus throughout life. Currently, various protein markers expressed during the progressions of adult hippocampal neurogenesis have been reported. The expression of these

biomarkers during brain development are also promising and has been widely studied but not yet fully appreciated because of the difference in rodent species. In this study, the expression of the neural cell adhesion molecule (NCAM), the polysialylated (PSA)-NCAM, the glial fibrillary acidic protein (GFAP), and the neurotrophic protein S100 were determined in fetus (E17), postnatal (P3, P5, P7 and P14) and adult ICR mice by using immunoperoxidase staining in dorsal hippocampus and Western blot analysis of brain tissue homogenate. NCAM mediates adhesion, guidance, synaptic plasticity and differentiation during neuronal growth, NCAM expression was localized on the cell surface of neurons, glia. In SGZ, NCAM found highly in adult and postnatal mice than embryonic mice. PSA-NCAM plays role in the modulation of cell-cell adhesive interactions for the migration and proliferation including the differentiation of neural stem cells. PSA-NCAM was found in cytoplasm, cell surface and some nucleus of neural cells, more densely staining in SGZ in early postnatal mice P3 than late stage P14 and adult mice but no staining found in embryonic mice E17. The amount of GFAP increased with increasing mice age reflecting general supporting of the cytoskeleton in astrocytes, GFAP expression was increased gradually from P3 to P14 and adult mice. More early expression of S100 is associated with its proliferative potential and migration of undifferentiated neuroblasts and astrocytes. The amount of the neuro- and gliotrophic protein S100 increased from young E17 due to secretion for proliferative phase then decreased and S100 expression increased again in P14 and adult mic, therefore S100 expression is also related to mature astrocytes. In conclusion, this finding provides valuable information on the developmental processes, the different up and down regulation of NCAM/PSA-NCAM, GFAP and S100 in various stages of developing mice are useful to understand not only brain functions but also brain developmental defects in offspring mice.
KEY WORDS: NCAM, PSA-NCAM, GFAP, S100, SGZ

Disclosures: S. Chompoopong: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Siriraj Developmental Fund. **C. Turbpaiboon:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Siriraj Research Developmental Fund. **B. Tassaneetrithep:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Siriraj Developmental Fund. **W. Wiriyarat:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Siriraj Developmental Fund. **P. Nimnoi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Siriraj Research Developmental Fund. **W. Siripan:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report

that research relationship even if those funds come to an institution.; Siriraj Research Developmental Fund.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.15/A15

Topic: A.01. Neurogenesis and Gliogenesis

Title: Longitudinal characterization of plasma fraction efficacy on neurogenesis in aging mice

Authors: I. GALLAGER, R. ALCANTARA-LEE, M. CASTRO, *R. A. ESTRADA-VERDUZCO, S. P. BRAITHWAITE, V. KHEIFETS
Alkahest, Inc., San Carlos, CA

Abstract: We have identified a fractionated plasma product that enhances neurogenesis within the dentate gyrus of the hippocampus in 12month old NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}/SzJ (NSG) immunodeficient mice. Here we examined NSG mice at various ages treated intravenously with the plasma fraction and compared the extent of their age-dependent decline in new-born neurons (doublecortin, DCX) and cell survival of BrdU labeled dividing cells six weeks post treatment compared to naïve animals. We identified a precipitous decline in total DCX positive cells in 6-month-old compared to 3-month-old animals concomitant with significant deterioration in spatial cognitive behavior. In all ages, the plasma fraction inhibited the decline in neurogenesis and cell survival occurring over 6 weeks post-dosing. We demonstrate that the increase in neurogenesis is likely due to increased precursor cell proliferation that occurs during the dosing of the plasma fraction and demonstrate that the proliferation increase is maintained for at least 1 week following cessation of dosing. Six-month-old animals were selected to be used for examination of an extended dosing paradigm to guide treatment methodology for clinical trials with plasma fractions.

Disclosures: I. Gallager: A. Employment/Salary (full or part-time):; Alkahest, Inc. **R. Alcantara-Lee:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **M. Castro:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **R.A. Estrada-Verduzco:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **S.P. Braithwaite:** A. Employment/Salary (full or part-time):; Alkahest, Inc. **V. Kheifets:** A. Employment/Salary (full or part-time):; Alkahest, Inc..

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.16/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: 5R01AA021402
Schaffer Family Foundation

Title: Single-cell whole-genome sequencing reveals widespread somatic copy number variations arising during neurodevelopment in the cerebral cortex

Authors: S. E. ROHRBACK[1], C. S. LIU[2], B. SIDDOWAY[3], C. APRIL[1], F. KAPER[1], *J. CHUN[4]
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Abstract: Somatic megabase scale copy number variations (CNVs) are present in adult neurons of the brain, however, little is known about the genesis, prevalence, and consequences of this phenomenon. We characterized mosaic CNVs in the developing cerebral cortex of *Mus musculus* using a novel wetlab approach. We also developed informatic tools to confidently identify somatic CNVs in the data generated by low depth single-cell whole-genome sequencing (scWGS). Using immune system recombination as a known locus for naturally occurring CNVs, we applied machine learning to create filters to remove unreliable CNVs. This resulted in removal of >90% of false positive CNV calls while maintaining identification of sub-megabase alterations smaller than previously reported brain CNVs identified through scWGS. Thousands of CNVs were identified in cells isolated during cortical neurogenesis and adulthood, allowing us to identify periods of CNV formation in brain development. These data support prenatal origins for the majority of mosaic CNVs present in adult neurons.

Disclosures: S.E. Rohrback: None. **C.S. Liu:** None. **B. Siddoway:** None. **C. April:** None. **F. Kaper:** None. **J. Chun:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.17/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: NRF Grant NRF-2017R1A2B4002704

Title: Differential expression of GRIM-19 (gene associated with retinoid-interferon induced mortality-19) in the adult mouse dentate gyrus: A regulator in adult neurogenesis

Authors: J.-C. KIM[1,2,3], S.-N. HWANG[1,2,3], *S. KIM[1,2,3]
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Abstract: Gene associated with retinoid-interferon-induced mortality-19 (GRIM-19), a subunit of mitochondrial respiratory chain complex I, is a multifunctional gene involved in cell death, proliferation, migration and metabolic balance between aerobic glycolysis and mitochondrial oxidative phosphorylation (OXPHOS). Although such functions of GRIM-19 are also closely related with adult neurogenesis, the role of GRIM-19 in adult neurogenesis is unknown. Thus, the present study investigated the expression pattern of GRIM-19 and analyzed cell types expressing GRIM-19 in the adult mouse hippocampal dentate gyrus, one of the regions where adult neurogenesis takes place. We performed double immunofluorescence staining on hippocampal sections of adult C57BL/6 mice (11 weeks old) using various specific markers related to adult neurogenesis stages (type-1, type-2a, type2-b, type-3, immature granule cell and mature granule cell; stage 1-6). Interestingly, GRIM-19-positive cells were prominently expressed in the dentate gyrus cell layer, but barely observed in the subgranular zone (SGZ) where neural stem and progenitor cells (NSPCs) are active. Further analysis revealed that GRIM-19 was nearly not expressed in GFAP-positive cells (type-1), Nestin-positive cells (type-1, 2a and 2b) and Ki-67-positive cells (type 2a, 2b and 3). Further, a few GRIM-19-positive cells were merged with DCX-positive cells (type 2b, 3 and immature), Prox1-positive cells (type 2b, 3, immature and mature), PSA-NCAM-positive cells (type 3, immature and mature). Furthermore, Most GRIM-19-expressing were co-labeled with Calretinin-positive cells (immature), NeuN-positive cells (immature and mature), Calbindin-positive cells (mature). These results indicate that GRIM-19 was not expressed at early neurogenesis stages including NSPCs, but at later stages including immature and mature granule cells.

Disclosures: J. Kim: None. **S. Hwang:** None. **S. Kim:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.18/A18

Topic: A.01. Neurogenesis and Gliogenesis

Title: Connectomics in the dentate gyrus

Authors: *M. BEINING[1], P. BASTIANS[2], M. HELMSTAEDTER[3]
[1]Connectomics, Max Planck Inst. for Brain Res., Frankfurt Am Main, Germany; [2]MPI for Brain Res., Frankfurt Am Main, Germany; [3]Dept. of Connectomics, Moritz Helmstaedter, MD, MS, Frankfurt, Germany

Abstract: In the mammalian brain adult-born granule cells (abGCs) are continously integrated into established hippocampal circuits throughout life. Whereas the evolution of in- and output connectivity on abGCs and GCs has already been studied in detail on the population level little is known about the per-cell connectivity, its development and the cellular output specifity of DG input axons in general. We used serial block-face scanning EM to acquire a large-scale 3D EM dataset from mouse (P28) dentate gyrus and densely reconstructed GCs and their synaptic input axons. The cellular organization of younger GCs towards deeper layers allowes the analysis of temporally different stages of GC maturation in the same dataset, aimed at uncovering the connectomic patterns of neurons newly integrated into an existing neuronal circuit.

Disclosures: M. Beining: None. **P. Bastians:** None. **M. Helmstaedter:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.19/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: CONACYT Grant CB-2014-22006
CONACYT Grant CB-2014-220342
DIECI UDEM Grant UIN18597

Title: Pattern of expression of the transcription factor Ebf2 in the lateral hypothalamus of the mouse brain

Authors: *R. VIDALTAMAYO[1], X. A. ACOSTA-VILLALOBOS[2], V. C. ZOMOSA-SIGNORET[2]
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Abstract: Neuron populations in the lateral hypothalamic area (LHA) regulate motivated behaviors such as food intake and metabolic energy balance through integrating internal and external sensory cues and modulating the output of arousal and reward systems. The cellular and molecular mechanisms responsible of these regulatory processes are not completely understood, due to the complex architecture and heterogeneity of the cell populations in the LHA. Three major populations of neurons have been described within the LHA, that participate in the formation of circuits regulating motivated behavior. These populations appear to express distinct neuropeptides in an exclusive manner, and each population is characterized by the expression of either orexin A and B, melanin concentrating hormone (MCH), or neurotensin. This latter population also expresses the large version of the leptin receptor (LepRb) as a distinct marker. EBF2 is a transcription factor involved in the development and maintenance of different neuron populations across the nervous system. Several studies have suggested a relationship between EBF2 and orexin neurons: *Ebf2* expression is decreased in hypothalamus samples from transgenic mice where orexinergic neurons are depleted by the targeted expression of a neurotoxin, and there is a corresponding decrease (roughly by 80%) in orexin- expressing neurons in *Ebf2* knockout mice, which leads to a narcoleptic phenotype. However, it is presently unknown if EBF2 is expressed by the orexinergic neurons of the LHA.
Here, we analyzed EBF2 expression in the LHA by immunofluorescence in the brains of female and male wild-type C57BL/6 at embryonic stages E14.5, E15.5, and young (7- to 9-week old) and senescent adult mice. We performed double stainings to evaluate coexpression of EBF2 and any of the characteristic markers of the neuron populations of the LHA: orexin-B, MCH, NPY, CART, neurotensin and LepRb.
A subpopulation of the LHA expressed EBF2, which is also expressed in other areas participating in the integration of motivated behavior such as the VTA, preoptical hypothalamic area and the insular cortex. The EBF2+ neurons of the LHA were located in close proximity to ORXB+ axons, but no colocalization of EBF2 and ORXB, MCH, CART or NPY could be detected in the somas expressing either one of these neuropeptides in the LH and ventral hypothalamic (arcuate nucleus) areas. Labeling with anti-neurotensin antibodies suggests that neurons belonging to this subpopulation of the LHA coexpress EBF2. The interaction between the neurotensin+ and ORX+ populations could lead to reciprocal regulation of gene expression.

Disclosures: R. Vidaltamayo: None. **X.A. Acosta-Villalobos:** None. **V.C. Zomosa-Signoret:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.20/A20

Topic: A.01. Neurogenesis and Gliogenesis

Title: Lead (Pb^{2+}) exposure alters cellular and behavioral neurodevelopment in a planarian model

Authors: *S. ABDALLAH[1], R. CANDIA[2], M. SCOTTO[2], N. MAGNAVITA[2], S. R. GUARIGLIA[3]
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Abstract: Lead is a well-characterized toxicant with known deleterious effects on nervous system function. How Pb^{2+} influences the critical period of early neurodevelopment is less understood. Here, we utilize *Dugesia Dorotocephala,* a planarian, to model the effects of lead on early nervous system development. To accomplish this task, we amputated the heads of adult planarians and allowed the tails to regenerate heads and brain in 0.01 ppm, 0.1 ppm, and 0.5 ppm Pb^{2+}. The duration of Pb^{2+} exposure was seven days, as entire head and brain regeneration occurs within seven days of amputation. We examined (1) the effect of varying concentrations of Pb2+ on regenerating blastema and the (2) impact of Pb^{2+} on CNS neuronal cell number at a 24h, 48h, 72h, 120h, 168h (during exposure) and two weeks post-amputation (after exposure) using a combination of immunohistochemistry, Western Blot, and qRT-PCR. We have found that Pb^{2+} exposure attenuated blastema formation and that Pb^{2+} exposure reduced the neuronal cell number in Pb^{2+} exposed planaria. Furthermore, we found that exposure to Pb^{2+} during brain development had persistent effects on behavior. Planaria exposed to all concentrations of Pb^{2+} showed hyperactive locomotor activity and increased body rotations. In an active avoidance fear conditioning assay, planaria exposed to all concentrations of Pb^{2+} demonstrated significant and persistent cognitive impairments. The sum of this data suggests that Pb^{2+} has deleterious effects on early neuronal patterning and lasting behavioral effects. Furthermore, we describe assays that are high throughput and may be useful for others in evaluating potential toxicological consequences of exposure during early neurodevelopment.

Disclosures: S. Abdallah: None. **R. Candia:** None. **M. Scotto:** None. **N. Magnavita:** None. **S.R. Guariglia:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.21/A21

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01 NS100471
NIH Grant R01 NS054941
FOXG1 Research Foundation
NIH grant R01 DK103661

Title: Corpus callosum formation requires FOXG1 action in cortical projection neurons

Authors: *F. CARGNIN[1], J.-S. KWON[2], B. CHEN[3], J. W. LEE[2], S.-K. LEE[4]
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Abstract: Cerebral hemispheres exchange and coordinate information derived from motor and somatosensory inputs via the major axonal transit that defines the corpus callosum. Awry neocortex maturation and agenesis of the corpus callosum are hallmarks of neurodevelopmental disorders, like FOXG1 syndrome, that emerge from mutations in genes pivotal to the organization of brain architecture. However, there are no prior evidences that mutations in a single neuronal gene may directly hijack both cortical lamination and corpus callosum formation. We discovered that FOXG1 gene, aside from its known function in neural progenitors, is strictly necessary for axon trajectory of callosal projection neurons (CPN). The neuron-specific actions of Foxg1 are achieved by forming a transcription complex with Rp58. The Foxg1-Rp58 complex directly binds and represses proneural and axon guidance genes, coordinating the laminar position of cortical neurons and the acquisition of CPN-defining traits. As FOXG1 syndrome results from mutations in a single *FOXG1* allele, we also found that deletion of one *Foxg1* allele specifically in cortical neurons was sufficient to cause cortical atrophy and corpus callosum agenesis. This study reveals a novel gene regulatory pathway that specifies neuronal characteristics during cerebral cortex development and sheds light on the etiology of FOXG1 syndrome.

Disclosures: F. Cargnin: None. **J. Kwon:** None. **B. Chen:** None. **J.W. Lee:** None. **S. Lee:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.22/A22

Topic: A.01. Neurogenesis and Gliogenesis

Title: Role of Fezf2 in maintaining corticospinal motor neuron identity in the mammalian cerebral cortex

Authors: *A. ZHANG[1], S. LODATO[2], J. L. SHERWOOD[1], J. R. BROWN[1], H.-H. CHEN[3], R. AMAMOTO[1], S. SIMMONS[4], J. LEVIN[4], P. ARLOTTA[1]
[1]Stem Cell and Regenerative Biol., Harvard Univ., Cambridge, MA; [2]Dept. of Biol. Sci., Humanitas Univ., Milan, Italy; [3]Genentech, South San Francisco, CA; [4]Broad Inst., Cambridge, MA

Abstract: In the mammalian cerebral cortex, distinct classes of neurons are generated embryonically and maintain their subtype-specific identities throughout the lifetime of the organism. While the developmental programs that control the generation of this heterogeneous neuronal output have begun to be elucidated, much less is known about the molecular mechanisms that preserve their identity through time. A potential mechanism to actively maintain subtype-specific neuronal identity is through the continuous expression of powerful, fate-determining transcription factors. We have previously shown that the transcription factor *Fezf2* as the first selector gene known for any class of projection neurons in the cortex (Lodato et al., 2014). Fezf2 is necessary for the birth and specification of corticospinal motor neurons (CSMNs), and it is sufficient to instruct corticofugal (CFuPN) neuronal identity (Molyneaux et al., 2005, Chen et al., 2005, Rouaux et al., 2010, 2013; De la Rossa et al., 2013; Ye et al., 2017), of which CSMNs are a subset. Here, we hypothesize that *Fezf2* is a *terminal* selector gene and is therefore needed to maintain CSMN identity throughout the life of the animal. To test this hypothesis, we employed a genetic strategy, which allowed for conditional inactivation of *Fezf2* specifically from CSMNs at distinct postnatal timepoints (P3 and P30), when CSMN fate specification and connectivity have already been established. This approach enabled us to test whether aspects of CSMN identity, such as their distinctive molecular signature and somatodendritic morphology, are affected upon Fezf2 deletion. By combining transcriptomic and morphological analysis, we assessed whether *Fezf2* deletion in in post-mitotic CSMNs, at different stages of their maturation, causes the neurons to *lose* their CSMN molecular identity. Transcriptional data suggests that, at least during early postnatal development, Fezf2 is needed to maintain distinctive CSMN traits, as well as repress those of closely related neuronal lineages. Whether *Fezf2* is also needed in the adult to maintain CSMN identity is still unknown, and we are currently pursuing this question by integrating our genetic approach with single cell transcriptomics. By exploiting *Fezf2* function in mature CSMNs as a model system to understand

class-specific identity maintenance, our work aims at illuminating a potential active molecular mechanism for CNS neurons to maintain their identity and function in the mature cerebral cortex.

Disclosures: A. Zhang: None. **S. Lodato:** None. **J.L. Sherwood:** None. **J.R. Brown:** None. **H. Chen:** None. **R. Amamoto:** None. **S. Simmons:** None. **J. Levin:** None. **P. Arlotta:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.23/A23

Topic: A.01. Neurogenesis and Gliogenesis

Support: ERA-NET NEURON Grant 01EW1605

Title: Essential role of RLS-associated MEIS homeobox proteins revealed by modeling human forebrain development

Authors: *V. R. KITTKE, D. D. LAM, C. ZHAO, J. WINKELMANN
Inst. of Neurogenomics, Helmholtz Zentrum München, Neuherberg, Germany

Abstract: The genes encoding the highly homologous homeobox transcription factors MEIS1 and MEIS2 are strongly associated with risk of restless legs syndrome (RLS). However, the functional role of MEIS proteins in RLS pathogenesis remains elusive. Since RLS-associated variants selectively affect expression of MEIS1 in the developing forebrain, we aimed to model human forebrain development *in vitro* in the context of engineered MEIS deficiency. We first generated *MEIS1* and *MEIS2* homozygous loss-of-function induced pluripotent stem cell (iPSC) lines through CRISPR/Cas9-mediated genome editing. We subsequently differentiated these cell lines to forebrain-like neurons of mixed excitatory and inhibitory types via a neural progenitor intermediate. Surprisingly, given the high homology of MEIS proteins and their functional redundancy in other contexts, homozygous deletion of single *MEIS* genes severely disrupted cell type composition. We also employed three-dimensional in vitro models of forebrain development, which develop greater complexity including neurogenic zones adjacent to ventricle-like structures. We examined the effects of MEIS1 and MEIS2 inactivation on the thickness of neurogenic zones and the formation of mature neurons.
In order to identify genomic binding targets of MEIS1 and MEIS2, we performed ChIP-seq on human neural stem cells. As in other tissues and cell types, MEIS bound both promoters and distal regulatory elements. Binding patterns in neural cells were highly distinct from other cell types, showing enrichment for genes involved in neural development. Among the direct MEIS targets we found other RLS-associated genes, suggesting a functional gene network in RLS pathogenesis. Together, these findings show the critical role of MEIS1 and MEIS2 in human

forebrain development and support aberrant neural development as a key factor in RLS pathophysiology.

Disclosures: V.R. Kittke: None. **D.D. Lam:** None. **C. Zhao:** None. **J. Winkelmann:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.24/A24

Topic: A.01. Neurogenesis and Gliogenesis

Support: DBT Grant, BT/PR4919/MED/30/787/2012
DBT Grant, BT/PR/21424
RGCB Intra-mural fund
CSIR, Govt of India

Title: Differential mode of Hes-1 activation maintains neural stem cells and promotes its transition into radial glial cells during neocortical development

Authors: *J. JAMES, R. ANN PAUL, L. SOUNDARARAJAN, S. PARVATHY, S. SURYA, V. MEERA, S. DHANESH, B. BUDHADITYA
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Abstract: It is known that the neural progenitors in the ventricular zone of neocortex are maintained through canonical Notch signaling. Recently, we have shown that the non-canonical mode of activation of Hes-1 (NIHes-1) maintains a subset of neural stem cells which later attain Notch dependency (NDHes-1) and transit into neural progenitor/Radial Glial Cells (RGCs) that eventually differentiate into neurons and glia populating the upper layers of neocortex. Even though we have demonstrated a differential activation of Hes-1 and its presence in different populations of stem cells/progenitors, we currently do not have any understanding regarding the functional significance of existence of such a differential activation of Hes-1 in neural stem cells/progenitors. Also, it is intriguing to know how the neural stem cells expressing NIHes-1 transit to a NDHes-1 expressing neural progenitor state. To address this, we transfected ES cells with reporter vector that is able to differentiate between the NIHes-1 and NDHes-1 expressing cells. These clones were further transfected with NIHes-$1^{f/f}$ plasmid to generate NIHes-$1^{f/f}$ sub clones. The NIHes-$1^{f/f}$ ES cells were transfected with Cre-recombinase expressing plasmid to generate NIHes-$1^{-/-}$ ES cell line. Cortical organoids were generated from the NDHes-$1^{f/f}$ and NIHes-$1^{-/-}$ ES cells. Organoids generated from NIHes-$1^{-/-}$ ES cells showed a drastic reduction in NDHes-1 expressing progenitors accompanied with cortical layer patterning. These results clearly showed that NIHes-1 expression is required for maintaining the subset of neural stem cells throughout early development of the neocortex. We also carried out transcriptomic analysis

between differentiating ES cell derived NIHes-1 and NDHes-1 expressing cells. Our results showed the involvement of stem cell maintenance pathways activated in NIHes-1 cells.To understand the mechanism of transition from NIHes-1 expressing neural stem cells to NDHes-1 expressing neural progenitors *in vivo*, we have developed NIHes-$1^{f/f}$ mice and also generated a reporter mice that can report all the NIHes-1 expressing cells as green and NDHes-1 expressing cells as red. Immuno fluorescence analysis with reporter transgenic mice showed that one of the reasons for the transition from NIHes-1 to NDHes-1 expression state is due to differential expression of Notch ligand DLL1 and Notch receptor in NIHes-1 and NDHes-1 expressing cells respectively. Overall, our results demonstrated a novel mechanism by which the neural stem cells are maintained in their niche in ventricular zone of developing neocortex and can have implication in treating neuro degenerative disorders.

Disclosures: J. James: None. **R. Ann Paul:** None. **L. Soundararajan:** None. **S. Parvathy:** None. **S. Surya:** None. **V. Meera:** None. **S. Dhanesh:** None. **B. Budhaditya:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.25/A25

Topic: A.01. Neurogenesis and Gliogenesis

Support: ALS Association
Travis Roy Foundation
Massachusetts DPH Spinal Cord Injury Fund

Title: Molecular controls over corticospinal neuron axonal segmental targeting

Authors: *V. V. SAHNI[1,2], S. J. SHNIDER[2], D. JABAUDON[2], J. SONG[2], F. DING[2], J. D. MACKLIS[2]
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Abstract: For execution of precise motor control, distinct corticospinal neurons (CSN) extend axons to, and innervate, distinct target spinal cord segments – from rostral targets in the brainstem and cervical cord to caudal targets in the thoracic and lumbar cord. The molecular basis for this segmentally specific connectivity is unknown.
Using anterograde and retrograde labeling and intersectional viral mapping, we identified that distinct CSN subpopulations, residing in distinct locations in sensorimotor cortex, exhibit striking axon targeting specificity during development. These developmental axon-extension decisions are maintained in adult mice, and correlate with their distinct spinal segmental collateralization, suggesting that early developmental axon extension decisions critically control

segmentally specific corticospinal connectivity.
Based on their distinct neocortical locations, correlated with anterograde and retrograde connectivity analyses, we isolated segmentally distinct CSN subpopulations during development, and identified differentially expressed genes between them at critical developmental times. Our data indicate that segmentally distinct CSN subpopulations are molecularly distinct from the earliest stages of corticospinal axon extension into the spinal cord, with these molecular identities beginning by the time of neuronal birth.
We next utilized stringent statistical criteria in our differential gene expression analysis, as well as the temporality of these differences, to further define molecular distinctions between CSN subpopulations that exhibit differential axon extension between bulbo-cervical and thoraco-lumbar spinal segments, beyond their spatial separation in the cortex. Collectively, these data enable the molecular delineation and prospective identification of developing CSN subpopulations well before their eventual axon-targeting decisions are evident in the spinal cord.
Finally, we functionally investigate a subset of these molecular controls, and identify their critical roles in directing CSN axons to appropriate spinal levels. These molecularly-controlled axon extension decisions occur prior to axonal collateralization, and, therefore, further indicate that mechanisms controlling CSN axon targeting to specific spinal segments are independent of mechanisms controlling spinal segment-specific axonal collateralization.
This work provides foundation for further investigation of mechanisms directing the development, evolution, and potential regeneration of specific corticospinal circuitry, and the roles of distinct CSN populations in execution of motor control.

Disclosures: V.V. Sahni: None. **S.J. Shnider:** None. **D. Jabaudon:** None. **J. Song:** None. **F. Ding:** None. **J.D. Macklis:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.26/A26

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH

Title: R-loops as mechanisms governing neural differentiation and cell-type specific transcription

Authors: *L. LAMARCA[1], S. ESPESO-GIL[2], E. FLAHERTY[2], P. RAJARAJAN[2], N. BARRETTO[2], N. TSANKOVA[2], K. BRENNAND[2], S. AKBARIAN[2]
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Abstract: Schizophrenia, bipolar disorder, and major depression together affect over 16% of the worldwide population, but their etiologies are poorly understood. Gene expression variation is a common attribute of these disorders, so research to identify and target aberrant mRNA regulation may provide novel therapeutic benefit. mRNA can anneal to template DNA during transcription, forming a DNA/RNA hybrid known as an R-loop. New genome-wide mapping strategies have identified a connection between R-loops and transcriptional regulation, suggesting a role for R-loops in gene expression variation. However, R-loops have never been characterized on a genome-wide scale in human brain cells, precluding research exploring their role in neuropsychiatric illnesses. Here, using DNA/RNA immunoprecipitation followed by deep sequencing (DRIP-seq), we show that R-loops are abundant in human neural cells and display a distinctive distribution relative to non-neural cells. We find evidence that R-loops may be poising genes for transcription, particularly those genes involved in neural differentiation and cell type-specific function. We predict that aberrant R-loop regulation may be involved in the pathophysiology of neuropsychiatric illness, and our future studies will test this hypothesis by directly manipulating R-loop formation and examining the phenotypic consequences in neural cells both in vitro and in vivo.

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Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.27/A27

Topic: A.01. Neurogenesis and Gliogenesis

Support: CNRS

Title: Knee joint inflammation: A new trigger for adult neurogenesis in the hippocampus and spinal cord of rats

Authors: *E. D. AL-CHAER[1], M. FOUANI[2], W. ABOU-KHEIR[2], N. LAWAND[3]
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Abstract: Knee joint inflammation causes pain and hypersensitivity to mechanical and thermal stimulation, and triggers a prolonged increase in the excitability and synaptic efficacy of central nociceptive neurons. In this study, we explored whether knee joint inflammation enhances neurogenesis in the dentate gyrus of the hippocampus, and induces proliferation of neural progenitor cells in the dorsal horn of the spinal cord. Male Sprague-Dawley rats were injected with kaolin and carrageenan in the synovial cavity of the knee joint. Rats received intra-articular

injection of saline served as control. Nociceptive tests including mechanical allodynia and heat hyperalgesia were performed prior to, and at 4, 8, 24 and 48hrs post induction. In addition, motor changes were assessed using the rotarod test. The knee joint circumference was also measured to evaluate the severity of inflammation. All rats received intraperitoneal injections of 5'-Bromo-2'-deoxyuridine (BrdU) (200 mg/kg) before induction of inflammation and were then perfused transcardially at 8, 24, or 48 hours' post-injection. Brain and spinal cord tissues were collected for immunofluorescence staining. Newly born neurons that are immunopositive for BrdU and neuronal nuclear antigen (NeuN), a mature neuronal marker, were identified using confocal microscopy.
Injection of K/C into the knee joint of adult rats produced swelling of the knee, increased paw sensitivity to innocuous mechanical and noxious heat stimulation, and decreased motor activity. The brain and spinal cord sections stained with anti-BrdU revealed an increase in BrdU-positive neurons both in the dorsal horn of the spinal cord and the dentate gyrus. This increase was correlated with the severity of the inflammation. Our results suggest that knee joint inflammation can induce the proliferation of neural progenitor cells at different levels of the central nervous system. These new cells may account for the changes in central nociceptive neurons and the enhanced pain sensitivity associated with inflammation.

Disclosures: E.D. Al-Chaer: None. **M. Fouani:** None. **W. Abou-Kheir:** None. **N. Lawand:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.28/A28

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 1U01 MH105991-03
BSCRC-CIRM Grant TG2-01169

Title: Molecular taxonomy of cell types in developing human neocortex

Authors: *L. DE LA TORRE-UBIETA[1], D. POLIOUDAKIS[2], J. LANGERMAN[3], J. L. STEIN[5], G. RAMASWAMI[2], C. OPLAND[2], C. VUONG[4], D. LU[2], T. ALLISON[3], S. SABRI[3], K. PLATH[3], D. H. GESCHWIND[2]
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Abstract: Key questions about the fundamental building blocks of the human brain, including the number, proportion, and lineage relationships of its distinct cell types remain unanswered.

We used multiple single-cell RNA-seq technologies to obtain and compare profiles for 40,000 cells from PCW15-17 human neocortex to define cell types and generate an unbiased molecular taxonomy. We identified expression profiles corresponding to all known major cell types at this developmental period including radial glia, intermediate progenitors, migrating and cortical plate excitatory neurons, interneurons, microglia, and oligodendrocyte precursors. We identified multiple transcription factors and co-factors expressed in specific cell types which provide a rich resource for understanding human neocortical developmental programs. We characterize the major developmental trajectories during early neurogenesis, showing that human neocortical cell type differentiation is on a gradual continuum and involves transcriptomic transitions tied to cell cycle progression with early cell fate decisions. Finally, we use this catalog to map neuropsychiatric disease genes to specific cell types, implicating dysregulation of specific cell types as the mechanistic underpinnings of several neurodevelopmental disorders. Together these results provide an extensive catalog of cell types in human neocortex, and extend our understanding of early cortical development and the cellular basis neuropsychiatric disease.

Disclosures: L. De La Torre-Ubieta: None. **D. Polioudakis:** None. **J. Langerman:** None. **J.L. Stein:** None. **G. Ramaswami:** None. **C. Opland:** None. **C. Vuong:** None. **D. Lu:** None. **T. Allison:** None. **S. Sabri:** None. **K. Plath:** None. **D.H. Geschwind:** None.

Poster

277. Neurogenesis and Gliogenesis: Neuronal Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 277.29/A29

Topic: A.01. Neurogenesis and Gliogenesis

Title: The role of lactate in neuronal differentiation

Authors: *M. M. DARWISH[1], N. TUERSUNJIANG[2], H. FIUMELLI[2], P. J. MAGISTRETTI[2]
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Abstract: During neuronal differentiation, cellular energetics is leveraged and undergoes profound remodeling. Although neuronal differentiation has been extensively studied, the exact role of metabolic reprogramming/shift in regulating neuronal differentiation has not been clearly elucidated. Here, by differentiating neuroblastoma SH-SY5Y cells with retinoic acid, we found that the glycolysis rate and L-lactate levels increased during the early stages of neuronal differentiation. The mRNA expression levels of key glycolytic enzymes such as 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), pyruvate dehydrogenase kinase 4 (PDK4), and lactate dehydrogenase A (LDHA) were upregulated upon retinoic acid treatment by 5, 3.3, and 2.3 fold, respectively. Moreover, the release of L-lactate was doubled over 48

hours. To investigate the significance of lactate elevation during neuronal differentiation, we treated SH-SY5Y cells with lactate (in addition to retinoic acid). We found at both the transcriptomic and proteomic levels that tyrosine hydroxylase, an SH-SY5Y differentiation marker, was significantly upregulated when the neuroblastoma cells were treated with either L-lactate or D-lactate. Observed increases at the mRNA levels were 2.1 and 5.8 fold ($p < 0.05$), respectively. Interestingly, when cells were treated with either of the enantiomers alone or in combination with retinoic acid, the effects of D-lactate were stronger than those of L-lactate, suggesting a possible signaling role of the lactate enantiomers rather than a metabolic effect in the differentiation of SH-SY5Y. This work gives an insight on the role of lactate in regulating neuronal differentiation.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.01/A30

Topic: A.03. Stem Cells and Reprogramming

Support: AMED 17bm0804003h0001
AMED 18bm0804014h0102
JSPS KAKENHI 17k10083

Title: Generation of maternal UBE3A knock-out pluripotent stem cell lines for a practical verification of Angelman syndrome pathogenesis

Authors: *R. OKOCHI[1], M. ISHIKAWA[2], T. SONE[2], H. OKUNO[2], H. OKANO[2]
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Abstract: Angelman syndrome (AS) is a neurodevelopmental disorder whose main features include intellectual disability, mental retardation, and epileptic seizures. AS is caused by deficient expression of the ubiquitin protein ligase E3A (UBE3A) gene, which displays paternal imprinting in neurons. Previous studies showed the gene expression of paternal UBE3A is suppressed by lncRNA whose transcription initiation site is within the imprinting center far upstream of UBE3A gene locus. Approximately 70% of all cases involve a large maternal deletion of the chromosome 15q11-q13 region, which includes UBE3A gene. The remaining known causes of AS include mutations within UBE3A, uniparental disomy (UPD), and imprinting defects. About 10% of cases are caused by currently unknown genetic or epigenetic mechanisms. There is a number of reports of UBE3A knock-out (KO) mice, and also UBE3A

homozygous KO induced-pluripotent stem cells (iPSCs). However, the expression level of UBE3A in neurons of AS patients is probably different from homo KO iPSCs-derived neurons, since imprinting effect are canceled in homozygous KO cell lines. Using genome editing, maternally specific KO in human iPSCs can be generated, although there are not any convenient method to discriminate whether gene mutation has occur in either maternal or paternal allele. Here, we produced maternal allele-specific UBE3A KO iPSCs lines. Establishing the highly efficient excitatory or inhibitory neuronal induction methods by tet-inducible ovexpression of Ngn2 or Ascl1+Dlx1/2, respectively, we measured expression level of UBE3A gene and 15q11-13 region-specific lncRNAs in the purified neurons, and tried to examine in which allele the mutation occur. The maternal KO iPS cell lines made AS studies more practical. Now we are investigating the reproducibility of AS-related phenotypes in purified excitatory or inhibitory neurons-derived from patients iPSCs of 15q11-13 deletion syndrome, UPD and UBE3A KO. AS phenotypes depend on genome imprint level. The maternally inherited UBE3A KO iPSCs provide crucial material for clarifying the AS pathogenesis.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.02/A31

Topic: A.03. Stem Cells and Reprogramming

Support: Grace Science Foundation
We would like to acknowledge the patients and their families for providing tissue samples

Title: Using iPSC-derived neurons to uncover cellular phenotypes associated with NGLY1 deficiency

Authors: *A. A. MANOLE[1], S. STERN[1], R. MARES[2], X. CHENG[2], G. WANG[2], K. J. LEE[3], C. MARCHETTO[1], F. H. GAGE[1]
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Abstract: Biallelic mutations in the gene that encodes for the N-glycanase 1 (NGLY1) protein cause a rare disease with multi-symptomatic features including developmental delay, neuropathy, seizures, axonal loss and hypotonia. NGLY1 is a deglycosylase involved in the endoplasmic reticulum-associated degradation pathway and its role is to deglycosylate misfolded proteins that are further degraded by the cytoplasmic ubiquitin-proteasome system. In the absence of NGLY1,

the initial deglycosylation cannot take place, disabling proteasomal breakdown of the misfolded protein. It is currently thought that this leads to an accumulation of misfolded proteins and proteotoxic stress but an increase in misfolded protein has not yet been directly observed. Neurons are one of the most vulnerable cell types in the face of disease-related aggregate formation. This is thought to lead to synaptic dysfunction, neuronal apoptosis and brain damage. Our aim was to evaluate the phenotypical changes in neural cells derived from NGLY1 deficient patients. For this we employed a rapid single-step induction of functional neurons from induced pluripotent stem cells. This conversion strategy gives rise to a major fraction of functional glutamatergic neurons and a very minor fraction of GABAergic cells in a short period of time. We observed an increase in the number of bead-like swellings in neuronal processes in the patients. Neuritic beading is an early hallmark of neuronal toxicity induced in a variety of pathological conditions including mitochondrial disease. Earlier in the differentiation process we observed lower mitochondrial membrane potential, abnormal morphology and distribution. We used whole-cell patch-clamp recordings to characterize single neuron properties from control individuals and NGLY1 patients. We found a lower rate and amplitude of excitatory postsynaptic currents in the patients compared to the controls. Using a rotor fluorescent dye we then looked for the presence of protein aggregates with and without proteasome inhibitor. We observed an increase in the number of cells that stained positively with this dye in basal conditions in the NGLY1 deficient patients but not in the controls. We then confirmed the presence of these aggregates using ultrastructural examination of neurons (including axons, dendrites and synaptic domains) in the NGLY1 deficient patients. Future studies will develop more robust, highly predictive and quantitative systems to explore the role of proteostasis networks in the regulation of aggregate formation and degradation, and would harness this knowledge for therapeutic development.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.03/A32

Topic: A.03. Stem Cells and Reprogramming

Title: Modeling benign adult familial myoclonic epilepsy (BAFME) using patient specific induced pluripotent stem cells (iPSCs)- derived neurons

Authors: *Y. NAGASAKO[1,2], S. MAEDA[2], H. TANABE[2], M. ISHIKAWA[2], H. ISHIURA[1], T. TODA[1], S. TSUJI[1], H. OKANO[2]
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Abstract: Benign adult familial myoclonic epilepsy (BAFME) is an autosomal dominant disorder characterized by myoclonic tremor and infrequent epilepsy with a benign clinical course. Recently, we have discovered that noncoding TTTCA and TTTTA pentanucleotide repeat expansions in introns of three different genes, *SAMD12*, *TNRC6A* and *RAPGEF2*, as causative mutations in BAFME families (Ishiura et al. Nat Genet, 2018), indicating that these pentanucleotide repeat expansions have key roles in the pathogenesis presumably through RNA-mediated toxicity mechanisms. This is also supported by the findings that RNA foci were observed in cortical neurons. Due to the lack of obvious neuropathological alterations in the brains of patients with heterozygous mutations, aberrant neural network rather than neurodegeneration appears to underlie the phenotype. To elucidate the mechanism by which these pentanucleotide repeat expansions become neurotoxic, we used human induced pluripotent stem cells (iPSCs)-derived neurons to model BAFME-associated pathophysiology *in vitro*. We have successfully generated integration-free iPSCs derived from the fibroblasts of two donors of BAFME using five non-integrative episomal plasmids (pCE-hOCT3/4, pCE-hSK, pCE-hUL, pCE-mp53DD and pCXB-EBNA1), encoding reprogramming factors of Oct3/4, dominant negative p53, Sox2, Klf4, L-Myc, Lin28, and EBNA1, under feeder free conditions. Recent studies suggested that the altered balance between inhibitory and excitatory neurons leads to the over-excitation of neural network and epileptic phenotypes. To elucidate the balance between inhibitory and excitatory neurons in BAFME, we employed the temporal over-expression method using *Neurogenin2 (Ngn2)* or *Ascl1/Dlx2* that can induce the neuronal differentiation toward excitatory and inhibitory neurons, respectively. First, we introduced the transgenes, that can drive the expression in DOX dependent manner, using PiggyBac transposon-mediated gene transfer and established stable cell lines. We differentiated the stable cell lines to excitatory neurons and found that iPSC derived from BAFME patients could be differentiated to excitatory neurons as well as that from normal controls, which is consistent with the assumption that BAFME is caused by neuronal impairment in adulthood but not in developmental stages. These neurons maintaining the patient's genetic background will provide a model allowing exploration of the downstream effects of the expansion as well as therapeutic interventions, such as drug screening and dual sgRNA-guided excision of the (TTTCA)n tract by CRISPR/Cas9 technology.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.04/A33

Topic: A.03. Stem Cells and Reprogramming

Support: NJ Governor's Council for Autism Research

Nancy Lurie Marks Family Foundation

Title: Subset of genes spanning chromosome 16p11.2 deletion contribute to a hyperproliferation phenotype observed in patient derived neural stem cells

Authors: *M. MEHTA[1], R. CONNACHER[1], P. G. MATTESON[2], S. PREM[1], M. WILLIAMS[1], M. AYALA[2], E. DICICCO-BLOOM[1], J. H. MILLONIG[1,2]
[1]Dept. of Neurosci. and Cell Biol. – Robert Wood Johnson Med. Sch., Rutgers Univ., Piscataway, NJ; [2]Ctr. for Advanced Biotech. and Med., Piscataway, NJ

Abstract: Current research supports the idea of multiple forms of autism: idiopathic with no known cause, as well as syndromic forms associated with single gene mutations, or copy number variations. Here we are studying a form of autism caused by a 28-gene deletion on Chromosome 16, known as Chromosome 16p11.2 deletion syndrome. The deletion is associated with speech and/or developmental delays in 85% of carriers, and autism spectrum disorders in 19-28% of carriers. For the present study, iPSCs were obtained from 2 individuals with the deletion syndrome, along with 6 unrelated sex matched controls. 3 clones from each individual were picked to serve as biological replicates, and were differentiated into neural stem cells (NSCs). Initial proliferation experiments comparing DNA synthesis via thymidine incorporation uncovered a hyperproliferation phenotype in NSCs derived from patients carrying the deletion. To determine which of the 28 genes spanning the deletion were contributing to the phenotype, a 28 gene multiplex Luminex assay was employed to measure gene expression. Of the 28 genes, only 11 were found to be expressed during the NSC time point. A significant reduction ($p < 0.01$) in gene expression was found for all 11 genes for the two 16p11.2 affected individuals when compared to 6 unique controls. We have hypothesized that these 11 genes, or a subset of the 11, are contributing to the hyperproliferation phenotype. As of now we have obtained 3 shRNAs per gene, 33 total, and have generated lentivirus in order to perform knockdown experiments in control NSCs to test if any of the knock-downs can phenocopy the 16p11.2 hyperproliferation effect. Future studies will involve overexpression experiments in the 16p11.2-affected NSCs in attempts to correct the phenotype. Uncovering the molecular basis of the Chr16p11.2 hyperproliferation phenotype will allow us to further identify subgroups of autism, which will lead to a more personalized treatment approach for the disorder in the future.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.05/A34

Topic: A.03. Stem Cells and Reprogramming

Title: Modeling an epilepsy-associated cortical malformation using hiPSC-derived organoids

Authors: *S. SONG, R. DHINDSA, D. WILLIAMS, E. HEINZEN COX, D. GOLDSTEIN, M. BOLAND
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Abstract: Periventricular nodular heterotopia (PVNH, OMIM #300049) is a malformation of cortical development that often presents with epilepsy, and currently no effective treatment exists. While a number of genes have been implicated in PVNH, it is most often caused by mutations in genes involved in cytoskeletal (i.e. *FLNA*) or cytoskeleton-associated pathways. Our group recently performed a trio-based whole-exome sequencing analysis of individuals with PVNH and discovered several heterozygous protein-truncating variants in *MAP1B*; a gene not previously implicated in PVNH. Interestingly, we identified both *de novo* and familial MAP1B mutations, and 2 out of 4 *MAP1B* PVNH cases also presented with polymicrogyria. MAP1B is a microtubule-associated protein that has known roles in growth cone dynamics, migration, and axon elongation and guidance in the nervous system. To date, PVNH causative genes have not been developmentally or functionally evaluated in human neurons or neural networks. Given that several proteins associated with the cytoskeleton are implicated in neuronal migration disorders (lissencephaly, polymicrogyria, heterotopias), and MAP1B's functions in microtubule and actin cytoskeleton dynamics, we hypothesize that *MAP1B mutations affect cellular polarity and migration, and result in morphological abnormalities and aberrant neuronal activity.* CRISPR/Cas9 was used to create a patient-specific *MAP1B* mutation (R303X) into an hiPSC line derived from a healthy female. In the process, we were also able to derive heterozygous ($^{+/-}$) and homozygous ($^{-/-}$) *MAP1B* knock-out hiPSC lines. Similar methods were used to generate *FLNA*$^{+/-}$ and *FLNA*$^{-/-}$ hiPSC lines. *FLNA* encodes the cytoskeletal protein Filamin-A; the most commonly mutated gene in PVNH. Together, these MAP1B and FLNA hiPSC lines were used to develop a cortical organoid (hCO) model to study the etiology of PVNH in human neural networks. We have identified striking morphological phenotypes related to neuronal progenitor polarity and migration defects in mutant hCOs relative to isogenic control hCOs. Furthermore, single-cell RNA-seq has begun to identify molecular network and cellular signatures of PVNH in MAP1B and FLNA hCOs. Taken together, this study will significantly enhance our understanding of the molecular machinery controlling neuronal migration and cortical development in humans, which may thereby improve the health of individuals with PVNH-related epilepsy.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

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Program #/Poster #: 278.06/B1

Topic: A.03. Stem Cells and Reprogramming

Support: The Grant of Excellence Departments, MIUR

Title: Ultrastructural analysis of motor neurons derived from induced pluripotent stem cells (iPSCs) of patients with Brown-Vialetto-Van Laere (BVVL) syndrome

Authors: *F. COLASUONNO[1], A. NICEFORO[1,2], A. FRACASSI[1,3], C. COMPAGNUCCI[2], E. BERTINI[2], S. MORENO[1]
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Abstract: Brown-Vialetto-Van Laere syndrome (BVVL) is a rare, childhood-onset neurological disorder characterized by hearing loss, sensory ataxia and spinal motor neuron (MN) neurodegeneration[1]. The disease is caused by loss-of-function mutations in two riboflavin transporters (RFT2 and RFT3). Riboflavin is the precursor for FMN and FAD, i.e., cofactors of flavoproteins, which are involved in several energy metabolism pathways. Particularly, redox reactions, such as mitochondrial electron transport chain, depend on flavoproteins, so that impaired mitochondrial functionality is likely to contribute to the disease. However, the role of oxidative stress and, more generally, the pathogenic mechanisms underlying BVVL syndrome are still unclear. Even morphological studies aiming at characterizing mitochondrial population in BVVL cells are lacking, encouraging research addressing this specific issue. On the other hand, the cellular effects of riboflavin, empirically used in systemic therapeutic treatment of patients, are so far unexplored[2]. In the present work, we took advantage of induced pluripotent stem cells (iPSCs) technology to perform ultrastructural analyses of BVVL cells, before and after treatment with riboflavin and the antioxidant N-acetyl-cysteine (NAC). Patient-specific iPSCs and iPSCs-derived MNs were analyzed by Focused Ion Beam/Scanning Electron Microscopy (FIB/SEM)[3], and compared with their counterparts, obtained from healthy individuals. BVVL iPSCs and derived MNs displayed aberrant mitochondrial ultrastructural features compared to control cells, compatible with the concept that riboflavin deficiency affects energy metabolism. Treatment with riboflavin in combination with NAC resulted in partial rescue of iPSCs-mitochondrial morphology in patients' cells. Consistent with ultrastructural results, molecular data obtained by a sensitive technique employing MitoSOX^{TM}Red probe, demonstrate significantly higher levels of superoxide anion in diseased cells *vs.* controls. Also in agreement with FIB/SEM observations, riboflavin and/or NAC supplementation restored normal $O_2^{-\cdot}$ levels. Our data support the use of iPSCs for *in vitro* modeling of BVVL syndrome, highlighting the pathogenic role of oxidative stress generated by mitochondrial dysfunction. Restoring redox balance by riboflavin/NAC treatment opens the way to future antioxidants-based therapeutic strategies aimed at ameliorating and/or preventing symptoms of BVVL syndrome. *1. Sathasivam S. Orphanet J Rare Dis 2008; 3: 9. 2. Bosch AM et al.Orphanet J Rare Dis 2012; 7: 83. 3. Colasuonno F et al. Aging (Albany NY) 2017; 9: 2209.*

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.07/B2

Topic: A.03. Stem Cells and Reprogramming

Title: Reduced neuronal complexity and -activity in human inducible pluripotent stem cell derived excitatory cortical neurons carrying the MELAS 3243A>G mitochondrial mutation

Authors: *T. M. KLEIN GUNNEWIEK[1], M. FREGA[2], D. CASSIMAN[3], E. MORAVA-KOZICZ[3], N. NADIF KASRI[4], T. L. KOZICZ[5]
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Abstract: Most individuals diagnosed with the most common mitochondrial disorder MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), carry the pathogenic variant m.3243A>G in their mitochondrial DNA (mtDNA). Patients show a broad range of symptoms, involving mainly the skeletal muscle and the central nervous system. In order to increase our understanding on the neuropathobiology, we generated human excitatory cortical neurons, derived from human inducible pluripotent stem cells (hiPSCs) and studied the impact of mt.3243A>G on mitochondrial- and neuronal function. Patient-derived fibroblasts were reprogrammed to hiPSCs, during which the mitochondrial bottleneck induced biphasic mitochondrial segregation. Two clones from the same patient, with different heteroplasmy levels (0%, and 83%) were expanded, as well as an external, commercial control cell line. These hiPSCs, one external control line, one isogenic control line, and one line containing the 3243A>G mutation, were differentiated into excitatory neurons by lentiviral rtTa- and Neurogenin 2 (Ngn2) expression.
We compared neurons of all three cell lines using a Seahorse Mito Stress test, and found that the presence of the m.3243A>G mutation in the neurons was accompanied by lower basal-, ATP-linked-, and maximal mitochondrial respiration ($P<0.05$). Using DsRed2-Mito7 transfection, we found a significantly lower abundance of axonal mitochondria in the neurons with the m.3243A>G mutation, whilst a MAP2/Synapsin immunohistochemical staining revealed a lower post-synaptic density ($P<0.05$). We also found a decreased sEPSC frequency in the m.3243A>G neurons ($P<0.05$) using single-cell voltage clamp recording. In addition, using micro-electrode arrays (MEAs), we observed a similar phenotype on the network level, with a reduced mean firing rate ($P<0.05$) as well lower synchronous network bursts ($P<0.005$), in the neurons carrying the 3243A>G mutation.
Our study illustrates for the first time, the potential role of a synaptic deficit in the neurological manifestations of MELAS, and highlights the relevance of a patient-specific in vitro

neurophysiologic model of MELAS disease. Our future goal is to employ our MEA system in validation of current forms of therapy, as well as a tool for the screening of new treatments.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.08/B3

Topic: A.03. Stem Cells and Reprogramming

Title: Investigation of the role of CHD8 in human brain development at single-cell resolution

Authors: *G. QUADRATO[1,2], B. PAULSEN[2], T. NGUYEN[1,2], S. SIMMONS[3], S. VELASCO[3,2], J. SHERWOOD[4,2], J. PAN[3], F. ZHANG[3], A. REGEV[3], J. LEVIN[3], P. ARLOTTA[2]
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Abstract: The ATP-dependent chromatin-remodeling factor CHD8 is one of the most commonly mutated genes in sporadic autism spectrum disorder (ASD), and results in an ASD subtype associated with a high prevalence of macrocephaly. Although this gene has been shown to regulate other ASD risk genes the study of its functional relationship to autism phenotypes has so far focused primarily on low-complexity cell culture models. To date, limited information is available on the cell-type specific cellular and molecular defects induced by CHD8 mutation in human brain cells. To address this question, we have used pluripotent stem cell (PSC) lines heterozygous for a CHD8 loss of function mutation and isogenic control lines. We have demonstrated that these lines can be used to generate different 3D brain organoids models, which can be grown over extended time periods. We have used these models to investigate developmental processes and cellular and molecular changes associated with the CHD8 mutation. These organoids can recapitulate the macrocephaly phenotype observed in several of the ASD patients carrying this mutation. In order to gain information on specific cell types affected we have performed single-cell analysis of CHD8 mutant and control organoids. We have profiled the RNA of a total of 128,000 single cells from both 4 and 6 month old organoids (n=4 per age and genotype) using the 10X Genomics Chromium system, and have performed clustering and differential gene expression analysis. Upon clustering of single cells we find that most clusters are populated by cell types of both genotypes. This indicates that most cell types are reliably made, and that comparisons can be performed even with a relatively small number of samples (n=4 organoids per age and genotype). Furthermore, preliminary analysis has identified

sets of genes that are differentially expressed between the CHD8-/+ and control organoids. Within specific clusters and subclusters we find that both the type and degree of molecular phenotypes differ between cell types. Altogether, these data provide first insight into cellular and molecular abnormalities associated with ASD genetics validate the use of organoids to model human cortical development and cell type specific changes in neurodevelopmental disorders.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.09/B4

Topic: A.03. Stem Cells and Reprogramming

Title: Using iPSC characteristics to test BSNIP psychosis Biotypes

Authors: *A. M. BOBILEV[1], E. I. IVLEVA[2], B. A. CLEMENTZ[3], E. GERSHON[4], M. KESHAVAN[5], G. PEARLSON[6], C. A. TAMMINGA[7]
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Abstract: Disease heterogeneity in psychotic illness presents a significant challenge. The BSNIP consortium has demonstrated that a battery of measures of cognition and brain activity collected from individuals with diverse psychosis diagnoses identified no diagnosis-specific biomarker, but rather suggested three distinct psychosis subgroups called Biotypes. We hypothesize that neural progenitor cells (NPCs) and neurons differentiated from patient-derived induced pluripotent stem cells (iPSCs) may uncover synaptic mechanisms and divergent cellular traits in these novel Biotypes. A panel of cognitive, neuropsychological and neuroimaging measures were previously collected for individuals with psychosis (schizophrenia, schizoaffective disorder, psychotic bipolar disorder) (N=711), relatives (N=883) and healthy comparison subjects (N=278). A subset of these individuals provided dermal biopsies for additional study, which were cultured to establish patient-derived fibroblast lines. The BSNIP phenotyping was used to define three Biotypes, each with divergent cognitive control and sensorimotor reactivity scores. Fibroblasts representing all three Biotypes and healthy comparisons (N=16) were reprogrammed into iPSCs. These iPSC lines were then validated and differentiated into neural progenitor cells (NPCs) and cortical-like neurons. Cellular adhesion and migration is being measured in NPCs. In mature neurons and cortical-like organoids, cellular morphology and

organization are being examined. Data on cellular migration and morphology from the cells will be presented, along-side of the human phenotypes from psychosis individuals. Biotype-1(B-1) shows significant cognitive impairment and EEG hypoactivity in basal and evoked conditions, therefore we hypothesize that B-1 NPCs will show impaired adhesion/migration and B-1 neurons will demonstrate reduced connectivity and dendritic arborizations. Since Biotype-2(B-2) shows EEG hyperactivity, we hypothesize that B-2 neurons will demonstrate cellular integration and connectivity. Since Biotype-3(B-3) are most similar to healthy, we expect B-3 neurons to have healthy developmental and morphological profiles. We are testing these outcomes to explore the biological bases for the BSNIP Biotypes, and test further stratification of psychosis subgroups The use of patient-derived iPSCs is a potential method for investigating cellular mechanisms of human disease, and may offer a novel translational platform for novel drug discovery.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.10/B5

Topic: A.03. Stem Cells and Reprogramming

Title: Optimization and characterization of protocols for 3D human brain models: Cerebral organoids and spheroids

Authors: *S. VELASCO[1], G. QUADRATO[2,3], T. NGUYEN[2,3], S. SIMMONS[1], A. NASH[1,3], M. ROCHA[1,3], J. LEVIN[1], A. REGEV[1], P. ARLOTTA[3,1]
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Abstract: Many 3D human brain models have been described in recent years: some of them rely on inducing early patterning of specific brain regions (patterned-brain organoids and spheroids), while others omit exogenous morphogenetic and fate-specifying cues and rely largely on self-organization and self-patterning (whole-brain organoids). Brain organoids and spheroids offer great promise for the study of the development and function of the human brain and provide an invaluable tool to model neurological disease. However, the utility of these model systems has been hampered by the limited characterization and comparison of the cell types and features produced by distinct protocols and their inherent reproducibility. In order to address these issues, we generated and optimized different 3D brain model systems and performed extensive comparison of the cell types produced in each, using large-scale single-cell molecular profiling. This type of systematic comparison, across stem cell lines and within sufficient resolution, is

necessary to be able to standardize and cross- compare these models. Single-cell transcriptomic atlases from the endogenous human brain, both existing and those that are currently being generated, will be used to compare and define the similarities and differences of the various cell types produced in 3D cellular models and their endogenous counterparts. The results of this study will pave the way for the future development and optimization of 3D brain models and will be crucial to inform the choice of models for distinct experimental applications.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.11/B6

Topic: A.03. Stem Cells and Reprogramming

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Title: Targeted activation of endogenous neuronal-fate determining genes using CRISPR/dCas9 advances induced neuron disease modeling for Jordan's syndrome

Authors: *J. L. CARTER, J. A. HALMAI[1,2], P. DENG[1,2,3], D. CAMERON[1,2], J. NOLTA[1], D. SEGAL[3], K. FINK[1,2]
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Abstract: Disorders of the central nervous system (CNS) result in one of the largest economic burdens on society. While research has made enormous contributions in the identification of CNS disease-related genes, the underlying molecular mechanisms associated with disease pathology in human neuronal cells remain unclear. Developing a method to recapitulate disease pathology in human neurons grown *ex vivo* is critical for furthering understanding on CNS disorders and advancing therapeutic development. Our research uses CRISPR guide RNAs (gRNA) with a nuclease-deficient Cas9 (dCas9) fused with a transcriptional activator to upregulate endogenous neuronal-fate determining genes in adult somatic cells to facilitate transdifferentiation to induced neurons (iN). We have successfully upregulated endogenous

BRN2, *ASCL1*, *MYT1L* and *NEUROD1* (*BAMN*) in human adult fibroblasts following delivery of a CRISPR-dCas9 activation complex and gRNAs targeted to *BAMN*. Our time course studies show downregulation of fibroblast markers and upregulation of immature, developing and mature neuronal markers via qPCR. Immunocytochemistry revealed subpopulations of cells that are positive for neuronal markers, suggesting transdifferentation. We are currently investigating methods to increase transdifferentiation efficiency that will enable *in vitro* disease modeling of genetic neurological disorders in patient-specific iNs. Our group is creating iN to advance understanding on neuronal dysfunction in patients with Jordan's Syndrome, a rare neurodevelopmental disorder arising from *de novo* mutations in protein phosphatase PP2A regulatory B56δ subunit gene (*PPP2R5D*). Our research is also focused on implementing the CRISPR/Cas9 nuclease to correct *PPP2R5D* mutations, thereby enabling disease-associated phenotypic analysis. We are currently characterizing Jordan's Syndrome patient-derived fibroblasts and employing CRISPR/Cas9 targeted correction of *PPP2R5D* with Homology Directed Repair (HDR), Homology-mediated End Joining (HMEJ) and Microhomology-mediated End Joining (MMEJ). To our knowledge we are the first to demonstrate endogenous upregulation of *BAMN* in human somatic cells with dCas9-VP64 and begin studies towards Cas9 gene-editing in patient somatic cells transdifferentiated with dCas9-VP64 and gRNAs. These studies support the potential of the CRISPR/dCas9 and Cas9 systems as alternative methods for creating disease models and advancing personalized medicine for individuals with neurological disorders.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.12/B7

Topic: A.03. Stem Cells and Reprogramming

Title: Three-dimensional cellular model of hypoxic brain injury of prematurity

Authors: *A. M. PASCA[1], J.-Y. PARK[2], H.-W. SHIN[2], Q. QI[4], O. REVAH[2], R. KRASNOFF[4], R. O'HARA[2], J. WILLSEY[2], T. PALMER[2], S. P. PASCA[3]
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Abstract: Progress in critical care has significantly improved the survival of extremely premature infants born before 28 weeks of gestation. However, extreme prematurity is associated with devastating consequences, particularly for brain development. Up to 70% of patients have significant life-long impairments, including intellectual disability, autism or ADHD. Little is

known about the cellular mechanisms leading to brain injury in this vulnerable population, but it is thought that low oxygen levels in the brain play a critical role. Here, we used human stem cells derived 3D brain region-specific organoids or spheroids that resemble the developing cerebral cortex to study the effect of oxygen deprivation at mid-gestation. We found defects in specific progenitor populations that are associated with the expansion of the human cerebral cortex. Moreover, we demonstrate that this effect is mediated through the unfolded protein response (UPR) and leads to cell cycle changes. We validate these findings in human fetal tissue and show that modulation of the UPR pathway can prevent the cell specific defects during oxygen deprivation. We anticipate this human cellular platform will serve as a powerful tool to study the effects of environmental insults and genetic susceptibilities underlying brain injury in premature infants and that it may facilitate drug discovery for preventing long-term neuropsychiatric conditions in premature infants.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.13/B8

Topic: A.03. Stem Cells and Reprogramming

Support: Åke Wiseberg stiftelsen (M17-0265 to S.I.)
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Psychiatry Research Foundation in Gothenburg (to S.I.)

Title: Disease modelling of bipolar disorder and drug evaluation in patient-derived induced pluripotent stem cell cortical circuits

Authors: *J. IZSAK[1], K. FUNA[3], H. ÅGREN[1], S. ILLES[2,4]
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Abstract: Bipolar disorder (BD) is neuropsychiatric mood disorder which is among the most disabling conditions worldwide. Since no suitable animal models exist for BD, revealing the etiology and pathophysiological mechanisms still represents a challenging task. In vitro cultivated human induced pluripotent stem cell (iPSC)-derived neural cells are emerging and

might hold promise to investigate the etiology, disease mechanisms and treatment options. However, *in vitro* human neurons that can faithfully reflect the basic principle of human brain functionality, i.e. synchronous network activity has not been achieved in solely person specific human iPSC-based in vitro models. In this study six BD and four control iPSC lines were established from abdominal fat samples of patients with bipolar disorder type 1 and healthy volunteers. We combined isogenic human iPSC-neural aggregates with microelectrode array (MEA) technology and demonstrate the development of functional human neuronal circuits *in vitro*, i. e. neuronal populations with autonomously generated synchronous network activity. We successfully mimic drug-overdose induced seizures in *in vitro* human neuronal networks. Moreover, we apply an anti-epileptic drug, Perampanel, and counteract pathophysiological neuronal network activity of human cortical circuits exposed to intoxicating concentrations of currently prescribed drugs, e.g. lithium salts. Our presented platform allows drug screening and the evaluation of drug repurposing approaches in the context of human specific neuropsychiatric disorders. Thereby, we close a conceptual gap between preclinical animal-based CNS disease modelling and human clinical trials.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.14/B9

Topic: A.03. Stem Cells and Reprogramming

Title: Modeling prenatal environmental challenges in placental cells derived from schizophrenic patients

Authors: *E. TIETZE[1], G. URSINI[1], D. R. WEINBERGER[1], J. VAN DE LEEMPUT[1], J. ERWIN[1,2]
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Abstract: Schizophrenia (SZ) is a devastating neuropsychiatric disorder affecting around 1.1% of the population. While it is well established that underlying genetic vulnerability interacts with environmental factors to cause SZ, the specific mechanisms contributing to risk are poorly understood. Epidemiological evidence suggests that perturbations to the intrauterine environment play a critical role in SZ etiology. A history of maternal respiratory infections increases the risk of SZ in offspring 3-7 fold. More broadly, pregnancy, labor and delivery, or early neonatal complications termed early life complications (ELCs) increases the risk of SZ by two fold.

Recent genomic analysis using a polygenic risk score model of SZ risk have found that ELCs interact with genomic risk to increase SZ liability by more than 5 fold. Interestingly, loci associated with placental genes that are highly expressed or differentially expressed in preeclampsia or intrauterine growth restriction mediate this effect. Emerging evidence support the idea that placental function plays a key role in brain development. The placenta acts as a dynamic interface that conveys changes between the maternal environment and the fetus. In the case of maternal infection, the placenta acts as a barrier to the infectious agent, while allowing pro-inflammatory cytokines such as IL-6 to enter the fetal circulation. The placenta also produces various compounds including serotonin, BDNF, IGF1/IGF2, and prostaglandins that play important roles in neurodevelopment. In order to investigate the role of the placenta in neuronal development we established iPS cell model of placental differentiation using SZ patient cells. We characterized the differentiation of these cells by single-cell RNAseq and the endophenotypes of these cells both with and without simulated intrauterine environmental challenges.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.15/B10

Topic: A.03. Stem Cells and Reprogramming

Title: Using forebrain assembloids to study the role of L-type calcium channels in human cortical interneuron function and dysfunction

Authors: *F. BIREY[1], R. M. AGOGLIA[2], S. P. PASCA[3]
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Abstract: Voltage-gated L-type calcium channels (LTCCs) variants are among the most replicable risk factors in genetic studies of neuropsychiatric disease. The mechanisms by which these genetic events lead to disease are not currently known. Previous work has indicated that LTCCs play a critical role in cortical interneuron migration and functional integration into cortical circuits. We have developed a tridimensional (3D) neural differentiation platform derived from human induced pluripotent stem cells (hiPSCs), termed forebrain assembloids, to study the migration and circuit integration of human cortical interneurons. Using this modular, region-specific organoid system, we identified migration defects in interneurons generated from Timothy syndrome, a monogenic form of autism caused by mutations in a LTCC subunit encoded by *CACNA1C*. Using transcriptional profiling, functional live imaging and

pharmacology in patient and control hiPSC-derived forebrain assembloids, we investigated the specific contributions of LTCCs to interneuron migration and underlying molecular mechanisms that are disturbed in interneurons derived from Timothy syndrome. Our results show that the forebrain assembloid system can be used to study the molecular underpinnings of dynamic cellular processes that take place in late human brain gestation towards revealing novel disease signatures.

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Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.16/B11

Topic: A.03. Stem Cells and Reprogramming

Title: Generation of functional cortico-spinal assembloids to study human development and disease

Authors: *J. ANDERSEN[1], O. REVAH[1], E. WALCZAK[3], C. FAN[3], N. THOM[1], J. R. HUGUENARD[2], R. REIMER[2], S. P. PASCA[1]
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Abstract: The corticospinal tract plays a central role in controlling muscle activity by mediating voluntary movements. In primates, this circuit possesses unique monosynaptic projections from corticospinal fibers to spinal motor neurons that are thought to be involved in fine distal motor control. Damage or degeneration of this circuit in spinal cord injuries, amyotrophic lateral sclerosis or autoimmune disorders results in severe motor dysfunction. We developed a novel approach to study human cortico-spinal development and neuromuscular function using 3D brain region-specific organoid or spheroid cultures generated from pluripotent stem cells (hPSCs). We first generated hPSC-derived ventral spinal cord spheres (hSCs), which include functional motor neurons able to promote muscle contraction when co-cultured with 2D and 3D human skeletal muscle (hSkM). Assembly of human cortical spheroids (hCSs), which include pyramidal neurons of all layers, with hSC-hSkM in cortico-spinal assembloids results in the formation of corticospinal projections. Using a combination of viral tracing, calcium imaging and electrophysiological methods we present evidence of the formation of the first in vitro model of the human cortico-spinal-muscular assembly that could be used to study the development and disorders affecting this circuit.

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Poster

278. Stem Cells and Disease Modeling I

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.17/B12

Topic: A.03. Stem Cells and Reprogramming

Support: FNS #320030_122419
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Alamaya Foundation

Title: Evaluation of redox dysregulation in schizophrenia using induced pluripotent stem cells

Authors: *B. GIANGRECO[1], D. DWIR[1], S. SACHCHITHANATHAM[1], J. KOCHER-BRAISSANT[1], L. BARTESAGHI[2], P. STEULLET[1], J.-H. CABUNGCAL[1], R. CHRAST[2], N. TONI[1], K. Q. DO[1]
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Abstract: Schizophrenia (SZ) is a psychiatric disorder that involves genetic and environmental factors. A decrease of glutathione (GSH), a major cellular antioxidant, was shown in patient's brain and CSF. Furthermore, polymorphisms in the key synthetizing enzyme for GSH were found associated with the disease. These observations lead to the hypothesis that redox dysregulation is a main hub in this disorder. In this study, we aim to investigate the role of the redox state on neuronal development using induced pluripotent stem cells (iPSC)-derived neuronal precursor cells (NPCs) from SZ patients and healthy controls. iPSC-derived NPCs were generated from one patient from a well-characterized cohort of SZ patients at the early stage of the disease and two aged-matched healthy controls. Here, we examined the role of redox dysregulation in iPSC differentiation. We found that a redox dysregulation led to a delay in the differentiation of iPSCs-derived NPCs into neurons. Differences of neuronal maturation between patients and controls are under investigation. This method, together with other approaches, will allow assessing whether the redox balance is endogenously altered in iPSC-derived neurons from patients compared to controls.

Disclosures: B. Giangreco: None. **D. Dwir:** None. **S. Sachchithanatham:** None. **J. Kocher-Braissant:** None. **L. Bartesaghi:** None. **P. Steullet:** None. **J. Cabungcal:** None. **R. Chrast:** None. **N. Toni:** None. **K.Q. Do:** None.

Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.18/B13

Topic: A.03. Stem Cells and Reprogramming

Title: Stem cell and genome engineering technologies to advance the understanding of neurological diseases

Authors: *R. VEGA, J. DIZON, J. WEBB, D. PIPER
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Abstract: Neurological disorders are a health concern since a large percent of the population suffers from it. The chronic disorders comprise a spectrum of symptoms that current therapies only partially ameliorate. Familial and mouse models have been valuable tools to gain insight into the diseases but do not completely support preclinical efforts needed for drug development. More effective and predictive models are needed to develop new therapies more reliably and economically. Recent advancements in the genome editing and stem cell field make it possible to establish disease-relevant in vitro models. Human induced pluripotent stem cells (iPSCs) can be differentiated into numerous cell types and in combination with CRISPR/Cas9 genome editing can provide new ways to study the pathophysiology of the brain in vitro. In this study, we utilize an iPSC line that stably expresses the Cas9 nuclease protein to efficiently introduce the disease-linked mutations. We derived neuronal progenitors and neurons from the normal and mutant lines to perform functional and High Content phenotypic assays. We demonstrate the cellular phenotypes of iPSC-derived neurons can be translated into disease models to accelerate the finding of new therapeutic targets for drug discovery.

Disclosures: R. Vega: A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **J. Dizon:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **J. Webb:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **D. Piper:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific.

Poster

278. Stem Cells and Disease Modeling I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 278.19/B14

Topic: A.03. Stem Cells and Reprogramming

Support: NIH U19 MH106434 02

Title: Alpha-tocopherol and polyunsaturated fatty acids treatment effects on quality and maturation of cultured human neurons derived from induced pluripotent stem (hIPS) cells

Authors: *K. M. GLANOWSKA[1], G. G. MURPHY[2], K. S. O'SHEA[3], C. J. DELONG[4]
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Abstract: Utilization of hIPS cells derived neurons as models of neurological and neuropsychiatric disorders has been growing rapidly in recent years. Existing differentiation protocols generate, at least in terms of expression of appropriate neuronal markers, neurons that appear to be relatively mature. However, mature electrophysiological properties of those neurons and their ability to reproduce firing behavior observed in tissue from both rodent or human brains have been difficult to obtain. Both passive and firing active properties of IPS cells derived neurons e.g.: high input resistance, depolarized resting membrane potential, and wide action potentials (APs) suggest immature developmental state. The relatively low fraction of mature IPS cells derived neurons in 2D cultures likely contributes to the high variability and low reproducibility of electrophysiological studies performed in these model systems. To overcome these challenges, we have begun to test the impact of factors known to be crucial for proper brain development and which can be easily incorporated into established cell culture protocols. Here we present data using tocopherol, a potent antioxidant demonstrated to enhance efficiency of neural stem cell differentiation in rodent cultures, and polyunsaturated fatty acids (FAs) critical for the fetal brain development. Human NPCs were derived from IPS cells via dual inhibition of BMP and TGFβ signaling using Dorsomorphin and SB431542. Neuronal differentiation was induced by culturing NPCs in complete BrainPhys supplemented weekly with α-tocopherol (α-t) and various FAs. Electrophysiological recordings were made after 8 weeks of differentiation. We have tested the following treatments: cont + α-t; + α-t + docosahexaenoic acid (DHA); + α-t +eicosapentaenoic acid; + α-t +arachidonic acid, and + α-t +oleic acid. To minimize bias, the experimenter performing recordings was blind to the culture conditions. We examined both passive properties and ability of neurons to fire evoked individual as well as repetitive APs and the presence of synaptic activity. The success rate defined as the fraction of recorded cells with stable seals over time and ability to fire repetitive APs was highest in the cont + α-t and lowest under control conditions. Most treatments with FAs appear to improve quality of recordings in comparison to controls with addition of DHA resulting in the highest proportion of spontaneously active neurons. Interestingly, the consistent synaptic activity was the highest in α-t alone. Our results provide a strong evidence that culture enrichment with α-t improves the quality of electrophysiological data from IPS cells derived neurons.

Disclosures: K.M. Glanowska: None. **G.G. Murphy:** None. **K.S. O'Shea:** None. **C.J. DeLong:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.01/B15

Topic: A.03. Stem Cells and Reprogramming

Support: NMSU Foundation

Title: Post-translational tubulin modifications in differentiated human neural stem cells

Authors: V. B. KNIGHT, M. P. JOGALEKAR, *E. E. SERRANO
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Abstract: The protein tubulin is assigned diverse cellular functions that range from chromosomal separation to locomotion. The functional diversity of tubulin is achieved through the expression of specific tubulin isotypes in different cell types or developmental time periods. Post-translational modifications (PTMs) of tubulin are also critical for specific intracellular objectives, such as binding and recruiting motor proteins. In neurons, the isotypic expression profile for tubulin is well characterized, and the importance of PTMs for proper neuronal function has gained recent attention due to their implication in neurodegenerative disorders. There are relatively fewer studies of tubulin PTMs and isotypes in astrocytes. It is well established that tubulin isotypes and specific PTMs are crucial for distinct cellular functions. However, the role of tubulin specializations in the specification of neural cell fate has not been evaluated. Therefore, we undertook an analysis of PTMs in basal and differentiated human neural stem cells (hNSCs) derived from the federally approved H9 embryonic stem cell line. Immunocytochemical methods, fluorescent antibody probes, and confocal microscopy facilitated image acquisition of fluorescent signals from class III β- tubulin (βIII-tubulin), acetylated tubulin, and polyglutamylated tubulin. Fluorescent probe intensities were assessed with the 'EBImage' package for the statistical programming language R, and compared using Student's t-tests. Qualitative analysis indicated that βIII-tubulin, acetylated tubulin, and polyglutamylated tubulin were expressed to some degree in all basal and differentiated hNSCs. Quantification and statistical analysis of fluorescence intensity demonstrated that the fluorescence probe intensity ratio for acetylated tubulin/ βIII-tubulin was greater than the ratio for polyglutamylated tubulin/ βIII-tubulin in differentiated astrocytes. These findings represent a snapshot of the tubulin expression profile during the specification of neural cell fate. Furthermore, these results imply that investigations of tubulin PTMs have the potential to advance our understanding of the generation and regeneration of nervous tissue.

Disclosures: V.B. Knight: None. **M.P. Jogalekar:** None. **E.E. Serrano:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.02/B16

Topic: A.03. Stem Cells and Reprogramming

Title: A novel approach for efficient dissociation of distinct adult mouse brain regions and subsequent sorting of neurons and neural stem cells using the MACSQuant® Tyto®

Authors: *A. BOSIO, S. REIß, C. WITTWER, J. GAISER, M. JUNGBLUT
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Abstract: Careful tissue dissociation and preparation of single-cell suspensions with high cell viability and a minimum of cell debris are prerequisites for reliable cellular analysis. In case of adult rodent brain, sophisticated mechanical and enzymatic treatments are required to successfully disaggregate the tightly connected neural cells. The process becomes even more challenging when only small brain regions serve as starting material for generation of single cell suspensions and highest possible viability, recovery and functionality are crucial for successful down-stream processing. In the past, we have set up elaborated technologies for the automated dissociation of adult rodent brain by combining mechanical dissociation using the gentleMACS™ Octo Dissociator with an optimized enzymatic treatment, followed by an efficient clearing procedure to eliminate debris and erythrocytes. The protocol was now further refined for highly effective generation of single cell suspensions from small brain regions with highest possible viability and neural cell yield and a minimum of contaminating debris. Dissociation of one cerebellum yielded 1.3x10E6 ± 6x10E5 cells (n=5), whereas 6.3x10E5 ± 2.8x10E5 cells were obtained one cortical hemisphere, 4.3x10E5 ± 7.6x10E4 cells from the SVZ tissue of one mouse (n=9), and 3.3x10E5 ± 9.5x10E4 cells (n=9) from 2 hippocampi (n=9). Viability rates were between 70 and 97%, depending on the brain region. Subsequently, cell isolation of neurons or Neural Stem Cells (NSCs) was carried out with the MACSQuant Tyto, a new multi-parameter cell sorting device that uses a micro-chip based sorting technology for sterile and gentle cell isolation. Unlike conventional droplet sorters, cells do not experience high pressures and no charge is applied, ensuring high viability and functionality. Neurons were indirectly identified by a combination of markers specific for non-neuronal cell populations. A number of 1.2x10E4 neurons with a viability of 97% was obtained from one cerebellum and a number of 4.4x10E3 neurons with a viability of 95% from one cortical hemisphere. NSCs were identified by labeling the positive markers GLAST and PlexinB2 and the negative markers CD24, TER119, and CD45 before subjected to the MACSQuant Tyto sorting. This protocol resulted in highly pure (>95%) and viable NSCs (>90%), which formed a high number of neurospheres, that differentiated into different neural cell types. In summary, we present a novel approach for isolation of neurons from various brain regions and NSCs from the SVZ by

combining an elaborated method for gentle and efficient dissociation of small brain regions with a sophisticated cell sorting Technology.

Disclosures: A. Bosio: None. **S. Reiß:** None. **C. Wittwer:** None. **J. Gaiser:** None. **M. Jungblut:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.03/B17

Topic: A.03. Stem Cells and Reprogramming

Support: Guy's and St Thomas's Charity Prize
MRC Fellowship MR/N014863/1

Title: Examining the role of sex hormones in postnatal depression and major depressive disorder: Polygenic risk scores and hippocampal neurogenesis

Authors: *D. SMEETH[1], I. KOUROUZIDOU[1], T. POWELL[2], S. THURET[1]
[1]Basic and Clin. Neurosci., [2]MRC Social, Genet. & Developmental Psychiatry Ctr., King's Col. London, London, United Kingdom

Abstract: Background: Genetic variation accounts for up to 54% of postnatal depression (PND) liability and 40% of major depressive disorder (MDD) liability. Alterations to sex hormones have been associated with the pathophysiology of depressive disorders and may partly explain the higher rates of MDD amongst females. However, few studies have considered whether genetic variants associated with sex hormone levels directly increase risk for depressive disorders. This risk may be mediated by alterations in adult hippocampal neurogenesis (HN), a cellular process which has been associated with mood regulation. Here we consider: i. the effects of oestradiol, testosterone and prolactin on human HN, and ii. whether polygenic risk for higher sex hormone levels directly affect risk for MDD or PND. Methods: To better understand how sex hormones affect HN, human female hippocampal progenitor cells (HPCs) were cultured with biologically relevant concentrations of each hormone. Immunocytochemistry and high-throughput analysis were used to quantify a range of markers of cell fate. To understand how polygenic risk scores (PRS) for sex hormones moderate risk, we used the PRSice software and sex hormone genome-wide summary statistics from the Twins UK cohort (n=2913). Our target dataset was the European RADIANT cohort consisting of 176 PND, 2772 MDD and 1588 control subjects. Sex and seven ancestry principal components were included as covariates in all logistic regressions. Results: When examining the effect of sex hormones on HPC fate, prolactin increased the proportion of Map2-positive cells ($N=4$, $F(6,21) = 7.04$, $p = 0.0003$) indicating an increase in neuronal differentiation, but had no effect on HPCs maintained in a proliferative

state. Conversely, oestradiol and testosterone had no effect on HPC differentiation, but increased cell number (N=3, $F(6,14) = 3.42$, $p = 0.027$ & $F(5,11) = 5.378$, $p = 0.0096$). Only the best-fit PRS for oestradiol levels was associated with a depressive disorder, specifically PND case-control status ($\beta = -1156.4$, SE = 423.7, uncorrected $p = 0.006$), where genetic risk for lower levels predicted higher risk for PND. Conclusions: Here we provide evidence that genetic risk for higher plasma oestradiol may explain a small amount of the variance in risk for PND, potentially lowering risk via its ability to increase HPC number. Furthermore, we provide evidence that prolactin possesses neurogenic properties, but that genetic risk for higher prolactin does not influence risk for depressive disorders. This work suggests that the relationship between sex hormones, HN and depression is complex, and that there may not be a clear-cut pathway for aetiology or risk moderation.

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Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

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Program #/Poster #: 279.04/B18

Topic: A.03. Stem Cells and Reprogramming

Support: the National Institute of Neurological Disorders and Stroke R01NS052741
the National Multiple Sclerosis Society RG3367

Title: Inhibition of the thrombin receptor promotes subventricular zone neural stem cell expansion and differentiation towards the oligodendrocyte lineage

Authors: *C. CHOI[1,2,3], H. YOON[1,2,3], M. LANGLEY[1,2,3], L. KLEPPE[1,2], I. A. SCARISBRICK[1,2,3]
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Abstract: Protease activated receptor 1 (PAR1) is a G-protein coupled receptor (GPCR) family that is widely expressed in the central nervous system and activated by proteolytic cleavage within its extracellular domain to elicit intracellular signaling. Thrombin activates PAR1 with high affinity and is frequently elevated in the context of neural injury. Although over activation of PAR1 has been linked to neural injury, little is currently understood regarding the mechanisms involved or whether PAR1 can be targeted to limit injury and foster repair. In this study, we investigate the regulatory role of PAR1 in the production and differentiation of adult subventricular zone (SVZ)-derived neural stem cells (NSCs) towards the oligodendrocyte lineage. First, we established that PAR1 is expressed by Sox2+ NSCs and by Nestin+ neural progenitors within the SVZ of the adult mouse brain. We then demonstrated that thrombin gates

Ca^{2+} signaling in SVZ NSC monolayer cultures in a PAR1-dependent manner. SVZ NSCs derived from PAR1 knockout mice showed an enhanced capacity for self-renewal in cell culture, including increases in neurosphere formation and in BrdU incorporation, and these effects were mimicked by a PAR1 small molecule inhibitor SCH79797. Monolayer cultures from the SVZ of PAR1-knockout mice contained more Nestin, NG2+ and Olig2+ cells indicative of enhancements in expansion and differentiation along the oligodendrocyte lineage. Also, cultures of NSCs lacking PAR1 expressed higher levels of myelin basic and proteolipid protein upon differentiation induced by growth factor withdrawal. Reflecting a potentially suppressive role for PAR1 in SVZ NSC production and differentiation, the SVZ of PAR1-knockout mice contained more Sox2+ and Ki-67+ self-renewing NSCs, in addition to Olig2+ oligodendrocyte progenitors. Furthermore, the corpus callosum and anterior commissure of adult PAR1-knockout mice contained greater numbers of Olig2+ progenitors and CC1+ mature oligodendrocytes. Altogether, these findings point to PAR1 as a novel target to foster the expansion of SVZ neural stem cells and their differentiation towards mature myelinating oligodendrocytes that may be of particular benefit in the context of neural injury in which PAR1 agonists such as thrombin are increased.

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Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.05/B19

Topic: A.03. Stem Cells and Reprogramming

Support: CIHR/SPOR

Title: Electrophysiological characterization of sensory neurons derived from human induced pluripotent stem cells (hIPSCs) using a small molecule inhibition protocol

Authors: *L. S. LESPERANCE[1], S. S. SHARMIN[3], J. ELLIS[2], S. A. PRESCOTT[4], A. PIEKNA[3], W. WEI[3]
[1]Neurosci. and Mental Hlth., [2]Developmental & Stem Cell Biol., The Hosp. For Sick Children, Toronto, ON, Canada; [3]Developmental & Stem Cell Biol., The Hosp. for Sick Children, Toronto, ON, Canada; [4]Neurosciences and Mental Hlth., Hosp. For Sick Children, Toronto, ON, Canada

Abstract: The use of human induced pluripotent stem cells (hIPSCs) is rapidly proving to be a valuable tool in the characterization of human disease and represents the forefront of patient-specific medicine. Through modulation of specific developmental pathways using small molecule inhibitors, differentiations can be guided to produce an array of neuronal types. Using

this approach, nociceptor-like neurons can be generated at an accelerated pace compared with previous differentiation methods (Chambers et al. 2012). One of the main limitations surrounding the use of hIPSC-derived neurons, however, is the substantial functional heterogeneity within a differentiated population. Here we report a detailed electrophysiological characterization of hIPSC-derived sensory neuron (hIPSC-PSN) cultures. Our results highlight the heterogeneous physiological profiles of the cells, suggesting that while repetitive spiking nociceptors represent the majority of the population, they are not the only type of neuron present. While certain electrophysiological properties of these neurons such as resting membrane potential and action potential half-width are consistent with values measured from human cadaveric dorsal root ganglion (DRG) neurons, other properties such as rheobase and soma diameter are markedly different, which may hint at differences (e.g. ion channel expression patterns) between regular and hIPSC-derived sensory neurons. Attempts to better direct hIPSC differentiation to achieve a more homogeneous neuron population using varying growth factor combinations reveal a substantial difference in the spiking patterns at 3 weeks post induction but, by 5 weeks, approximately 85% of cells exhibit a repetitive spiking pattern (during sustained somatic current injection) as well as AMPA receptor-mediated excitatory post synaptic currents. Future work will focus on further optimization of the differentiation protocol and the validation of these neurons as model systems with which to elucidate underlying mechanisms of neuropathic pain and human disease using electrophysiology, pharmacological blocking, imaging based approaches and gene expression studies. These findings suggest that careful attention should be taken when interpreting the physiology of hIPSC derived sensory neurons and advocates for methods with which to purify these populations and the need for cell-specific characterizations. Funded through the CHIR and SPOR (Chronic Pain Network).

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Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.06/B20

Topic: A.03. Stem Cells and Reprogramming

Support: National Natural Science Foundation of China, No. 31701287

Title: Elevated MeCP2 in starved neural stem cells

Authors: *X.-B. HE, F. GUO
Shanghai Univ. of Med. & Hlth. Sci., Shanghai City, China

Abstract: This study aims at exploring potential epigenetic regulation of autophagy in neural stem cells. Neural stem cells extracted from mouse embryonic day 14 cortex were challenged with PBS-induced starvation for 10 minutes, half, one, three and six hours respectively. Autophagy was induced from one hour starvation evidenced by increased ratio of LC3II/LC3I protein level, and accumulation of LC3 puncta in cytoplasm. Interestingly elevated MeCP2 protein expression was observed mainly in LC3-weakly expressed cells. Inhibition of autophagy with Bafilomycin A1 or 3-methyladenine further increased the proportion of high MeCP2 expressing cells. Knockdown of MeCP2 in neural stem cells altered their autophagic performance in response to starvation. We also found that DNA methylation pattern of autophagy-related genes was differentially regulated in normal and starved neural stem cells. Taken together, these results suggest that MeCP2 is a negative regulator to autophagic response of neural stem cells.

Disclosures: X. He: None. **F. Guo:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.07/B21

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant AA024659

Title: Sex differences in the proteome of exosomes secreted by fetal neural stem cells

Authors: *D. CHUNG[1], M. PINSON[1], S. KOO[1], L. DANGOTT[2], R. MIRANDA[1]
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Abstract: Cells release nano-sized membrane vesicles termed exosomes, that may serve as a mode of intercellular communication by transferring biological information between cells. Neural stem cells (NSCs) reside in a complex microenvironment rich in exosomes. However, the roles of exosomes in mediating interactions between NSCs and their surrounding environment are largely unknown. Using fetal mouse derived cortical neuroepithelium, cultured ex-vivo as non-adherent neurosphere cultures, we found that exosomes could transfer information between donor and recipient cells, serving as a novel means for communication within the fetal NSC niche. While many studies have focused on NSCs in the fetal brain, it has long been assumed that the genetic sex-of-origin of NSCs do not have a significant role in the behavior of NSCs. We therefore initiated an investigation into the impact of genetic sex on the proteome of exosomes secreted by NSCs. Exosomes were isolated by ultracentrifugation from male and female derived NSCs, maintained as neurosphere cultures, and their proteome was assessed by liquid

chromatography-tandem mass spectrometry (LC-MS/MS). Sample data were analyzed using Mascot (Matrix Science, London, UK; version 2.6.0). Scaffold (version 4.8.5, Proteome Software Inc., Portland, OR) was used to validate MS/MS based peptide and protein identifications. Preliminary analysis identified 348 proteins in exosomes that were expressed at approximately equal levels in exosomes derived from both male and female NSCs. However, a number of proteins were expressed uniquely in male or female-derived exosomes. These data suggest that exosomes from male and female-derived NSCs may exert sex-specific control over the behavior of the neurogenic niche during early fetal development.

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Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.08/B22

Topic: A.03. Stem Cells and Reprogramming

Title: Investigating the promyelinating properties of the quinolone GSA-10

Authors: L. TIROU[1], C. DEMONGIN[1], H. FAURE[1], A. DEL GIOVANE[2], E. NOCITA[2], A. RAGNINI-WILSON[2], *M. RUAT[1]
[1]NeuroPSI, UMR9197, CNRS, Gif Sur Yvette, France; [2]Univ. of Roma "Tor Vergata", Roma, Italy

Abstract: Adult subventricular zone (SVZ) neural stem cells (NSCs) of the lateral ventricles and parenchymal oligodendrocyte progenitor cells (OPCs) are proposed as the main sources of remyelinating oligodendrocytes (OLs). Various remyelination strategies have been developed to mobilize these cells and to stimulate their differentiation into OLs in animal models of demyelination (Juarez et al, *Brain Res*, 2016). Several small molecules, including the antifungal agent miconazole, the corticosteroid clobetasol, the muscarinic agents benztropine and clemastine, have been shown to promote differentiation of neural progenitors into OPCs and to promote functional remyelination *in vivo* (Deshmukh et al, *Nature*, 2013; Najm et al, *Nature*, 2013; Porcu et al, *PlosOne*, 2015). Interestingly, pharmacological inhibition of Gli1, a transcription factor associated to the Hedgehog (Hh) pathway, using GANT61 increased both SVZ-derived NSCs progeny recruitment to the corpus callosum and their differentiation into OLs, enhancing remyelination (Samanta et al, *Nature*, 2015). Thus, modulators of Smoothened (Smo), the main transducer of Hh, by acting either on NSCs or OPCs to stimulate the rebuilding of the damaged tissue, may have therapeutic value for demyelinating diseases (Ruat et al, *Top Med Chem*, 2015). To further identify active molecules promoting remyelination, we have now investigated the pro-myelinating properties of the quinolinone GSA-10, a Smo agonist acting

through an AMPK non-canonical pathway associated to inhibition of Gli1 transcription (Manetti et al, *EJMC*, 2016; Fleury et al, *Sci Rep*, 2016). We have determined its efficacy to induce the expression of Myelin Basic Protein (MBP) in the mouse immortalized oligodendrocyte precursor cell line (Oli-neuM) expressing the Myelin Regulatory Factor (Porcu et al, *PlosOne*, 2015). Preliminary data indicate that this quinolinone promotes high expression of MBP in an increased number of cells compared to the non-selective Smo agonist clobetasol and relative to Vehicle. These data suggest that GSA-10 is a potent myelin gene inducer. Experiments are underway for evaluating its potency to induce the expression of oligodendrocyte markers and to identify Hh signaling implicated in these effects. We are further characterizing Hh signals regulating the plasticity of the SVZ neurogenic niche using GLAST^{CreERT2}-Ptc$^{+/+}$-YFP and GLAST^{CreERT2}-Ptc$^{-/-}$-YFP mouse reporter lines (Daynac et al, *Stem Cell Reports*, 2016) during remyelination. Altogether, these experiments should bring novel strategies and tools for developing active drugs for demyelinating diseases.

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Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.09/B23

Topic: A.03. Stem Cells and Reprogramming

Support: NSF EPSCoR

Title: Nanocellulose surfaces promote neural differentiation

Authors: *S. C. PANDANABOINA[1], A. B. RANGU MAGAR[2], K. D. SHARMA[1], B. CHHETRI[2], A. GHOSH[2]
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Abstract: Injury or diseases of the nervous system results in permanent loss of function as neurons cannot divide and replace the dead neurons. A possible treatment for restoring normalcy to those patients will be transplantation of functional neurons, prompting our efforts to significantly increase population of neurons differentiating from neural stem cells (NSCs). Of late, matrices fabricated from natural or biocompatible polymers have been tested for neural stem cell differentiation. Cells can grow and differentiate on scaffolds formed by various combinations of polymers and biocompatible materials. In addition, conductive polymers such as polypyrrole (ppy), coupled with natural materials are being tested to check if they are capable of enhancing the differentiation of stem cells into neurons. The use of natural materials such as

nanocellulose (NC) used as cell culture surface has been receiving attention as cellulose is widely available, biocompatible and non-corrosive. Therefore, we differentiated rNSCs on (i) poly-D-lysine (PDL) (ii) NC+polypyrrole (NCPPy) (iii) quaternized NC+polypyrrole (QNCPPy). After differentiation for two weeks, we determined the percentage of cells positive for the neuronal marker βIII tubulin and the glial marker GFAP relative to the total cell count. The highest percentage of rNSCs differentiated into neurons was on NCPPy (69±9.4%) in comparison to the PDL (51±1.04%). Interestingly, astrocyte differentiation was least on NCPPy (12±4.6%) compared to the other surfaces (17±5.2% on QNCPPy and 26±0.8% on PDL). Based on these results, we plan to optimize the surfaces in an effort to further test and check at different time periods if they can promote higher neuronal differentiation.

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Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.10/B24

Topic: A.03. Stem Cells and Reprogramming

Title: *In vitro* system to dissect the molecular basis of vanilloid/TRPV1 mediated anti-tumoral activity of human neural progenitor cells in glioblastoma multiforme

Authors: *L. AZMITIA, SR[1], R. UYAR[2], R. KÄLIN[2], B. BRÄNDL[3], F. MÜLLER[3], R. GLASS[2], M. SYNOWITZ[4]
[1]Uksh-Kiel, Kiel, Germany; [2]LMU, München, Germany; [3]UKSH-Kiel/ZIP, Kiel, Germany; [4]Neurosurg., UKSH-Kiel, Kiel, Germany

Abstract: Malignant gliomas are the most frequent primary brain tumor in adults, with no curative therapy (Curado *et al.* 2007). Endogenous vanilloids secreted by neural progenitor cells (NPCs) induce cytotoxicity in GBM cells. Thus appears to be mediated by stimulation of the Transient Receptor Potential Vanilloid 1 (TRPV1,) specifically of GBM. We turned to neural progenitors differentiated from human induced pluripotent stem cells as well as directly induced from fibroblasts as in vitro model (Fig. 1 and 2).
Human induced pluripotent stem cells (iPSCs) were differentiated into long-term expandable neural stem cells (lt-NSCs) (Koch *et al*. 2009) and directly reprogrammed fibroblasts into induced NPCs (iNSCs). Both cell lines were expandable, expressed NPCs markers, differentiated into mature neurons and glial cells, showed a stable karyotype and had active membrane potentials (Fig 3).
Human GBM cells were exposed to conditioned media from lt-NSC and iNSCs. We observed an increased cell death in GBM. Exposure of TRPV1-deficient GBM to the same conditioned media

preparations resulted in an attenuated cytotoxic response, suggesting an involvement of endogenous vannilloids secreted by lt-NSC and iNSC in the observed GBM cell death (Fig 4). We have established a model with two different source for human neural progenitors in order to molecularly dissect vanilloid -mediated GBM cytotoxicity. This system may be either exploited via transplanted, isogenic neural progenitors in GBM patients or to identify metabolic pathways leading to the synthesis of individual vanilloids as chemotherapeutic agents.

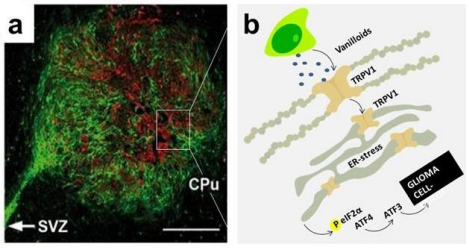

Fig. 1 (A) Migration of NESTIN positive cells from the subventricular zone towards a DsRed+ Glioma in the caudate putamen (CPu) of young mice. **(B)** Schematic illustration of NPCs constitutively release of endovanilloids and their induction of glioma's cell-death. Adapted from Stock, K. *et al.* 2012.

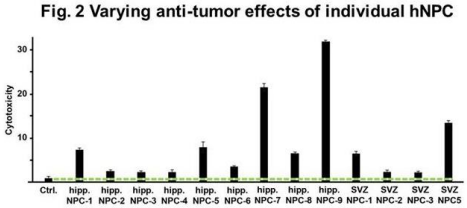

Fig. 2. U87 glioma cells were cultured with conditioned media from hNPC cultures (hippocampus or SVZ) and cytotoxicity was compared to controls: baseline cytotoxicity levels are indicated as a dashed line.

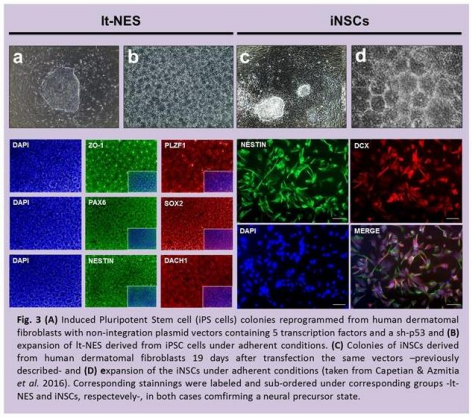

Fig. 3 (A) Induced Pluripotent Stem cell (iPS cells) colonies reprogrammed from human dermatomal fibroblasts with non-integration plasmid vectors containing 5 transcription factors and a sh-p53 and **(B)** expansion of lt-NES derived from iPSC cells under adherent conditions. **(C)** Colonies of iNSCs derived from human dermatomal fibroblasts 19 days after transfection the same vectors –previously described- and **(D)** expansion of the iNSCs under adherent conditions (taken from Capetian & Azmitia *et al.* 2016). Corresponding stainnings were labeled and sub-ordered under corresponding groups -lt-NES and iNSCs, respectevely-, in both cases comfirming a neural precursor state.

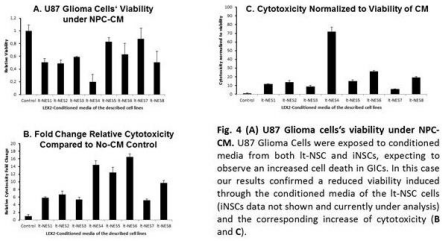

Fig. 4 (A) U87 Glioma cells's viability under NPC-CM. U87 Glioma Cells were exposed to conditioned media from both lt-NSC and iNSCs, expecting to observe an increased cell death in GICs. In this case our results confirmed a reduced viability induced through the conditioned media of the lt-NSC cells (iNSCs data not shown and currently under analysis) and the corresponding increase of cytotoxicity (**B** and **C**).

Disclosures: L. Azmitia: None. **R. Uyar:** None. **R. Kälin:** None. **B. Brändl:** None. **F. Müller:** None. **R. Glass:** None. **M. Synowitz:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.11/B25

Topic: A.03. Stem Cells and Reprogramming

Title: Zika Virus E protein modulates proliferation and differentiation of human fetal neural stem cells by modulating of microRNA circuitry

Authors: *R. BHAGAT[1], B. PRAJAPATI[2], S. NARWAL[2], Y. K. ADLAKHA[2], P. SETH[2]
[1]Cell. and Mol. Neurosci., [2]Natl. Brain Res. Ctr., Gurgaon, India

Abstract: Zika Virus (ZV) infection has gained worldwide attention following large outbreaks in Brazil during 2015-2016 epidemics and has been linked to severe clinical condition called microcephaly where fetuses are born with abnormally small brain. Emerging literature demonstrate that ZV infection causes death and quiescence in neural stem cells hence reducing overall pool of cells leading to microcephaly. However to date molecular mechanisms of ZV induced microcephaly are poorly understood. We have employed well characterized in-vitro model system of primary human fetal neural stem cells (fNSCs) for understanding the molecular mechanisms of ZV induced microcephaly. We delineated ZV E protein over expression hampers proliferation of fNSCs and reduces growth of neurospheres. Moreover there was induction of proneural gene post E protein expression in fNSCs cultured in proliferating medium, suggesting pre-mature differentiation of cells. Differentiation of fNSCs into neuronal lineage in the presence of E protein induces apoptosis at day-3 of differentiation and migration from differentiating neurospheres is also disrupted. Further we analyzed the global miRNA expression (miRNA Seq) which shows disrupted miRNA circuitry in fNSCs post E protein expression. Among differentially expressed miRNAs (DEM), we validated miR-204-3p, miR-1306-5p, miR-6087, miR-23c and miR-676 using qPCR. These miRNAs are also reported to play role in other viral infections. GO analysis for biological process of targets of differentially expressed miRNAs revealed particular enrichment of DEM targets in cell cycle and cell cycle processes which further substantiates our findings that E protein alters cell cycle dynamics. PANTHER pathway analysis of targets of DEM showed enrichment of crucial developmental pathways including WNT, CCKR, PDGF, EGF, p53, FGF and notch signaling pathways. Our study not only provides novel insights into the mechanisms of ZV induced complications but also function as valuable resource to the field for further understanding of mechanisms.

Disclosures: R. Bhagat: None. **B. Prajapati:** None. **S. Narwal:** None. **Y.K. Adlakha:** None. **P. Seth:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.12/B26

Topic: A.03. Stem Cells and Reprogramming

Support: VR-MH
BCF
CF
MWLC

Title: The neural stem/glioblastoma cell marker GlioStem associates with GOLGA2/GM130, a golgi apparatus protein

Authors: *O. HERMANSON, B. MIGLIORI
Dept. of Neuroscience, Karolinska Institutet, Stockholm, Sweden

Abstract: Certain polymers, such as oligothiophenes (LCOs), can function as single molecule LEDs. LCOs are able to cross physiological cell membranes without additional reagents and to illuminate when interacting with certain biological structures, such as insulin. We have with our collaborators generated and characterized an LCO called p-HTMI or GlioStem that specifically detects embryonic cortical stem cells and subpopulations of cells derived from glioblastoma (GB), including stem cell-like cells and rapidly migrating cells. GlioStem is at least as sensitive and specific than previous methods to detect these cell types (e.g., CD133 or CD44).
We have previously made a thorough verification and validation of the molecule, and found that i) GlioStem passes the cell membrane without any additional reagent or modification, and within a maximum of 10 minutes specifically detects subpopulations of patient-derived GB cells *in vitro* by omitting fluorescence at a wavelength similar to GFP just by simple dispersion in the existing media, ii) GlioStem-positive human GB cells can efficiently be sorted out from mixed cell populations by cell sorting techniques (FACS), iii) the specificity of GlioStem is dependent on a methylation modification of two imidazole rings making the molecule similar in structure to histidine/histamine, iv) GlioStem labels the same GB cells as CD271 (NGF receptor p75) which in turn labels stem cell-like cells and rapidly migrating cells in GB, and v) pilot studies have shown that GlioStem indeed detects patient-derived GB cells also *in vivo* in a rodent model.
We have now pursued a thorough screen for putative intracellular structures GlioStem may interact with, and we have found that the main intracellular target for GlioStem is GOLGA2/GM130, a protein of the Golgi apparatus. GlioStem was found to be in close proximity and sharing pixels with around 80% of GOLGA2 immunoreactivity and GOLGA2 in turn occupied around 60% of GlioStem-positive pixels. We conclude that GOLGA2, or a protein very closely associated with it, is the major intracellular target of GlioStem. Current investigations focus on elucidating the structure of GOLGA2 as well as similarities and differences in the Golgi apparatus between GB cells, embryonic neural stem cells, and other - GlioStem-negative - cell types.

Disclosures: O. Hermanson: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IPR, Celluminova. **B. Migliori:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.13/B27

Topic: A.03. Stem Cells and Reprogramming

Title: High-throughput screening of induced pluripotent stem cell derived motor neurons on qube and qpatch

Authors: K. R. ROSHOLM[1], *D. SAUTER[2], M. SCHUPP[1], R. B. JACOBSEN[1]
[1]Sophion Biosci., Ballerup, Denmark; [2]Sophion Biosci., Woburn, MA

Abstract: Human induced pluripotent stem cells (hiPSCs) can be differentiated into many cell types, including neurons and cardiomyocytes, and therefore constitute a novel way to model human diseases for drug-testing *in vitro*[1]. Ion channels represent highly attractive therapeutic targets in the nervous and cardiovascular systems[2], rendering electrophysiological studies of hiPSCs critical for their usage in drug-discovery. However, such studies have traditionally been limited by the labour-intensive and low-throughput nature of patch-clamp electrophysiology[2]. Here we present the electrophysiological characterization of hiPSC derived motor neurons using our Automated Patch Clamp (APC) platforms, Qube 384 and QPatch. Our results include a measure of channel expression versus time in culture, the pharmacological dissection of endogenous ion channels (e.g. Na_v and K_v), identification of ligand-gated receptors, and recordings of action potentials using current clamp. The major challenge when investigating neurons using APC platforms is the requirement to dissociate the cells from their neuronal network while maintaining cell viability and membrane integrity[3]. By optimization of the harvest- and whole-cell protocols we have overcome this obstacle resulting in success rates of up to 60% using our 384 well system. Our results demonstrate the feasibility of conducting electrophysiological characterization and drug-screening on hiPSC derived neurons on APC platforms like Qube 384 and QPatch, thus paving the way for high-throughput ion channel-targeted screening of drugs for neurological disorders.
1. Ko, H. C. & Gelb, B. D. Concise Review: Drug Discovery in the Age of the Induced Pluripotent Stem Cell. *STEM CELLS Transl. Med.* **3,** 500-509 (2014).
2. Dunlop, J., Bowlby, M., Peri, R., Vasilyev, D. & Arias, R. High-throughput electrophysiology: an emerging paradigm for ion-channel screening and physiology. *Nat. Rev. Drug Discov.* **7,** 358-368 (2008).
3. Raman, I. M. & Bean, B. P. Resurgent Sodium Current and Action Potential Formation in Dissociated Cerebellar Purkinje Neurons. *J. Neurosci.* **17,** 4517-4526 (1997).

Disclosures: K.R. Rosholm: None. **D. Sauter:** None. **M. Schupp:** None. **R.B. Jacobsen:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.14/B28

Topic: A.03. Stem Cells and Reprogramming

Support: TUBITAK COST 115Z804

Title: The role of Elk-1 transcription factor in tumoursphere formation of brain tumour cells

Authors: *M. SAVASAN SOGUT[1,2], B. YILMAZ[3], I. KURNAZ[1]
[1]Biotech. Inst., Gebze Tech. Univ., Kocaeli, Turkey; [3], Med. Faculty, Dept. of Physiol., [2]Yeditepe Univ., Istanbul, Turkey

Abstract: ELK-1 transcription factor, a member of ETS oncogene superfamily, is responsible for many crucial processes within the cell through its phosphorylation via MAPK/ERK pathway. However, little is known about its biological significance in the formation of brain tumours, especially glioblastoma and neuroblastoma. Over-expression or down-expression of ELK-1 through transfection has been shown to be related with the expression of certain stemness factors. In this study, we aimed to investigate the functions of ELK-1 in tumoursphere formation of both glioblastoma and neuroblastoma cell lines. We assessed the effects of ELK-1 over-expression and its knock-down via short hairpin RNA (shRNA) on glioblastoma and neuroblastoma cell lines *in vitro*. Tumoursphere formation was provided by sphere formation medium and CD133(+)-cell enrichment was conducted by magnetic separation with MACS CD133 microbeads. The change in gene expression pattern and protein levels of certain stemness genes and tumoursphere markers were evaluated with qPCR and Western blot analysis, respectively. The interaction on the chromatin level was checked with chromatin immunoprecipitation (ChIP) experiments. Brain tumour cell lines, incubated in sphere formation medium that was supported with EGF and bFGF, formed distinct tumourspheres, depending on whether they were stemmed from glia or neurons. The results show ELK-1 is effective in the regulation of stemness gene expressions. This study may pave the way for the biological triangle of brain tumour cell lines: tumourigenesis, survival and ELK-1.

Disclosures: M. Savasan Sogut: None. **B. Yilmaz:** None. **I. Kurnaz:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.15/B29

Topic: A.03. Stem Cells and Reprogramming

Support: MH-059852
MH-075916

Title: Neuronal conversion of olfactory epithelial cells using mir-9/9-124

Authors: *C.-G. HAHN[1], R. RAY[2], H. LIN[4], J. FULLARD[5], P. ROUSSOS[5], K. BORGMANN-WINTER[3]
[1]Dept Psychiat, Univ. Pennsylvania Sch. Med., Philadelphia, PA; [2]Univ. of Pennsylvania,

Phildelphia, PA; [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Univ. of Pennsyvania, Philadelphia, PA; [5]Mt. Sinai, New York, NY

Abstract: The paradigms of induced pluripotent stem cell (iPSC) and induced neurons (iNs) offer an opportunity to study neurons derived from patients with neuropsychiatric illnesses. A critical question remains, however, to what extent neurobiological characteristics of donors, epigenomic markings in particular, are maintained in neurons derived via these paradigms. Increasing evidence suggests that reprogrammed cells reflect molecular characteristics of source cells. It follows that it will be preferable to use source cells that are more likely to harbor neural characteristics and to convert them with least modification of epigenetic landscape. Presently, skin fibroblasts or blood cells are most often used as source cells for genomic reprogramming. Here we examined olfactory neuroepithelial (OE) cells derived from human subjects for their neurogenic potential and changes in chromatin conformation following transduction of miR-9/-124. Upon transduction with miR9/124, OE cells showed significantly decreased cell proliferation. In addition, 20 to 25% of OE cells showed neuron-like morphology within 5 to 7 days of culture in differentiation condition. Neuronal morphology of these cells were maintained or further elaborated over the next 21 days, during which time these neuronal cells changed their morphology, their positions and contacts with other cells. OE cells transduced with mir9/124 or with mirSS were analyzed by quantitative polymerase reaction for expression of molecular markers specific for exiting the proliferative cell cycle (BM88), cellular commitment to the neuroprogenitors (Doublecortin) and neuronal markers (Map 2, Map 1b, Tuj-1). A critical question is the extent to which the chromatin conformation of OE cells is accessible to the genes that have been implicated for neuropsychiatric illnesses. ATAC seq results from OE cells before and after neuronal conversion will be presented compared to those of human skin fibroblasts with respect to chromatin accessibility in genes that have been implicated for neuropsychiatric illnesses.

Disclosures: C. Hahn: None. **R. Ray:** None. **H. Lin:** None. **J. Fullard:** None. **P. Roussos:** None. **K. Borgmann-Winter:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.16/B30

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant AA024659
NIH Grant HD086765

Title: Calcium dynamics identify neural progenitor populations altered by ethanol exposure and withdrawal

Authors: *A. H. MAHNKE, R. C. MIRANDA
Neurosci. and Exptl. Therapeut., Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX

Abstract: Aberrant cortical development is one of the hallmarks of Fetal Alcohol Spectrum Disorders. While prenatal ethanol exposure can activate cell death pathways in developing neurons, the neural stem and progenitor cell populations are largely spared. Instead, our data suggests these cells are reprogrammed to favor premature maturation and decrease self-renewal capacity. Calcium dynamics are known to affect cell cycle progression and differentiation as well as coordinate behavior across neural progenitors. Here, we examined how chronic ethanol exposure and withdrawal affect calcium dynamics in a model of the neural stem and progenitor cell niche. Neurosphere cultures, derived from GD12.5 mouse dorsal neuroepithelium and maintained in mitogenic media, were exposed to ethanol for 5 days at levels reflecting control (0 mg/dL), low (60 mg/dL), binge (120 mg/dL), and chronic (320 mg/dL) drinking behavior. Subsequently, these neurospheres were then either loaded with Fluo-4 AM for calcium dynamic imaging or allowed to withdraw from ethanol for an additional two days prior to imaging. We found that some baseline calcium attributes were affected by low levels of ethanol, such as elevation of resting calcium, while others were altered in a dose-dependent manner, such as calcium event frequency. We also found that there were dose-specific effects on the calcium response to subsequent exposure to acute ethanol and nicotine. These effects may be mediated directly following chronic exposure through alterations to ryanodine receptor composition and after withdrawal by alterations to inositol-3-phosphate receptor composition. Principal component analysis identified three distinct sub-populations of neural progenitors which define the diversity of observed calcium signaling behaviors observed. Moreover, these three sub-populations exhibited varying sensitivity to ethanol exposure and withdrawal as well as to subsequent acute drug exposure. These data show that ethanol perturbs calcium dynamics within the neural progenitor cells in a dose-dependent manner and that some alterations are enhanced only after withdrawal. These data indicate that ethanol's effect on reprogramming cells may be mediated by calcium signaling mechanisms, and that intracellular calcium dynamics are robust indicators of both ethanol exposure and withdrawal.

Disclosures: A.H. Mahnke: None. **R.C. Miranda:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.17/B31

Topic: A.03. Stem Cells and Reprogramming

Support: FAPESP Grant 2015/24001-1
CNPQ Grant 447949/2014-4

Title: Let-7 MicroRNA inhibits adult ciliary epithelium cells neurosphere formation

Authors: *C. B. DEL DEBBIO, L. T. FRASSON
Cell Biol. and Develop., Univ. of Sao Paulo, Sao Paulo, Brazil

Abstract: The Ciliary Epithelium (CE) of adult mammalian eyes contains a quiescent population of retinal progenitor/stem cells that are able to proliferate and generate neurospheres in vitro. These cells express retinal progenitor genes and proteins and are known to generate different and functional retinal neurons after induction. Despite this regenerative capacity, the reprogramming efficiency is low due to the presence of unknown mechanisms and regeneration inhibitory factors such as microRNAs (miRNAs), small non-coding RNAs responsible to regulate a variety of progenitor and pluripotent genes expression. Here, we investigated the expression of Let-7 family of miRNAs and its regulatory protein Lin28 in CE cells from rodents, and its influence on neurospheres formation. CE cells from normal newborn and adult animals (Wistar) were carefully separated from retina and the expression of Let-7 miRNA family, as well as Lin28 transcripts and protein levels were analyzed. We found that Lin28 was highly expressed in newborn CE tissues while Let-7 family indicated low expression levels at this age. Adult CE tissues expressed an inverted pattern, with Let-7 family 10-fold higher and Lin28 6-fold lower in comparison to newborns. This shows that Let-7 miRNA are highly expressed in adult CE cells. We induced adult CE neurospheres formation by culturing these cells with growth factors (EGF and FGF) for 7 days and found higher levels of Lin28 in comparison to Let-7 miRNAs, similar to newborn tissues, indicating that neurospheres and newborn CE cells share similar Let-7-Lin28 expression patterns. Latter we added chemically modified single-stranded oligonucleotides designed to bind to and inhibit endogenous Let-7 or to mimic endogenous mature Let-7 in CE cells culture at early neurosphere formation stage. The overexpression of Let-7 in CE cells gradually decreased neurospheres formation (Let-7 mimic 10nM, 20nM and 30nM, decreased 70%, 90% and 100% neurospheres respectively), with complete inhibition of neurospheres formation at 30nM. No differences in neurospheres numbers were observed with Let-7 inhibition. Our results suggest that up-regulation of Let-7 miRNAs are sufficient to prevent the mechanisms involved in stem cells activation. However, down-regulation of Let-7 expression alone is not capable to improve CE cells stem/progenitor cells reprogramming efficiency. The information gleaned from this study may provide valuable insight into the cellular and molecular events that underlie the reprogramming response of CE cells and the mechanism of retinal recovery.

Disclosures: C.B. Del Debbio: None. **L.T. Frasson:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.18/B32

Topic: A.03. Stem Cells and Reprogramming

Title: Development and characterization of an *in vitro* human iPSC-derived neurospheroid model

Authors: *J. L. MOHN, M. KLAUSNER, P. J. HAYDEN
MatTek Corp, Ashland, MA

Abstract: Objective and Rationale: Multiple approaches have recently been described to generate *in vitro* neural organoid models from human induced pluripotent stem cells (iPSC). While these models are effective at recapitulating many features of human fetal brain development, the processes used to generate them are not amenable to large-scale production and high-throughput applications. The goal of this exploratory research is to develop a scalable and reproducible *in vitro*, 3-dimensional neurospheroid model that may be used for high-throughput applications assessing neurodevelopmental toxicology and drug development.
Methods: iPSCs (male, 68 years old) were differentiated to neural progenitor cells (NPCs) by blocking TGF-β/BMP-dependent SMAD signaling. Differentiation was assessed by immunofluorescent staining for NPC markers nestin and SOX2. An additional NPC line was commercially obtained. To generate neurospheroids, NPCs were seeded in ultra-low adhesion multi-well plates at various cell densities, and neuronal differentiation was induced with BNDF and GDNF. Neurospheroids were maintained in culture for up to 8 weeks. Immunofluorescent analysis of neurospheroids was performed on frozen sections.
Results: NPCs differentiated from iPSCs expressed NPC markers SOX2 and nestin. The size of neurospheroids grown in ultra-low adhesion plates steadily increased up to 8 weeks in culture at all cell seeding densities tested. Neurospheroid size was very consistent over time, both within and across batches. Immunofluorescent analysis of frozen neurospheroid sections revealed widespread expression of neuronal markers MAP2 and βIII-tubulin, as well as VGLUT1, indicating presence of presynaptic glutamatergic specializations.
Conclusions: Neurospheroids of consistent size containing mature neurons were successfully generated using this approach. The model is easily scalable and can be adapted to either 96- or 384-well plate formats, allowing use in high-throughput applications. Further efforts will continue to characterize the cell types present in neurospheroids and assess the maturity of synaptic connections, and this characterization will be expanded to include neurospheroids generated from iPSCs representing an array of ages, gender and disease conditions.

Disclosures: J.L. Mohn: None. **M. Klausner:** None. **P.J. Hayden:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.19/C1

Topic: A.03. Stem Cells and Reprogramming

Title: Quantification of functional network electrophysiology from stem cell derived neurons with multiwell microelectrode array technology

Authors: *D. C. MILLARD, H. B. HAYES, A. M. NICOLINI, C. A. ARROWOOD, M. CLEMENTS
Axion Biosystems, Atlanta, GA

Abstract: The flexibility and accessibility of induced pluripotent stem cell technology has allowed complex human biology to be reproduced in vitro at high throughput scales. Indeed, rapid advances in stem cell technology have led to widespread adoption for the development of in vitro models of neural disease and for screening applications in drug discovery and safety. However, to effectively characterize stem cell derived models, or to extract meaningful and predictive information from these models, new technology is required for evaluating functional cellular and network responses. For electro-active cells, like stem cell derived neurons, measurements of electrophysiological activity across a networked population of cells provide a comprehensive view of function. Microelectrode array (MEA) technology offers such a platform by directly connecting key biological variables, such as gene expression or ion channel distributions, to measures of cellular and network function in stem cell derived neurons. A planar grid of microelectrodes interfaces with cultured neural networks, modeling complex, human systems in a dish, such that the electrodes detect the raw electrical activity of nearby neurons in the population. Furthermore, the advent of multiwell MEA platforms has enabled high throughput capacity for applications including drug discovery, toxicological and safety screening, disease models, and stem cell characterization and optimization. Here, we present results from evaluation of stem cell derived neural cultures on the Maestro Pro multiwell MEA platform. The stem cell derived neurons were cultured on 48- and 96-well MEA plates and monitored throughout maturation of the network connections. To characterize the cultured networks, advanced metrics describing the burst, synchrony, and evoked aspects of the functional population activity were computed in response to ion channel blockers and compounds altering synaptic activity. In comparing across wells, the stem cell derived networks displayed reliable and expected functional responses. These results support the continued development and use of stem cell derived neural network assays on multiwell MEA technology for high throughput drug discovery and evaluation of phenotypic disease-in-a-dish models of neural disease.

Disclosures: D.C. Millard: A. Employment/Salary (full or part-time):; Axion Biosystems, Inc. **H.B. Hayes:** A. Employment/Salary (full or part-time):; Axion Biosystems, Inc. **A.M. Nicolini:** A. Employment/Salary (full or part-time):; Axion Biosystems, Inc. **C.A. Arrowood:** A. Employment/Salary (full or part-time):; Axion Biosystems, Inc. **M. Clements:** A. Employment/Salary (full or part-time):; Axion Biosystems, Inc..

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.20/C2

Topic: A.03. Stem Cells and Reprogramming

Support: NIH (NS080913)
Whittier Foundation funding to M.A.B

Title: An improved cell culture system to recapitulate endogenous neural stem cell behavior

Authors: *N. ZHANG, T. OUGHOURLIAN, L. PENG, J. SHEPPARD, M. BAY, M. BONAGUIDI
Eli and Edythe Broad Cirm Ctr. of Stem Cell and, Los Angeles, CA

Abstract: Adult neural stem cells (NSC) were first isolated and characterized using cell culture over 25 years ago. However, recent advances in lineage tracing have elucidated that NSC properties *in vitro* do not mimic their native behavior *in vivo*. Using adult hippocampus, we developed a simple and scalable culture approach to recapitulate endogenous NSC fate choices. We determined that commonly used growth factor concentrations promote NSC symmetric divisions while suppressing neuronal fate, and amplify glial-committed progenitors. Instead, low growth factor application during an ‘expansion phase’ balances NSC symmetric, neurogenic and astrogenic fate choices akin to multipotential NSC behavior *in vivo*. Further, we show that NSC fate choices are reversible, which permits both amplification of NSC number and proper cell fate outcome. Our study provides a new system to study new cell generation, neural circuit formation, mechanistic regulation, and perform drug screening with high throughput capacity.

Disclosures: N. Zhang: None. **T. Oughourlian:** None. **L. Peng:** None. **J. Sheppard:** None. **M. Bay:** None. **M. Bonaguidi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH (NS080913) and Whittier Foundation funding to M.A.B.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.21/C3

Topic: A.03. Stem Cells and Reprogramming

Title: Utilizing CRISPR/Cas9 genome editing in human induced pluripotent stem cells to model neuropathologies in cortical progenitors and neurons

Authors: *J. WEBB, J. DIZON, R. VEGA, C. REVANKAR, E. WILLEMS, X. LIANG, D. PIPER
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Abstract: The advent of the CRISPR/Cas9 system complexed with induced pluripotent stem cells (iPSCs) provides a powerful tool to support *in vitro* disease modeling and drug discovery efforts. CRISPR/Cas9 mediated genome editing in iPSCs coupled with the ability to differentiate into numerous cell types, either Neural Stem Cells (NSCs) or neurons, can be used to study disease-specific genetic defects in physiologically-relevant cellular models. Here, we demonstrate the ability to use our CRISPR tools to edit the genome efficiently in iPSCs to create disease-relevant genetic changes to relate to neurological disease primarily in the cortical region of the brain. We subsequently differentiated these edited iPSCs into NSCs and further into cortical neurons as *in vitro* neurobiological disease models that manifest cellular phenotypes commonly observed in human disease. Furthermore, we developed several scalable assays to screen the isogenic iPSC-derived NSCs and cortical neurons generated using the above method. These assays can measure cell health and viability, neurite outgrowth, synaptogenesis, calcium influx and variations in channel activity, and electrophysiological changes. By combining genome editing of iPSCs and subsequent differentiation to relevant cortical cell types followed by downstream phenotypic identification using these assays, we have created a system that enables deeper understanding of neurobiological diseases, thereby enabling the potential identification new drug targets, and advancement in the development of personalized medicine.

Disclosures: J. Webb: A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **J. Dizon:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **R. Vega:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **C. Revankar:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **E. Willems:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **X. Liang:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **D. Piper:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.22/C4

Topic: A.03. Stem Cells and Reprogramming

Support: PAPIIT-DGAPA-UNAM -IA208118

Title: Neuronal differentiation of dental pulp mesenchymal stem cells (DPSCs) as a model to study neurodegeneration

Authors: *M. CARDENAS-AGUAYO[1], G. LOPEZ-TOLEDO[2], M. SILVA-LUCERO[1], L. ZHANG[4], D. E. GARCIA-DIAZ[5], J.-A. ARIAS-MONTANO[3]
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Abstract: Dental tissue contains dental pulp stem cells (DPSCs), that are mesenchymal stem cells, capable to differentiate into multiple linages including neuronal. The study of the differentiation potential of the DPSCs has implications on the development of therapeutic applications for neurodegenerative diseases and has been applied for cell therapy and tissue engineering. The aim of this study was to explore the differentiation potential of the DPSCs to the neuronal phenotype. For this purpose, we culture the mesenchymal stem cells in a chemical defined medium (with Insulin, Transferrin and Selenium, ITS), supplemented with or without growth factors (BDNF and GDNF). We isolated DPSCs from a healthy 46 years old female first molar. The cells were expanded in a growing medium (DMEM/F12) containing 10 % FBS. By Western blotting, Confocal imaging of Immunofluorescence, RT-PCR and FACS of several phenotype markers, we demonstrate in the DPCs cultured in growing medium, the expression of the mesenchymal and stem cells markers: CD105, CD90, CD73, SOX2, Oct3/4, NANOG and the absence of the expression of hematopoietic markers CD45, CD34, CD14. Furthermore, when the DPSCS were cultured in the ITS medium with or without growth factors, we were able to detect the expression of neuronal markers, such as NF-M, MAP-2 and Neu at 35 days in vitro. At this long culture time point, the mesenchymal markers were no longer expressed. To validate the maturation the Neuronal cells differentiated from DPSCs, we evaluate the passive membrane properties by hole cell recording (Rin, RMP and Cm).

Disclosures: G. Lopez-Toledo: None. **M. Silva-Lucero:** None. **L. Zhang:** None. **D.E. Garcia-Diaz:** None. **J. Arias-Montano:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.23/C5

Topic: A.03. Stem Cells and Reprogramming

Title: Ag Nps induce apoptosis, mitochondrial damages and MT3 and OSGIN2 expression changes in an *in vitro* model of human dental pulp stem cells derived neurons

Authors: *S. CAVALLARO[1], G. BONAVENTURA[1], V. LA COGNATA[1], R. IEMMOLO[1], M. ZIMBONE[2], A. CONTINO[3], G. MACCARRONE[3], B. FAILLA[4], M. BARCELLONA[4], F. CONFORTI[1], V. D'AGATA[5]
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Abstract: Silver nanoparticles (Ag-NPs) are one of the most popular nanotechnologies because of their unique antibacterial and antifungal properties. Given their increasing use in a wide range of commercial, biomedical and food products, exposure to Ag-NPs is now a reality in people's lives. However, there is a serious lack of information regarding their potential toxic effects in the central nervous system. In this study, we investigated the biocompatibility of "homemade" Ag-NPs in an *in vitro* model of human neurons derived from dental pulp mesenchymal stem cells. Our results, showed that acute exposure to Ag-NPs cause cytotoxicity, by triggering cell apoptosis, damaging neuronal connections, affecting the mitochondrial activity and changing the mRNA expression level of *MT3* and *OSGIN2*, two genes involved in heavy metals metabolism and cellular growth during oxidative stress conditions. Further studies are needed to understand the molecular mechanisms and the physiological consequences underlying Ag-NPs exposure.

Disclosures: S. Cavallaro: None. **G. Bonaventura:** None. **V. La Cognata:** None. **R. Iemmolo:** None. **M. Zimbone:** None. **A. Contino:** None. **G. Maccarrone:** None. **B. Failla:** None. **M. Barcellona:** None. **F. Conforti:** None. **V. D'agata:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.24/C6

Topic: A.03. Stem Cells and Reprogramming

Support: The MESO-BRAIN project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 713140.

Title: Growing human induced pluripotent stem cell-derived cortical neuronal networks on biocompatible two-photon polymerised scaffolds

Authors: *J. A. CROWE[1], D. NAGEL[1], E. J. HILL[1], S. SOKOLOVSKY[1], A. EL-TAMER[2], A. V. KOROLEVA[2], B. N. CHICHKOV[2], E. U. RAFAILOV[1], R. PARRI[1]
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Abstract: Determining the functional cellular and network mechanisms of the human cortex is an important step in understanding human brain function and investigating deficits underlying dysfunction. A major impediment to studying these processes has been a lack of available tissue. However, innovations in the field of human induced pluripotent stem cell (hiPSCs) are now providing efficient differentiation protocols of cortical neuronal and glial subtypes to enable this research in interrogatable *in vitro* cultures. An important feature of neuronal networks that is absent in traditional planar 2D cultures is however their 3D structure and connections. A possible way forward would be to produce different non-planar cell-supporting structures using two-photon polymerization (2PP), part of our aim in the MESO-BRAIN project. An important first step is the identification of 2P-polymerizable materials which are biocompatible, and have the capacity to allow electrophysiological and fluorescence calcium imaging monitoring of network activity. Biomaterials chosen from a panel of commonly utilized polymers were tested against prerequisites: amenability to the 2PP printing process at μm resolutions, biocompatibility to promote healthy long-term neural cultures, and ability to optically interrogate for dynamic network imaging and fluorescence-sensitive identification of cell populations. HiPSC-derived neural progenitors (Axol Bioscience Ltd., UK) were initially cultured upon planar 2PP-polymerized candidate biomaterials: Organically-modified silica (Ormosil), Polyethylene glycol diacrylate (PEG-DA), Polylactic acid (PLA). Culture development was quantified using phase-contrast microscopy, nuclei-counting, live/dead viability staining, and fluorescence immunocytochemistry. All materials tested displayed no overt toxicity to hiPSC-derived cultures in CellTitre-Blue® viability assays. All materials displayed some degree of auto-fluorescence, with Ormosil and PLA being excluded from further investigation due to their incompatibility with fluorescent probes. Neural progenitors ($PAX6^+$ / $SOX2^+$ / $NESTIN^+$) cultured on PEG-DA differentiated into mature neuronal populations ($MAP2^+$ / $TBR1^+$ / $CTIP2^+$) as assessed via immunocytochemistry using Alexa Fluor® 488, 561 and 633 fluorescent probes. PEG-DA cultures were also calcium imaged with Fluo-4 acetoxymethyl ester, exhibiting increased responses to 25 μM glutamate, and subsequent block of activity with addition of 1μM tetrodotoxin. Our data currently determines PEG-DA to be a suitable polymer for 2PP-fabrication of 3D biocompatible scaffolds for growing hiPSC-derived neuronal networks.

Disclosures: J.A. Crowe: None. **D. Nagel:** None. **E.J. Hill:** None. **S. Sokolovsky:** None. **A. El-Tamer:** None. **A.V. Koroleva:** None. **B.N. Chichkov:** None. **E.U. Rafailov:** None. **R. Parri:** None.

Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.25/C7

Topic: A.03. Stem Cells and Reprogramming

Support: MESOBRAIN EU Horizon 2020 Grant 713140
MINECO grants FIS2016-80455-R (AEI/FEDER, UE)
Severo Ochoa SEV-2015-0522
Fundació Privada Cellex
Fundación Mig-Puig
CERCA program

Title: Inference of neuronal networks in three-dimensional cultures

Authors: *A.-A. LUDL[1,2], E. ESTÉVEZ[1,2], O. E. OLARTE[3], J. MADRID-WOLFF[3,4], P. LOZA-ALVAREZ[3], J. SORIANO[1,2]
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Abstract: In this work we study how functional connectivity between neurons can be influenced by the structure of the substrate they grow on. We study the connectivity of neurons in three-dimensional (3D) cultures to understand how neurons connect in developing tissue.
We report the evolution of functional 3D neuronal networks over several days. We have applied network inference methods to recordings of calcium fluorescence imaging at a resolution allowing the segmentation of individual neurons into Regions of Interest (ROI), and the extraction of their activity time series. ROIs with identical dynamics occurring at overlapping coordinates in adjacent volumes have been grouped as representing a single neuron.
Networks are inferred using Generalised Transfer Entropy and Time Delays methods. These methods yield the direction and relative weight of connections. A surrogate method has been applied to the activity traces to eliminate spurious connections.
Functional connections persistent in a given culture during development are identified. The evolution of local network properties such as degree and clustering coefficient of given nodes are compared along development of the culture over several days. Additionally, we compared the network patterns obtained for rat primary cortical cultures to those of human induced pluripotent stem cell derived cultures.
This research is part of MESOBRAIN. MESOBRAIN has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 713140.

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Poster

279. Stem Cells and Reprogramming: Neural Stem Cells: *In Vitro* Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 279.26/C8

Topic: A.03. Stem Cells and Reprogramming

Support: MESOBRAIN Horizon 2020 Grant 713140
MINECO Grant FIS2016-80455-R
Severo Ochoa Grant SEV-2015-0522
Fundació Privada Cellex
Fundación Mig-Puig
CERCA program

Title: Neuronal 3D network dynamics of primary cultures and human-derived neural precursor cells on a semisynthetic hydrogel using light-sheet microscopy

Authors: *E. ESTEVEZ PRIEGO[1,2], O. E. OLARTE[3], A. A. LUDL[2,1], J. MADRID-WOLFF[3,4], A. V. KOROLEVA[5], P. LOZA-ALVAREZ[3], J. SORIANO[2,1]
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Abstract: Three-dimensional (3D) *in vitro* neuronal cultures mimic extracellular conditions more accurately than standard 2D networks. Cells remain healthy for longer periods, develop richer connectivity architectures, and show much more complex activity patterns. These 3D networks have become a valuable tool for tissue engineering, with promising applications for the modeling of brain functions and the study of neuropathologies.
In the present study we investigate 3D networks grown in a semisynthetic hydrogel termed 'PEGylated Fibrinogen', which allows for a biocompatible yet mechanically tunable environment. We monitored spontaneous activity using fluorescence calcium imaging with GCaMP6s, a genetically encoded calcium indicator, that allows the observation of network development and behavior along several days. We used light-sheet microscopy to image neurons in the entire 3D volume of the network. This imaging technology grants a sufficiently fast recording speed and image quality to capture the details of neuronal dynamics and render functional connectivity maps. In our setup, we considered a 1 mm^3 volume, and imaged activity in 10 planes of the volume at 200 frames per second.
Tests with primary embryonic cortical neurons demonstrate the capacity of 3D networks to show

rich spontaneous activity already from day in vitro 7. Neuronal cultures derived from human induced pluripotent stem cells (HiPSC, provided by AXOL Bioscience) were also tested, with the goal to compare both culture conditions and characterize their functional connectivity. This research is part of MESOBRAIN.

Disclosures: E. Estevez priego: None. **O.E. Olarte:** None. **A.A. Ludl:** None. **J. Madrid-wolff:** None. **A.V. Koroleva:** None. **P. Loza-alvarez:** None. **J. Soriano:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.01/DP01/C9

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: HHMI

Title: Patterned spontaneous network activity accompanies synapse development in the *Drosophila* visual system

Authors: *B. T. BAJAR[1], O. AKIN[1], M. F. KELES[2], M. A. FRYE[2], S. L. ZIPURSKY[1]
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Abstract: Stereotyped synaptic connections define the neural circuits of the brain. In vertebrates, synapse development is accompanied by a sustained period of spontaneous network activity. The mechanisms driving this activity and its contribution to establishing synaptic specificity remain poorly understood. Using two-photon microscopy in live, intact animals, we report that patterned spontaneous network activity (SNA) accompanies synapse development in the *Drosophila* visual system. SNA begins halfway through metamorphosis, shortly after synapses begin to form. This activity is oscillatory, in which each cycle exhibits an “active phase”, where all neurons in the optic lobe exhibit multiple bouts of activity, and a shared “silent phase”. SNA lasts for about 50 hours, during which activity evolves from an initial periodic stage, characterized by cycles of regular frequency, to a later chaotic stage, in which this consistent periodicity is lost. Using a combination of calcium imaging, voltage imaging, and pharmacology, we showed that SNA is dependent on voltage-gated sodium channels, independent of visual stimuli, and accompanies neurotransmitter release. Next, we investigated activity patterns at the level of individual cell types using cell-type specific expression systems. We analyzed the spatiotemporal structure of SNA for 14 different neuronal cell types, based on the degree of participation of cells in the active phases, and the relative timing of their activity. These two metrics, termed “coordination” and “coherence”, provided distinct activity signatures for different cell types and revealed

similarities between cell types that are synaptically coupled in the adult. Indeed, pairwise imaging showed that such cells have more correlated activity relative to uncoupled pairs. However, neither the proximity in coordination-coherence values nor direct correlation between pairs of cell types strictly follow the relative strength of the synaptic coupling observed in the adult. Together, these results suggest that the early connectome of the developing brain reflects that of the adult, but synaptic weights may continue to be modulated throughout development. Our observations indicate that SNA is a shared feature of both vertebrate and invertebrate brain development, and its discovery in *Drosophila* offers a complementary track to studying its contribution to synaptogenesis.

Disclosures: **B.T. Bajar:** A. Employment/Salary (full or part-time):; UCLA. **O. Akin:** None. **M.F. Keles:** None. **M.A. Frye:** None. **S.L. Zipursky:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.02/C10

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant 5R01NS031651
NIG Grant 1R21NS053807

Title: Target-dependent signaling mediates synaptic plasticity at the *Drosophila* neuromuscular junction

Authors: *H. S. KESHISHIAN[1], B. A. BERKE[2,1], L. LE[2]
[1]MCDB Dept., Yale Univ., New Haven, CT; [2]Biol. Sci. Dept., Truman State Univ., Kirksville, MO

Abstract: Drosophila motoneurons undergo activity-dependent expansion of their neuromuscular junctions (NMJs). This form of synaptic plasticity requires a TGF-β growth factor, Glass bottom boat (Gbb), which is released by the muscle fiber to activate a BMP receptor complex at the presynaptic bouton. This retrograde, trans-synaptic signal results in the local phosphorylation of the R-Smad transcription factor pMad, and leads to pMad-dependent transcription that is required for NMJ growth and plasticity. Since transcription occurs at the cell body, distant from the NMJs, it raises the question as to how a neuron that innervates multiple cells can control activity-dependent plasticity at specific subsets of its targets. To test this, we examined the ventral Common Exciter motoneuron (vCE), a cell that innervates multiple ventral muscle fibers. Using GAL4 driver lines specific to subsets of the vCE muscle fiber targets, we expressed transgenes postsynaptically, opposite specific branches of the neuron, leaving the

other branches to serve as controls. RNAi knockdown of the dGluRC or dGluRA subunits of glutamate receptors, in just one of the vCE target muscles, resulted in reduced presynaptic quantal release at that contact, and also blocked the ability of that vCE branch to undergo activity-dependent expansion. The adjacent branches of the vCE on unaltered muscles showed normal synaptic function and plasticity. Loss of postsynaptic glutamate receptors at a single muscle fiber target of the vCE also resulted in the loss of local presynaptic pMAD accumulation at the corresponding branch's boutons, with normal pMAD accumulation at adjacent, unaffected vCE contacts. This indicates that branch-specific pMAD accumulation is under the direct local control of the corresponding postsynaptic cell. To address a role for trans-synaptic signaling, a wild-type Gbb transgene was driven in a subset of the vCE targets of a *gbb* mutant, which rescued the functional and plasticity phenotypes, but only in the branch opposite the Gbb-rescued muscle fiber. Conversely, growth and plasticity of specific vCE branches was locally suppressed by RNAi knockdown of Gbb in the corresponding muscle fiber, with the other branches of the vCE remaining unaffected. We propose that presynaptic pMad accumulation in synaptic boutons plays a key role in locally determining the potential for activity-dependent plasticity through an unknown non-canonical mechanism. This may be an example of "synaptic tagging", governing the capture of molecules transported from the soma that are essential for synaptic growth and plasticity.

Disclosures: H.S. Keshishian: None. **B.A. Berke:** None. **L. Le:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.03/C11

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Alterations in MHCI subclass expression in neurally restricted IKK2 conditional knockout mice

Authors: *J. OGAWA
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Abstract: The Rel homology NFkB transcription factors are well known to have nearly ubiquitous expression and are mostly associated with innate immune functions in many metazoans and are especially well represented in mammalian organisms. The critical regulator in most cases is the I kappa B kinase (IKK) complex which regulates the pathway by regulation of protein stability of the IkB inhibitors are well as the activation of transactivation by phosphorylating the transcription factors themselves. Although ubiquitously expressed, a function for the IKK2 or the NFkB function in the brain has remained elusive. Here, in the

present study we show that the expression of Major histocompatibility complex (MHC I) proteins is altered when the IKK2 kinase is conditionally deleted in the CNS. Transcriptome data derived from RNA-seq of P0 pup brains, reveals an alteration of MHC class I subtype levels in IKK2 KO brains. This alteration however, was not observable in cultured neural progenitor cells. No visible structural alterations in neuroanatomy were observed. Similarly, no overt immune or inflammatory changes were observed in postnatal mice up into adulthood. The preliminary results suggest that unlikley previously assumed, there is a possible function of IKK2 in the brain through its regulation of MHC class I that has recently been shown to play a role in synaptogenesis, pruning and postnatal neurodevelopmental maturation pathways.

Disclosures: J. Ogawa: None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.04/C12

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: State of Florida Dept. of Health 7AZ04
NIH NS057994

Title: Synaptic acetylcholinesterase in the mouse brain increases following administration of donepezil or galantamine

Authors: *R. L. ROTUNDO, S. G. ROSSI
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Abstract: The predominant form of acetylcholinesterase (AChE), the enzyme responsible for terminating cholinergic neurotransmission, expressed in neurons is the globular G4 form consisting of four catalytic subunits anchored by a 125 amino acid transmembrane peptide called PRiMA. This AChE form is synthesized and assembled in the endoplasmic reticulum and subsequently transported through the secretory pathway for externalization at the plasma membrane. In neurons this includes transport down the axons via rapid axoplasmic transport and deposition at cholinergic synapses. Many cholinesterase inhibitors can stabilize the protein to thermal denaturation. However active site directed inhibitors have a unique ability to enhance AChE expression in tissue cultured cells. When HEK 293 cells expressing mouse AChE are incubated with either Donepezil (Don) or Galantamine (Gal), the two most common drugs used to treat Alzheimer's patients, there is a large 200-300% increase in AChE expression due to enhanced protein folding and stabilization. This increase in catalytically active AChE occurs without changes in total AChE protein indicating that the source of active enzyme is the

intracellular pool of inactive enzyme molecules. When these drugs are injected into mice at the same relative concentrations used to treat humans there is a large increase in total brain AChE within several hours. The increased AChE consists almost exclusively of the synaptic G4 AChE form, and occurs without apparent changes in total AChE protein as well. At a transport rate of 200 mm/day it would only take a couple hours for the newly-synthesized AChE to reach most cholinergic synapses in the mouse brain. Moreover, an increase in synaptic AChE could possible reduce the efficiency of cholinergic transmission in the brain thereby reducing the effectiveness of the very drugs designed to enhance cholinergic transmission. Future behavioral studies are planned to test this hypothesis.

Disclosures: R.L. Rotundo: None. **S.G. Rossi:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.05/C13

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: UW S&T Award

Title: Development and activity-dependence of spinules in primary sensory cortex

Authors: *M. NAHMANI[1], A. ERISIR[2], C. CAMPBELL[1], S. KIM[1], A. KNYAZ[1], W. SONG[1]
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Abstract: Spinules are thin projections that emanate from one neurite and protrude into an adjacent (often pre- or postsynaptic) neurite. Increased prevalence of these evolutionarily conserved features of neuronal anatomy has been correlated with experimental regimes that induce high frequency neuronal activation (e.g. long-term potentiation, KCl application) within particular microcircuits (e.g. stratum radiatum of CA1 in hippocampus), suggesting a role for spinules in neuronal circuit remodeling (Toni et al, 1999; Tao-Cheng et al, 2009). In addition, the appearance of spinules at a synapse is correlated with ‘perforations’ in the postsynaptic density and coated endocytic pits at spinule tips in the developing and adult brain, indicating a role for spinules in neuronal communication (Jones and Calverley, 1991; Spacek & Harris, 2004). Yet, the developmental profile, activity-dependence, and possible functions of spinules at cortical synapses remain unknown. Here, we have determined the developmental prevalence and ultrastructural features of spinules within presynaptic terminals forming excitatory cortical synapses in layer 4 of primary visual cortex (V1) from developing and adult ferrets. Furthermore, we present preliminary evidence exploring whether perturbations of in vivo activity (i.e.

monocular deprivation and early eye opening) are correlated with altered spinule prevalence at excitatory synapses in layer 4 of V1. In analyzing > 100 randomly collected synapses per age group (n=2-3 male & female animals/age) with experimenters blinded to condition, we find that the percentage of spinules within excitatory synapses remain largely unaltered from the age of eye opening around postnatal day 35 (p35) through the end of the critical period for ocular dominance plasticity (p60). However, the percentage of spinules within excitatory synapses in V1 rapidly peaks near the age of sexual maturity (> p90). These data suggest that spinules within excitatory synapses of primary sensory cortex may serve as ultrastructural 'anchors' that aid in stabilizing mature synapses, rather than purely filopodial-like structures that participate in circuit remodeling.

Disclosures: M. Nahmani: None. **A. Erisir:** None. **C. Campbell:** None. **S. Kim:** None. **A. Knyaz:** None. **W. Song:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.06/C14

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Synapse elimination triggered by BMP4 exocytosis and presynaptic BMP receptor activation

Authors: *T. HIGASHI, S. TANAKA, T. IIDA, S. OKABE
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Abstract: The process of synapse turnover is regulated by specific signaling mechanisms. Various molecules that promote formation and differentiation of synapses have been identified. Some of these molecules were classified as synapse organizers, because they were shown to initiate differentiation of hemi-synapses when they were expressed in non-neuronal cells and co-cultured with neurons. That said, little is known about the mechanisms underlying destabilization and elimination of unnecessary synapses. Here, we report that bone morphogenetic protein (BMP) 4 released from axons has the ability to eliminate synapses. BMPs are members of the transforming growth factor β(TGF-β) superfamily. Multiple members of the TGF-β superfamily are expressed in hippocampal neurons, but neuronal activity dependent regulation of the genes encoding this group has not been systematically analyzed. we investigated the expression profiles of genes related to TGF-βsuperfamily signaling in response to downregulation of neuronal activity in hippocampal neurons. Blocking neuronal activity using a sodium channel blocker induced *Bmp4* upregulation.At the synaptic level, molecular mechanisms and significance of BMP signaling have not been fully investigated. There has been no direct

evidence of BMP release at synapses. Whether BMP regulates synaptogenesis positively or negatively is still an open debate. These questions should be answered by direct monitoring of BMP release, its binding to receptors, and subsequent effects on synaptic structure and function. BMP4 transported into axons was secreted and accumulated on the axonal surface close to synaptic sites via type I receptors. BMP4 overexpression or knockout in culture reduced or increased presynaptic structures, respectively. *In vivo* single-cell knockout of BMP4 and subsequent two-photon imaging of synaptic dynamics confirmed the importance of BMP4 in the regulation of appropriate synaptic density. These results suggest an active role of BMP4 on the axonal surface in eliminating inappropriate synapses during neural circuit development.

Disclosures: T. Higashi: None. **S. Tanaka:** None. **T. Iida:** None. **S. Okabe:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.07/C15

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Brain-specific actinfilin that is associated with infantile spasms modulates dendrite arborization and spine formation

Authors: *H.-T. HU, Y.-P. HSUEH
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Abstract: Dendritic spines, the actin-enrich protrusions emerged from dendrites, are subcellular locations of excitatory synapses in the mammalian brain. Many actin-regulating molecules modulate dendritic spine morphology and synapse plasticity in response to neuronal activity. Actinfilin (AF), an actin-binding protein, is predominantly expressed in brain. It contains N-terminal Broad-Complex, Tramtrack and Bric a brac (BTB) domain, which is involved in CUL3-dependent ubiquitination, and C-terminal kelch domain, which interacts with F-actin. Human genetic study indicated the association of AF with infantile spasms, a rare childhood epilepsies and related to mental retardation, suggesting that AF plays a role in brain development and function. Here, we used cultured hippocampal neurons to explore the role of AF in neuronal morphogenesis and synaptic plasticity. We found that AF is presented in dendrites, including dendritic branching site and dendritic spines. Its expression was regulated by neuronal activity. Using miRNA knockdown approach, we found that loss of AF influenced dendritic arborization, spinogenesis and functional synapse formation. We further suggested that AF regulates F-actin intensity at dendritic spine and alters activity-induced spine enlargement. In addition to knockdown of AF expression, overexpression of AF fragments was also performed to disrupt the function of endogenous AF in neurons. Both AF-N terminal and AF-C terminal truncated

mutants had impact on F-actin rearrangement and synapse formation. In addition to morphology change, loss of AF also altered surface AMPAR expression, suggesting that AF may modulate synaptic strength. Furthermore, CRISPR-Cas9 AF knockout mice also show alteration of dendrite arborization, dendritic spine formation and activity-induced spine enlargement. In conclusion, our results provide the evidence that AF, a gene associating with infantile spasms, contributes to neuronal morphogenesis and synapse plasticity.

Disclosures: H. Hu: None. **Y. Hsueh:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.08/C16

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: CIHR
NSERC
FRQS
Heart and stroke Foundation

Title: Role of histone deacetylase 2 (Hdac2) in PV cell circuit development

Authors: *M. LAVERTU JOLIN, B. CHATTOPADHYAYA, F. DUMOUCHEL, P. CHEHRAZI, G. DI CRISTO
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Abstract: Cortical parvalbumin-positive basket cells (PV cells), the major source of GABAergic inhibition in the brain, innervate hundreds of postsynaptic targets with multiple synapses clustered around the cell body and proximal dendrites. These cells are particularly important for the regulation of multiple cognitive functions and developmental cortical plasticity. Although PV cell function is being explored extensively, the mechanisms that control their development and plasticity have not been entirely resolved.
Molecular mechanisms involved in synapse formation and strengthening include the activation/repression of specific subsets of genes by epigenetic modifications. In particular, Histone Deacetylase 2 (HDAC2) regulates excitatory synapse plasticity and memory formation, however, whether and how HDAC2 affects PV cell synapse development is unknown. Here, we first show that HDAC2 is expressed by PV neurons. In order to dissect the role of HDAC2 in PV cell development *in vivo*, we used the conditional KO mice (PV_Cre;HDAC2$^{lox/lox}$), which express Cre selectively in PV cells after P14. We observed that PV expression levels and putative perisomatic synapses density formed by PV cells are significantly reduced in both the

prefrontal cortex (PFC) and basolateral amygdala (BLA) by P60. We also found a reduction in both the number and intensity of perineural nets (PNN) around PV cells somas of the BLA. Behaviorally, we found that adult PV_Cre;Hdac2$^{lox/lox}$ mice extinguish fear memories more efficiently than control littermates. The reduced fear memory retrieval and renewal is accompanied with an increase in putative perisomatic PV synapse remodeling during fear memory extinction. Moreover, we used a new specific Hdac2 inhibitor which reduced fear memory retrieval in wildtype adult mice. Finally, in order to directly prove that Hdac2 in PV cells is important for fear memory extinction, we will rescue extinction behavior following viral-induction of Hdac2 protein expression specifically in PV cells of the BLA in PV_Cre;Hdac2lox/lox mice.
Globally, our work supports the model in which PV cells play a pivotal role in fear extinction and suggests that modulation of Hdac2 activity in combination with behavioral therapy can increase plasticity during the treatment of post-traumatic stress disorder (PTSD).

Disclosures: M. Lavertu Jolin: None. **B. Chattopadhyaya:** None. **F. Dumouchel:** None. **P. Chehrazi:** None. **G. Di Cristo:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.09/C17

Topic: A.06. Synaptogenesis and Activity-Dependent Development

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Title: A unique tyrosine in the intracellular domain of neuroligin-1 regulates the recruitment of AMPA receptors during synapse differentiation and potentiation

Authors: *O. THOUMINE[1], Z. SZIBER[1], I. CHAMMA[1], C. SAPHY[1], I. PAPASIDERI[1], B. TESSIER[1], H. JANOVJAK[2], M. SAINLOS[1], K. CZONDOR[1], M. LETELLIER[1]
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Abstract: The molecular mechanisms by which early neuronal connections mature into excitatory or inhibitory synapses are still debated. We examined here the impact of neuroligin-1 (Nlg1) tyrosine phosphorylation on synapse differentiation in hippocampal neurons, focusing on

a unique intracellular residue (Y782) which differentially regulates Nlg1 binding to PSD-95 and gephyrin. By expressing two Nlg1 point mutants (Y782A/F) in hippocampal neurons, we show using imaging and electrophysiology that the Nlg1 phosphorylation state modulates the recruitment of functional AMPA versus GABA-A receptors. Nlg1-Y782F impaired both dendritic spine formation and AMPA receptor diffusional trapping, but not NMDA receptor recruitment, suggesting that this mutant assembles silent synapses. Furthermore, replacing endogenous Nlg1 by either Nlg1-Y782A or Nlg1-Y782F impaired LTP, indicating that these Nlg1 mutants differently retain AMPA receptors. A screening of candidate tyrosine kinases points to Trk family members as major regulators of endogenous Nlg1 phosphorylation and synaptogenic function in neurons. Finally, optogenetic stimulation of endogenous Nlg1 tyrosine phosphorylation using a photoactivatable receptor tyrosine kinase selectively increased the number of dendritic spines and AMPA- (but not NMDA-) receptor mediated synaptic responses in hippocampal neurons. Thus, Nlg1 tyrosine phosphorylation critically regulates excitatory synapse differentiation and function.

Disclosures: O. Thoumine: None. **Z. Sziber:** None. **I. Chamma:** None. **C. Saphy:** None. **I. Papasideri:** None. **B. Tessier:** None. **H. Janovjak:** None. **M. Sainlos:** None. **K. Czondor:** None. **M. Letellier:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.10/C18

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH grants NS40296

Title: Functional changes in connectivity induced by differential silencing or ablation of tonic versus phasic motoneurons in *Drosophila*

Authors: *N. A. APONTE-SANTIAGO[1], J. T. LITTLETON[2]
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Abstract: Structural plasticity induced by neuronal competition is a common feature of developing nervous systems, and alterations in this process may contribute to neurodevelopmental disorders. The Drosophila larval neuromuscular junction (NMJ) provides a glutamatergic model synapse to study synaptic competition and compensation. Most larval muscle fibers are innervated by at least two motor neurons, a type Ib “tonic” motor neuron and a type Is “phasic” motor neuron. The Ib neuron innervates a single muscle, while Is neurons

innervate a subset of muscles to coordinate contraction of distinct muscle groups. If and how the postsynaptic muscle can differentiate between these two inputs, and how it might preferentially regulate them, is unknown. We are examining if Ib and Is motor neurons compete for synaptic drive to the postsynaptic cell by creating an input imbalance through genetic manipulation of one of the two neurons. We identified cell-type specific motor neuron drivers to genetically increase or decrease synaptic activity at either the Ib or Is motor neuron of muscle 1 (M1). Overexpression of Reaper in MN1-Ib to induce early cell death causes developmental changes in the synapses at M1. No type I motorneurons (Ib or Is) are present in M1 following MN1-Ib ablation, indicating synapse formation or retention may require early Ib function. Ablation of the Is neuron by Reaper expression did not disrupt the MN1-Ib connection at M1. Decreasing the activity of MN1-Ib or MNIs neuron (rather than ablating it) by expressing tetanus toxin light chain (TeTXLC) resulted in structural changes of synaptic boutons at muscle 1. In non-perturbed animals, Ib boutons are bigger than Is boutons. When release of MN1-Ib or MNIs is perturbed, Ib and Is boutons onto M1 are indistinguishable. Furthermore, the morphological changes observed are muscle specific, with the Is bouton increasing in size only at M1 due to MN1-Ib silencing. Additional studies are underway to test molecular pathways that control synaptic balance of tonic and phasic input at Drosophila NMJs.

Disclosures: N.A. Aponte-Santiago: None. **J.T. Littleton:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

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Program #/Poster #: 280.11/C19

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NINDS Grant NS42595
McDonnell Center for Cellular and Molecular Neurobiology at Washington University in St. Louis

Title: Mechanisms regulating the alternative splicing of synaptic adhesion molecules in somatosensory neurons

Authors: *J. YOO, R. W. GEREAU, B. COPITS
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Abstract: Processing external information from distinct sensory modalities is vital for generating the diversity of somatic sensations that we perceive. However, altered communication within these pathways can result in chronic pain states. While the plasticity of nociceptive circuits is well established, we possess a limited understanding of the molecular mechanisms that

establish the wiring of sensory circuitry, and how this connectivity may be altered in chronic pain. Neurexins (*Nrxn*s) are presynaptic cell-adhesion molecules that are essential in coordinating synapse formation through trans-synaptic interactions with myriad post-synaptic ligands. Extensive alternative splicing of neurexins generates thousands of unique isoforms which has been proposed to impart a combinatorial "splice-code" for connectivity. In the central nervous system, *Nrxns* have been shown to regulate synaptic properties critical to coordinating neuronal circuitry, yet the role of *Nrxns* in somatosensory circuits remains largely unexplored. Here we tested whether peripheral sensory neurons regulate *Nrxn* alternative splicing in response to changes in activity or injury to alter somatosensory circuit connectivity. We found that both mouse and human sensory neurons dynamically regulate exon inclusion at SS4, a site known to regulate synaptic connectivity. Additionally, we found that *Nrxn* alternative splicing at SS4 is highly conserved in human sensory neurons despite variation in age, sex, and race, suggesting a critical role for this splice-site in peripheral somatosensation. However, we observed significant changes in *Nrxn* splicing in sensory neurons from donors in which spinal neurons had degraded, suggesting that these changes can be regulated by a lack of activity or connectivity. To test the effects of activity on splicing, we treated cultured mouse sensory neurons with KCl, glutamate, and prostaglandin E2 to stimulate activity *in vitro*. We found in preliminary experiments that each treatment resulted in differential splicing changes. We are currently testing how *Nrxn* alternative splicing is differentially regulated by activity or synaptic connectivity to understand the mechanisms underlying these dynamic changes, and how they might influence somatosensory circuit rewiring in chronic pain.

Disclosures: J. Yoo: None. **R.W. Gereau:** None. **B. Copits:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Research Grants Council of Hong Kong SAR 16102717
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Area of Excellence Scheme of the University Grants Committee AoE/M-604/16

Title: IL-33/ST2 signaling enhances the formation of excitatory synapses in the hippocampus

Authors: *Y. WANG[1,2,3], K.-W. HUNG[1,2,3], C.-Y. CHUANG[1,2,3], W.-Y. FU[1,2,3], A.-Y. FU[1,2,3], N. Y. IP[1,2,3]
[1]Div. of Life Sci., [2]Mol. Neurosci. Ctr., [3]State Key Lab. of Mol. Neurosci., The Hong Kong Univ. of Sci. and Technol., Hong Kong, China

Abstract: Emerging evidence suggests that immune molecules play important roles in modulating neuronal functions. Interleukin 33 (IL-33), originally identified as an alarmin, is a crucial mediator in the regulation of both innate and adaptive immunity during tissue injury. Upon tissue damage, IL-33 initiates immune responses by binding to the ST2/IL-1RAcP receptor complex. We recently reported that IL-33 rescues synaptic plasticity deficits and cognitive impairment in an Alzheimer's disease transgenic mouse model. We further investigated whether IL-33 has a physiological role in synapse formation and/or maintenance. We found that IL-33 enhances the formation of excitatory synapses in hippocampal neurons, as revealed by increased excitatory synaptic transmission. Deletion of ST2 or IL-1RAcP in hippocampal neurons abolished the IL-33-induced increase of excitatory synaptic transmission, suggesting that IL-33 promotes synaptogenesis through the activation of the ST2/IL-1RAcP-dependent signaling pathway. Thus, our findings collectively demonstrate a novel role of IL-33/ST2 signaling in excitatory synapse formation and function in the hippocampus.

Disclosures: Y. Wang: None. **K. Hung:** None. **C. Chuang:** None. **W. Fu:** None. **A. Fu:** None. **N.Y. Ip:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.13/C21

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant RO1-NS092578
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Title: SIRPα: An activity-dependent regulator of synaptic refinement

Authors: *S. NAGAPPAN CHETTIAR, E. M. JOHNSON-VENKATESH[1], H. UMEMORI[2]
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Abstract: Synapses are the sites of information transfer that are central to brain function. Synapses develop through distinct stages beginning with synaptic differentiation, followed by the neural activity-dependent stage of synaptic refinement. During synapse refinement, active

synapses are preferentially strengthened and stabilized, while inactive synapses are eliminated. Defects in this process of refinement are implicated in various neuropsychiatric disorders. Therefore, it is important to understand the molecular mechanisms that detect synaptic activity and determine which synapses to stabilize and which to eliminate. Our previous work has identified the postsynaptically-expressed transmembrane protein, Signal Regulatory Protein-α (SIRPα) as a critical regulator of activity-dependent synaptic maturation. At active synapses, the ectodomain of SIRPα is cleaved and released to retrogradely signal presynaptic maturation. However, how SIRPα senses synaptic activity such that it releases its ectodomain in an activity-dependent manner is not known. Furthermore, whether SIRPα serves as a stabilization signal for active synapses and prevents them from elimination is unknown. Here, we demonstrate that the activity-dependent tyrosine phosphorylation of SIRPα is critical for SIRPα ectodomain cleavage and synaptogenic function. We further show that SIRPα is critical to prevent aberrant synaptic elimination during refinement. We biochemically establish that SIRPα is highly tyrosine phosphorylated in the mouse hippocampus at the start of synapse maturation and that this tyrosine phosphorylation of SIRPα is driven by neuronal activity. Using immunochemistry and electrophysiology in combination with a phosphorylation-deficient mutant of SIRPα, we determine that the tyrosine phosphorylation of SIRPα drives presynaptic maturation and SIRPα ectodomain cleavage in neurons. Finally, we electrophysiologically demonstrate that in the absence of SIRPα signaling, synapses undergo greater elimination during synapse refinement *in vivo*. Together, these results support a model where SIRPα tyrosine phosphorylation detects synaptic activity and directs activity-dependent synapse maturation by driving SIRPα ectodomain cleavage. This SIRPα signaling serves as a stabilization signal to prevent the elimination of active synapses in the brain. This work sheds light on the molecular mechanisms by which synapses are precisely refined in response to neural activity to ensure proper brain function.

Disclosures: E.M. Johnson-Venkatesh: None. **H. Umemori:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.14/C22

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: VIEP-BUAP-2018

Title: Amyloid-β(25-35) peptide administration into the CA1 subfield decreases dendritic spines number but not their morphology in the hippocampus of rats with spatial memory

Authors: *C. SÁNCHEZ MALDONADO, E. RAMÍREZ HERNÁNDEZ, I. D. LIMÓN PÉREZ DE LEÓN
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Abstract: It has been shown that the administration of the $A\beta_{25-35}$ into cognitive regions of the brain reproduces some of the neurotoxic mechanisms described in Alzheimer's disease, some of which decrease dendritic spines density. Dendritic spines morphological changes are associated to their function: stubby and branched spines are immature forms that express predominantly in the post-natal days; thin spines are highly dynamic mature forms associated to learning, and mushroom spines are stable mature forms linked to memory. The effect of $A\beta_{25-35}$ administration on dendritic spines morphological changes and its association with cognitive impairment is still unknown. The aim of this study was to typify dendritic spines in the hippocampus and dentate gyrus of rats administrated with $A\beta_{25-35}$ peptide into the CA1 subfield. Twenty four male Wistar rats (4 months old, 350-400 g) were divided in two groups for stereotaxic surgery (n=12 each). One group was anesthetized and bilaterally injected 1 μL of $A\beta_{25-35}$ solution [0.1 μg/μL] into the CA1 subfield of the hippocampus (AP -4.0, LM ±2.6, DV -2.3 mm, from Bregma). Six rats from each group (Intact+LM, $A\beta_{25-35}$+LM) performed learning on days 6 to 10 post-surgery and memory tests on days seventeen and thirty-eight post-surgery in the Morris water maze. Next day all animals were euthanized, brains were obtained and processed for Golgi-Cox staining. Dendritic spines were evaluated in distal dendrites randomly chosen in 5 neurons per region and in both hemispheres. Typing was done according to spines morphology in mushroom, thin, stubby or branched. Total spines decreased in $A\beta_{25-35}$ group, compared to Intact group. Similarly, total spines decreased in $A\beta_{25-35}$+LM group, compared to Intact+LM group. Proportion of mushroom spines increased in the $A\beta_{25-35}$, Intact+LM and $A\beta_{25-35}$+LM groups, compared to Intact group. Proportion of stubby and thin spines decreased in $A\beta_{25-35}$ and Intact+LM groups, compared to Intact. Results indicate that $A\beta_{25-35}$ decreases dendritic spines number in the hippocampus but does not modify their morphology, which could be associated to extinction, as shown in memory evaluation.

Disclosures: C. Sánchez Maldonado: None. **E. Ramírez Hernández:** None. **I.D. Limón Pérez de León:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.15/C23

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Functional maturation of mossy fiber terminals from adult-generated hippocampal dentate granule cells

Authors: *N. P. VYLETA, D. R. SEIB, J. S. SNYDER
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Abstract: The dentate gyrus of the hippocampus is one of few regions in the mammalian brain to exhibit continued neurogenesis throughout adulthood, and these neurons may be uniquely suited to contribute to information transfer through hippocampal circuits. Understanding the mechanisms of how these new neurons signal in the mature network—both receiving inputs and transmitting output signals—is fundamentally important to understanding their roles in hippocampal function. It is well established that adult-generated granule neurons experience a period of enhanced excitability of the somato-dendritic compartment, as well as greater plasticity at the input synapses coming from the entorhinal cortex (Schmidt-Hieber et al., 2004; Ge et al., 2007). However, the time course of the development of output synapses from these neurons into the CA3 region of the hippocampus remains far less clear. Because the shape and dynamics of the action potential waveform at a presynaptic bouton determines calcium entry and ultimately the efficacy of release of neurotransmitter (Geiger and Jonas, 2000), how the electrical impulse at output mossy fiber terminals from adult-generated granule neurons develops with cell age could have important time-dependent effects on synaptic plasticity. Here, we have systematically characterized electrical properties of output mossy fiber terminals from adult-generated granule neurons using direct patch clamp recordings (Geiger and Jonas, 2000; Vyleta and Jonas, 2014). Recordings were made at various time points after induction of a fluorescent reporter in granule neurons in $Ascl1^{CreERT2}$;$CAG^{floxstopTom}$ mice. Neurons were labeled during adulthood (6- to 8-weeks of animal age) and during early development (postnatal day 0-3). The size and kinetics of action potentials, dynamics of the action potential waveform during trains of stimuli, excitability threshold, input resistance and resting capacitance were evaluated as a function of cell age, and compared between adult-born and early development-born groups.

Disclosures: N.P. Vyleta: None. **D.R. Seib:** None. **J.S. Snyder:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

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Program #/Poster #: 280.16/C24

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant 4R01NS078294-05

Title: Single cell RNAseq of mouse olfactory bulb reveals cellular heterogeneity and activity dependent molecular census of adult-born neurons

Authors: *B. TEPE[1,2], M. C. HILL[2], B. T. PEKAREK[3], T. J. MARTIN[4], J. F. MARTIN[1,4,2], B. R. ARENKIEL[3,5,2]
[2]Program in Developmental Biol., [3]Mol. and Human Genet., [4]Mol. Physiol. and Biophysics, [5]Neurosci., [1]Baylor Col. of Med., Houston, TX

Abstract: In mammals, olfactory sensory neurons (OSNs) located in the nasal epithelium gather odor information from the environment, and relays it to the olfactory bulb (OB). Within the OB, this olfactory information is received by mitral and tufted cells, and further shaped by local inhibitory interneurons. Uncovering contributions of diverse interneuron subtypes towards OB circuit processing is essential to fully understand olfaction. Interneuron diversity in the OB is heavily influenced by ongoing adult neurogenesis. Additionally, survival and integration of adult-born neurons is known to be influenced in an activity-dependent manner. To investigate cellular heterogeneity in the mouse OB and query the developmental program of adult-born neurons, we utilized single cell RNA sequencing (scRNA-seq) and computational modeling. Our data reveal 38 transcriptionally distinct neuronal and non-neuronal cell types, and suggest novel markers for each. Additionally, we analyzed molecular changes throughout the development of adult-born interneurons, and uncovered changes in their patterns of gene expression that are differentially regulated throughout their development. Finally, we investigated changes in tissue composition upon sensory deprivation and enrichment, and discovered distinct mechanisms that differentially affect the development of adult-born neurons. Together, we provide a transcriptome-based foundation for studying subtype specific neuronal function in the OB, a map of molecular changes throughout maturation and integration of adult-born neurons, and document activity-dependent changes in the cellular composition of the olfactory system. These data provide a valuable resource of cell type specific markers that allow for the investigation of cell type-specific functions in the olfactory bulb. Furthermore, the associated list of genes that are differentially regulated in adult-born neurons throughout development can be utilized in ongoing work towards better understanding synapse formation and maintenance in adult brain tissue.

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Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

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Title: The protein arginine methyltransferase PRMT8 regulates dendritic spine maturation and localization of excitatory synapses

Authors: *K.-O. LAI, L. H. Y. LO, R. DONG, A. CHAI, Q. LYU
Sch. of Biomed. Sci., The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Most excitatory synapses are located in the dendritic spines, which exist as various morphologies. The formation of mature mushroom spines is crucial for long-term storage of memory, while higher abundance of the immature thin spines and filopodia is associated with autism and Fragile-X syndrome. Spine maturation is influenced by neuronal activity and requires dendritic translation of specific mRNAs. Characterizing dendritically localized transcripts might therefore identify key molecules and signaling pathways that control spine maturation. PRMT8 (protein arginine methyltransferase 8) belongs to a family of enzymes that catalyze arginine methylation, a form of post-translational modification (PTM) that is most-studied as a regulatory mechanism during transcription and splicing in the nucleus. Among the nine PRMTs, PRMT8 is unique because of its anchorage to the plasma membrane via myristoylation. Here we found that PRMT8 was localized in dendritic spines of dissociated hippocampal neuron. The PRMT8 mRNA was present in the dendrites, and the expression of PRMT8 protein was regulated by neuronal activity. Depletion of PRMT8 resulted in the loss of mushroom spines and an increase in the number of immature filopodia. This change in spine morphology was coupled with a shift of excitatory synapses from dendritic spines to the dendritic shaft without affecting the number of functional synapses. Our findings have identified PRMT8-mediated arginine methylation as a novel regulatory PTM at the synapse that is crucial for dendritic spine maturation.

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Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

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University of Hong Kong Seed Funding for Basic Research 201511159170
University of Hong Kong Seed Funding for Basic Research (201607170668

Title: Non-redundant functions of different kinesin I motor proteins in dendritic mRNA transport and synapse development

Authors: *J. ZHAO, R. FAN, H. K. FOK, H.-L. CHAN, L. H. Y. LO, J. D. HUANG, C. S. W. LAI, K.-O. LAI
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Abstract: Most excitatory synapses are located on dendritic spines, which exist in heterogeneous shapes. Mushroom spines are believed to contribute to long-term memory storage, and their formation depends on local dendritic protein synthesis. Dendritically localized mRNAs are transported in the form of RNA granules by the motor proteins kinesin and dynein along microtubule. There are 45 kinesin genes in the mammalian genome, and different classes of kinesin proteins may exhibit functional specificity by transporting distinct cargos to different subcellular localization. The conventional kinesin, Kinesin I, consists of three homologous members (KIF5A, KIF5B and KIF5C), which form complexes with RNA granules in the brain. Whether the three highly homologous Kinesin I motor proteins have redundant or non-overlapping roles in RNA transport and dendritic spine development have not been explored. Here we found that specific depletion of individual Kinesin I family member in dissociated hippocampal neurons led to distinct dendritic spine phenotypes. By labeling RNA with SYTO 14 or expression of GFP-FMRP followed by time-lapse confocal imaging, we demonstrated that KIF5B regulates dendritic mRNA transport. Transcriptome analysis of synaptoneurosomes isolated from wild-type and *kif5b* knockout mice was performed to identify putative mRNA transcripts that showed differential synaptic localization. Our findings have shed new light on the non-redundant roles of different kinesin motor proteins in regulating intracellular transport, synapse development and function.

Disclosures: J. Zhao: None. **R. Fan:** None. **H.K. Fok:** None. **H. Chan:** None. **L.H.Y. Lo:** None. **J.D. Huang:** None. **C.S.W. Lai:** None. **K. Lai:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.19/C27

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH MH105426

Title: Functional diversity between splice variants of the neurodevelopmental disorder gene Kirrel3

Authors: *M. TAYLOR, E. A. MARTIN, M. E. WILLIAMS
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Abstract: Cell adhesion molecules (CAMs) play critical roles in synapse development. The diversity of CAMs at individual synapses and the fact that different classes of synapses use different CAMs suggests that these proteins are not simple glues holding synaptic membranes together. Rather, different CAMs provide specificity for synaptic structure and function. We previously found that Kirrel3 is a homophilic CAM expressed only in specific subsets of hippocampal neurons. Loss of Kirrel3 leads to loss of synapses between Kirrel3 expressing neurons, ultimately creating an excitation/inhibition imbalance within the hippocampus. Interestingly, Kirrel3 is alternatively spliced, but the function of these alternative splice forms in synapse development is unknown. Potentially, alternative splicing at the Kirrel3 locus creates variants that work together, separately, or in opposition to build specific synapses. Here we determine the functional differences of two Kirrel3 splice forms with respect to cell adhesion, subcellular localization and synapse formation.

Disclosures: M. Taylor: None. **E.A. Martin:** None. **M.E. Williams:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.20/C28

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Autism Speaks Weatherstone Predoctoral Fellowship
Eunice Kennedy Shriver National Institute Of Child Health & Human Development of the National Institutes of Health T32HD007491
NIH Grant 1R01MH105426

Title: The functional impact to synapse formation of Kirrel3 variants associated with neurodevelopmental disorders

Authors: *E. A. MARTIN[1], M. R. TAYLOR[2], M. E. WILLIAMS[3]
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Abstract: Neurodevelopmental disorders are often diseases of the synapse, yet few molecules are identified that link specific mutations to impaired synapse function. Kirrel3 is a homophilic transmembrane cell adhesion protein expressed within hippocampal DG and GABA neurons. We showed that structurally, loss of Kirrel3 reduces mossy fiber DG-to-GABA synapses and functionally, loss of Kirrel3 significantly increases the excitation/inhibition ratio of CA3 neurons. These defects may underlie neurodevelopmental disorders associated with Kirrel3 in humans. Currently, many Kirrel3 protein coding variants have been identified as potentially damaging in patients with autism spectrum disorders and mild to severe intellectual disability. Yet to date, no study has examined the functional relevance of these Kirrel3 variants in synapse formation. Here we examine the function of several Kirrel3 variants in cell adhesion, subcellular localization, and synapse formation. These results are necessary to determine if specific Kirrel3 variants may be pathogenic and lead to synaptic defects relevant to neurodevelopmental disorders.

Disclosures: E.A. Martin: None. **M.R. Taylor:** None. **M.E. Williams:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.21/C29

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH grant 1R01MH105426

Title: The role of Kirrel3 in presynaptic structural plasticity

Authors: *R. L. RAWSON, D. WOODRUFF, T. TUIFA, M. WILLIAMS
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Abstract: All behaviors, from simple reflexes to complex cognitive tasks, require neuron communication via synapses. Consequently, many neurological disorders are linked to impairments in synapse form and function. Synapses must be correctly established during development, yet they must also be flexible to accommodate future adaptations. Synapse flexibility is critical for learning and memory and includes altering synapse architecture, known as structural plasticity. Very little is known about mechanisms mediating structural plasticity, and even less still about the structural plasticity of presynaptic structures. In the hippocampal mossy fiber system, DG neurons make elaborate presynaptic structures that are physically altered during learning and memory. They form large boutons that connect with CA3 neurons and filopodia-like extensions that synapse with both GABA and CA3 neurons. The Williams lab has recently demonstrated that the cell adhesion molecule Kirrel3 is required for mossy fiber filopdia number, as well as their synapses onto GABA neurons. Preliminary data also show that Kirrel3 is regulated by neuronal activity. To test the model that Kirrel3 is a potential mechanism behind presynaptic structural plasticity during learning and memory, we are investigating *in vivo* if Kirrel3 is required for altering filopodia number in response to changes in neuronal activity and during learning and memory. This is likely to have clinical relevance as mutations in Kirrel3 have been repeatedly associated with Autism and intellectual disability.

Disclosures: R.L. Rawson: None. **D. Woodruff:** None. **T. Tuifa:** None. **M. Williams:** None.

Poster

280. Synaptogenesis and Activity-Dependent Development: Synapse Maturation and Remodeling

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 280.22/C30

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NSERC

Title: Heterogeneous expression of glutamatergic receptor genes in normally developing human cortex and adult schizophrenia

Authors: *S. MANCINI[1], D. G. JONES[3], K. M. MURPHY[2]
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Abstract: Biological heterogeneity of the human brain is a common finding in studies of neurological or neuropsychiatric disease. These disease-related heterogeneities are found at many levels from behaviour to molecular mechanisms. We have been studying heterogeneity in normal brain development and found a wave of high inter-individual variability in expression of glutamatergic proteins in visual cortex in young children but relatively homogeneous expression

at other ages.
We chose to look at glutamatergic mechanisms because they are involved with both adaptive and maladaptive experience-dependent plasticity. Here we asked if: glutamatergic gene expression has a similar wave of heterogeneity; other cortical areas have waves of heterogeneity in childhood, and adult heterogeneity in diseases like schizophrenia (SZ) is similar to the heterogeneity found during normal development?
We analyzed transcriptome data for glutamatergic receptor subunit expression in human cortex during normal development and in adults with SZ. We used two databases one with developmental data (Allen BrainSpan) (n=41), age range 8pcw-40yrs, 9 cortical areas, and 19 glutamatergic receptors. The other database (GDS4523[ACCN] accessed through Gene Expression Omnibus) contained data from the anterior prefrontal cortex of adults (age range 25-88 yrs) with SZ (n=28) or control cases (n=23). We plotted gene expression by age and calculated heterogeneity (variance-to-mean ratio, VMR) for a sliding window of 5 adjacent ages. During normal development several cortical areas and genes including GRIN2A, GRIN3A, GRIN3B, GRIA1, GRIA2, and GRIA3 showed a wave of heterogeneity in young childhood, peaking at ~1-2 years of age, with relatively homogeneous expression at other ages. We compared heterogeneity at the peak in childhood with young adults by calculating a contrast index using the VMRs and found as much as 80% greater heterogeneity in young children. We then applied the same approach to compare heterogeneity in glutamate gene expression between adult SZ and control cases. Here we found that GRIN2A, GRIN3A, GRIN3B, GRIA1, GRIA2, and GRIA3 had ~25-50% greater heterogeneity in SZ cases.
Thus, glutamatergic genes, like proteins, have a wave of heightened heterogeneity in childhood and this pattern is part of normal development for many areas of the human cortex. Also, in adults with SZ, there is heightened heterogeneity for some glutamatergic genes suggesting that these regulators of experience-dependent plasticity may maintain or re-entered that wave of childhood heterogeneity.

Disclosures: S. Mancini: None. **D.G. Jones:** None. **K.M. Murphy:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.01/C31

Topic: A.09. Adolescent Development

Support: NIH R01HD082257
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Title: Gray Matter and Neuroprediction: Brain-age outperforms chronological age in prediction of antisocial behavior

Authors: *N. E. ANDERSON[1], K. A. KIEHL[1,2], E. AHARONI[3], J. M. MAURER[2], K. A. HARENSKI[1], V. RAO[1], E. D. CLAUS[1], M. R. KOENIGS[4], J. DECETY[5], D. KOSSON[6], T. D. WAGER[7], V. CALHOUN[1], V. R. STEELE[8]
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Abstract: Age is an important variable in a number of psychological and biological models, including those predicting antisocial behavior. However, individual variation in biological processes assures that chronological age may not be the best proxy for capturing important neurodevelopmental differences in such models. Neuroimaging-based quantifications of brain-age have been previously developed, and these models have demonstrated high accuracy in predicting chronological age and psychological outcomes related to aging, cognitive development, and cognitive decline. While age is also highly relevant to antisocial outcomes, brain-age measures have not yet been applied to models predicting antisocial behavior. Here we utilize independent component analysis (ICA) of structural MRI data to identify intrinsic networks of gray matter (GM) that are discriminative of age among a large incarcerated sample (n = 1332). We then carry these age-related components forward in models predicting re-arrest in a separate sample of offenders recently released from prison (n = 93). After an average of four years follow-up, 54% of the sample was re-arrested. Feature selection in a support vector machine framework identified two components of GM volume and five components of GM density that were predictive of re-arrest. These components were included with a number of other relevant variables in a series of Cox proportional hazards analyses, examining time to re-arrest. Model comparisons indicated that brain-age consistently outperformed chronological age in predicting re-arrest when examined alone or in conjunction with other variables including psychopathic traits, drug and alcohol dependence, behavioral performance on an inhibition task, and neural activity in the anterior cingulate cortex. These findings support the relative value of examining more precise neural indicators of brain maturity compared with chronological age, suggesting certain neural indices are promisingly more sensitive to some important behavioral and psychological outcomes.

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Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.02/C32

Topic: A.09. Adolescent Development

Support: NIH Grant MHO98348

Title: Race, violence exposure, and the psychosocial stress response

Authors: *E. DAVIS[1], A. M. GOODMAN[1], T. R. OREM[1], N. G. HARNETT[1], M. D. WHEELOCK[1], S. MRUG[1], M. A. SCHUSTER[2], M. N. ELLIOTT[3], S. R. TORTOLERO[4], D. C. KNIGHT[1]
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Abstract: African American, in comparison to European American, individuals have higher rates of violence exposure throughout their lifetimes (Roberts et al., 2010). Violence exposure in adolescence has been linked to changes in brain structure and function, and appears to alter the way people respond to stress (Teicher et al., 2016; Teicher & Samson, 2016). However, it remains unclear whether race and prior violence exposure interact to affect the stress response. Therefore, the present study investigated the relationship between prospectively measured adolescent violence exposure (ages 11-19 years) and the neural response to psychosocial stress as young adults (age = 19.54 ± 1.31). In the present study, 262 African American and European American participants completed the Montreal Imaging Stress Task (MIST). Violence exposure was greater in African American than European American participants, and self-reported stress ratings to the MIST were higher in European American than African American participants. Further, a significant interaction was observed between race and cumulative violence exposure on self-reported stress ratings ($p < 0.01$). Specifically, stress ratings decreased as violence exposure increased among African American but not European American participants. Functional magnetic resonance imaging (fMRI) results showed differences in prefrontal cortex activity that varied with violence exposure, race, and the interaction of race and violence exposure ($p < 0.05$). These findings demonstrate racial differences in stress reactivity that vary with violence exposure.

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Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.03/C33

Topic: A.09. Adolescent Development

Support: National Institute of Drug Abuse grant R01 DA 016423

Title: The effects of early childhood trauma and gender on brain structure

Authors: *S. MCQUINN
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Abstract: Background
Early childhood stress or trauma has many lasting psychological and physiological effects. Stress in early development can lead to changes in brain structure and function. Little is known as to whether early life stress (ELS) may affect men and women differently. The aim of this study was to examine the differential effects of ELS on cortical thickness in a group of healthy men and women.
Methods
48 healthy participants between the ages 18-45 were asked to complete the Family Life Experience Questionnaire to determine the extent to which they had experienced early life stress. Each participant was scanned and T1-weighted MRI scans were collected. The Computational Anatomy Toolbox (CAT12) for SPM was used to measure cortical thickness and determine whether there were significant cortical thickness differences between groups (i.e., Men vs Women, ELS vs no ELS) and test for interactions between ELS and sex.
Results
Females exhibited greater cortical thickness than males within visual and auditory association areas (XYZ = -15, -101, 13, T=5.06, p_{FWE}=0.011, XYZ = 67, -34, 6, T=3.89, $p<0.001_{uncorrected}$), the ventral temporal cortex (XYZ = 36, -6, -37, T=4.31, $p<0.001_{uncorrected}$), the premotor cortex (XYZ = -41, 6, 50, T=3.93, p<0.001, uncorrected), and the superior parietal lobule (XYZ = 36, -47, 50, T=3.59, $p<0.001_{uncorrected}$). Males had thicker cortices than females within the middle occipital gyrus (XYZ = -46, -79, 3, T=4.51, p_{FWE}=0.041), the extrastriate cortex (XYZ = 25, -54, 2, T=3.89, $p<0.001_{uncorrected}$) and the dorsal temporal cortex (XYZ = 44, -20, -3, T=3.84, $p<0.001_{uncorrected}$). Those who experienced ELS showed greater cortical thickness on the middle occipital gyrus (XYZ = -5, -90, -3, T=5.06, $p<0.001_{uncorrected}$). When testing the interaction between sex and trauma, we found a difference in a small region of the orbitofrontal cortex (XYZ = 41, 29, -16, Z=3.64, $p<0.001_{uncorrected}$).
Discussion
Our findings suggest that early life stress does indeed have an effect on cortical thickness and

that sex may play a role in that effect.

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Disclosures: S. McQuinn: None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.04/C34

Topic: A.09. Adolescent Development

Support: NIH/NIDA U01 DA041048-03

Title: Associations between socioeconomic factors and brain structure in preadolescence

Authors: M. R. GONZALEZ[1], K. A. UBAN[1], M. M. HERTING[2], E. KAN[1], *E. R. SOWELL[3]
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Abstract: Previous findings from our group (Noble et. al., 2015) suggest that indices of socioeconomic status (SES), such as family income and parental education, are associated with brain development. These effects are particularly notable among the most disadvantaged individuals. Importantly, differences in SES predict differences in brain structure during a time when youth are at-risk for substance use. Here, associations between SES and brain structure were examined in a cross-sectional sample of 4,500 preadolescent children ages 9 - 10 years of age participating in the Adolescent Brain Cognitive Development (ABCD) study. The Data Analytics Exploration Portal (DEAP) was used to run multilevel regression models (gamm4) to test the effects of SES on cortical surface area. We examined FreeSurfer measures of total cortical surface area (SA), as well as SA in regions of interest in brain structure related to executive function and language. Measures of SES examined were household income and highest parental education. All models included age, sex, and ethnicity/race as fixed effect covariates and family relationship and site as random effects. Higher parental income predicted larger total cortical SA ($F = 17.48$, $p < 0.001$) and accounted for an additional 0.87% of variance (Null model: AIC=87,745.45; BIC=87,820.95; Full model: AIC=87,805.71; BIC= 87,868.62). Similar associations were found for higher income and larger SA in the left superior frontal ($F = 14.00$, $p < 0.001$), right superior frontal ($F = 15.49$, $p < 0.001$), left pars orbitalis ($F = 9.81$, $p < 0.001$), and right pars orbitalis ($F = 14.75$, $p < 0.001$). In a separate model, higher parental education predicted larger total cortical SA ($F = 8.49$, $p < 0.001$) and accounted for an additional 0.78% of variance (Null model AIC=94,958.88; BIC: 95,048.08; Full model: AIC=95,045.32; BIC=95,109.03). Similar associations were found for higher parental education and larger SA in

the left superior frontal (F = 8.96, p <0.001), right superior frontal (F = 6.98, p <0.001), left pars orbitalis (F = 4.92, p <0.001), and right pars orbitalis (F = 7.17, p <0.001). Factors such as environmental toxins and physiological measures will be examined as potential underlying mechanisms influencing the impact of SES on brain structure using a model of mediation. These preliminary results confirm and extend findings from Noble et. al., (2015) to a larger sample with a narrower age range.

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Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.05/C35

Topic: A.09. Adolescent Development

Support: NIH Grant MH098348

Title: The influence of neighborhood disadvantage during adolescence on volume of the adult amygdala, hippocampus, and thalamus

Authors: *K. BELL[1], N. G. HARNETT[2], S. MRUG[2], M. A. SCHUSTER[3], M. N. ELLIOTT[4], S. R. TORTOLERO[5], D. C. KNIGHT[2]
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Abstract: Depression and anxiety have been linked to changes in the gray matter volume of the amygdala, hippocampus, and thalamus (Mervaala et al., 2000; Merz, Tottenham, and Noble, 2018). Additionally, children that live in disadvantaged neighborhoods are at increased risk for depression and anxiety (Xue, Leventhal, brooks-Gunn, and Earls, 2005). Prior research has linked household socioeconomic status (SES) to amygdala and hippocampal volume, however, studies of the impact neighborhood environment has on the gray matter of these structures have been inconsistent. Determining the impact neighborhood disadvantage has on amygdala, hippocampus, and thalamus volume may offer new insight into mechanisms by which adverse life experiences impact developing neural systems. The current study investigated the impact of living in a disadvantaged neighborhood during childhood on the gray matter volume of the amygdala, hippocampus, and thalamus in young adults. Using geocoded addresses for each participant at age 11, multiple indicators of neighborhood disadvantage from the U.S. Census were combined. Magnetic resonance imaging (MRI) was used to collect anatomical images from these individuals in young adulthood (N=249; Mean age 19.53 years; SD = 1.11). Results

demonstrate a positive correlation between neighborhood disadvantage and right amygdala volume ($r(241) = .196$, $p < .002$). Likewise, a positive correlation between neighborhood disadvantage and left ($r(241) = .178$, $p = .006$) and right ($r(241) = .178$, $p = .005$) thalamus volume was observed. There were no significant correlations between neighborhood disadvantage and hippocampal volume. These findings suggest neighborhood disadvantage can impact brain structures that are important for healthy emotional function.

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Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

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Program #/Poster #: 281.06/C36

Topic: A.09. Adolescent Development

Support: NIH/NIAAA 1R01AA01998301

Title: Differential brain response between OPRM1 genotypes to reward feedback during early adolescence

Authors: *V. C. MUCCIARONE[1], R. A. SCHROEDER[1], B. W. STEVENS[1], D. H. FISHBEIN[2], J. W. VANMETER[1]
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Abstract: Adolescence is a developmental period characterized by greater risk-taking and reward-seeking behaviors, influenced by both environmental and genetic factors. The single nucleotide polymorphism (SNP) rs1799971 in the μ-opioid receptor (OPRM1) gene has been implicated in reward processing (Ray et al., 2014) and substance use disorders (Miranda et al., 2010), where the minor G-allele is implicated in higher risk. Few studies have investigated the effects of this SNP on adolescent reward processing, and no studies have examined a substance-naïve population. To assess the effect of this allelic variation on reward processing before exposure to drugs and alcohol, we analyzed blood oxygen level-dependent (BOLD) response during a Wheel of Fortune (WoF) functional MRI task, as well as moderation by family history of alcohol use/abuse and beliefs about substance use.
Participants were typically developing, alcohol and drug naïve youth aged 11-13, N = 115 (25 AG; 63 F), enrolled in the Adolescent Development Study, a prospective longitudinal neuroimaging study of substance use in adolescents. BOLD signal was acquired during the WoF task on a Siemens 3T scanner. Image preprocessing and analysis were conducted in SPM8. Adolescents completed a survey querying beliefs about alcohol use. Parents reported on family

history of alcohol use/abuse via a family tree questionnaire.
A whole brain analysis of activation patterns during feedback for winning versus losing trials in the WoF task revealed a significant cluster of activation (466 voxels, p = 0.019 FWE cluster-corrected) in the right middle frontal gyrus (MFG; peak 24, 28, 44) for AA homozygotes greater than AG heterozygotes. This region is involved in goal planning (Fincham et al., 2002) and attention to positive emotions (Kerestes et a., 2012), possibly implying greater reflection on positive reward feedback in the AA homozygotes compared to G-allele carriers. The reduced MFG response to reward in the G-allele carriers suggests that they are less stimulated by natural reward.
No significant difference was found in family history of alcohol use/abuse. However, a significant difference (p = 0.002) was found in the adolescents' beliefs about parental alcohol consumption, such that G-allele carriers believed their parents drank more alcohol than AA homozygotes believed of their parents. Taken together, results showing a heightened awareness of parental alcohol consumption and decreased brain response to reward, suggest G-allele carriers may be at increased risk for substance use disorders.

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Poster

281. Adolescent Development: Human Imaging

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Program #/Poster #: 281.07/C37

Topic: A.09. Adolescent Development

Support: NIH Grant 5U01MH108168-03

Title: fMRI activation predicts depressive episodes in highly -comorbid adolescents

Authors: *I. FROSCH[1], N. A. HUBBARD[1], M. GONCALVES[1], V. SILESS[2], J. WANG[2], G. VERGARA[3], K. CONROY[4], C. BAUER[1], F. VAZ DE SOUZA[5], J. R. KACZMARZYK[1], I. ROSSO[3], D. HISCHFELD-BECKER[5], A. HENIN[5], S. HOFMANN[4], D. PIZZAGALLI[3], S. GHOSH[1], R. AUERBACH[6], A. YENDIKI[2], J. D. E. GABRIELI[1], S. WHITFIELD-GABRIELI[1]
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Abstract: Depression is one of the most common psychiatric illnesses among adolescents. There is a high rate of comorbidity with depression and anxiety in adolescence, and often overlapping symptomatology between these disorders. Heterogeneity within depressive samples is a likely contributor to the current lack of reliable neural markers of depression during adolescence. Here,

we assessed the degree to which activation information from task fMRI can accurately predict a current major depressive episode (MDE) in a sample of anxious and depressed adolescents (ages 14-15). We recruited two comorbid patient groups: (1) all participants had a current MDE, but also many had comorbid anxiety disorders (e.g., generalized anxiety disorder); (2) all participants had an anxiety disorder, and many also had previous diagnoses of MDEs. Participant diagnoses were classified in a diagnostic interview. Targeting overlapping and comorbid groups of adolescents allowed our sample to closely resemble typical adolescent psychiatric populations and to differentially predict MDEs from two diagnostically-similar groups. Single-layer neural networks were trained to predict (1) whether adolescents had a current MDE; or (2) a continuous variable of depressive symptom severity (via the Mood and Feelings Questionnaire [MAFQ]). Blood-oxygen-level dependent (BOLD) activation data from voxels in three regions-of-interest (amygdalae, striatum, and middle frontal gyrus) were gathered from three tasks targeted to elicit activation in one of these regions. Neural networks modeling BOLD data showed exceptional accuracy in predicting MDEs (*K*-fold out-of-sample Accuracy = 93.3%) and depressive symptom severity (*K*-fold out-of-sample R^2 = .564). The neural network using BOLD data showed greater predictive accuracy for MDEs compared to models using the MAFQ (*K*-fold out-of-sample Accuracy = 71.4%), and models using additional anxiety and depression self-report measures (*K*-fold out-of-sample Accuracy = 85.7%). These preliminary results (*N* = 43) demonstrated that task fMRI can provide a useful tool, beyond that of standard diagnostic rating scales, to identify current depression in adolescents.

Disclosures: I. Frosch: None. **N.A. Hubbard:** None. **M. Goncalves:** None. **V. Siless:** None. **J. Wang:** None. **G. Vergara:** None. **K. Conroy:** None. **C. Bauer:** None. **F. Vaz De Souza:** None. **J.R. Kaczmarzyk:** None. **I. Rosso:** None. **D. Hischfeld-Becker:** None. **A. Henin:** None. **S. Hofmann:** None. **D. Pizzagalli:** None. **S. Ghosh:** None. **R. Auerbach:** None. **A. Yendiki:** None. **J.D.E. Gabrieli:** None. **S. Whitfield-Gabrieli:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.08/C38

Topic: A.09. Adolescent Development

Support: NIH Grant MHO98348

Title: Alterations in gray matter volume of the prefrontal cortex, hippocampus, and amygdala persist into adulthood following alcohol, tobacco, and cannabis use during adolescence

Authors: *J. B. PURCELL[1], N. G. HARNETT[1], S. MRUG[1], M. N. ELLIOTT[2], S. TORTOLERO EMERY[3], M. A. SCHUSTER[4], D. C. KNIGHT[1]

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Abstract: Alcohol, tobacco, & cannabis are the most commonly used substances during adolescence (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2017). In fact, approximately 61%, 28%, and 45% of adolescents report using alcohol, tobacco, & cannabis, respectively, by grade 12. Given the relatively rapid brain development occuring at this age, (Toga, Thompson, & Sowell, 2011), adolescence may represent a particularly sensitive period to the deleterious effects of alcohol, tobacco, & cannabis use. Evaluating gray matter volume in young adulthood can provide indirect information about whether substance use disrupts brain development and maturation (Jacobus & Tapert, 2014). Therefore, the present study investigated whether adolescent alcohol, tobacco, or cannabis use varies with gray matter volume within the prefrontal cortex, hippocampus, and amygdala as young adults. A community sample of adolescents were interviewed prospectively (at ages 11, 13, 16 & 19) regarding their use of alcohol, tobacco, & cannabis. Following the final assessment, participants completed a single magnetic resonance imaging (MRI) scanning session. Anatomical images were obtained using a 3T Siemens Allegra MRI scanner. Analyses were completed using AFNI (Cox, 1996) and FreeSurfer software packages (Fischl, 2012). Anatomical information about cortical and subcortical structures was obtained from FreeSurfer and was output into SPSS for further analysis. Frequency of binge drinking was associated with increased volume of the left hippocampus and amygdala ($r = 0.168$, $p < 0.05$; $r = 0.195$, $p < 0.05$, respectively) in males, but not females. Within the right hemisphere, frequency of binge drinking was negatively correlated with ventromedial prefrontal cortex volume (vmPFC; $r = -0.231$, $p < 0.01$). Sex differences in neural development may account for the observed differences in the effects of binge drinking. Further, there was a significant negative correlation between the number of cigarettes smoked and bilateral hippocampal and amygdala volume (L hippocampus: $r = -0.137$, $p < 0.05$; R hippocampus: $r = -0.128$, $p < 0.05$; L amygdala: $r = -0.158$, $p < 0.05$; and R amygdala: $r = -0.145$, $p < 0.05$). Similarly, there was a significant negative correlation between the number of cigarettes smoked and bilateral vmPFC volume (left hemisphere: $r = -0.158$, $p < 0.01$; right hemisphere: $r = -0.114$, $p < 0.05$). There were no associations between frequency of cannabis use and cortical or subcortical volume. These findings suggest substance use during adolescence, particularly alcohol and tobacco use, influence the neural development of the amygdala, hippocampus, and ventromedial prefrontal cortex.

Disclosures: J.B. Purcell: None. **N.G. Harnett:** None. **S. Mrug:** None. **M.N. Elliott:** None. **S. Tortolero Emery:** None. **M.A. Schuster:** None. **D.C. Knight:** None.

Poster

281. Adolescent Development: Human Imaging

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.09/D1

Topic: A.09. Adolescent Development

Support: NIH Grant P20GM109097

Title: Parental involvement predicts posterior ínsula hemodynamic activation in response to child's costly error

Authors: *E. L. RATLIFF[1,2], K. T. COSGROVE[2,3], K. L. KERR[1,2], D. C. DEVILLE[2,3], K. BURROWS[2], A. MOORE[2,1], J. BODURKA[2,4], W. K. SIMMONS[5], A. S. MORRIS[2,1]
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Abstract: Parental involvement, including attention, awareness, and supervision, strongly influences connectedness and trust in the parent-child relationship. Parental involvement has been implicated in studies of parental emotional responsiveness and warmth, with higher levels related to greater parental responsiveness to a child's emotional distress. Additionally, neuroimaging studies have found that activation in the insular cortices of mothers is associated with levels of maternal responsiveness and empathetic reactions to their infant's expressions of emotional distress (Lenzi et al., 2008). This association has yet to be examined in adolescents; therefore, we sought to assess the association between adolescent reports of parental involvement and empathy-related activation in the insular cortices of parents. The current study examined this association in the context of parent-adolescent interactions using fMRI hyperscanning (e.g., simultaneous fMRI scanning of two interacting participants using identical MRI scanners). Twenty-one psychiatrically healthy, control parents (*Mean* age = 43 years, 90% female) and their adolescent children (*Mean* age = 15 years, 62% female) were included in this study. Prior to the scan, parents and adolescents completed a battery of measures assessing parent-adolescent relationship quality, emotion awareness, and parenting styles and techniques. During the scan, parents and adolescents participated in the Testing Emotional Attachment and Mutuality (TEAM) task, which is a collaborative game intended to examine brain activity when either member of the dyad makes a costly error. The TEAM task includes several fixed trials in which each member of the dyad believes the other member has made an error, costing the dyad $5. A one-sample t-test with parental involvement scores (as rated by their adolescent) entered as a covariate in AFNI's 3dttest++ program was used to examine the relationship between parental involvement and parent's brain responses to their child's costly error. Adolescent reports of lower levels of parental involvement were found to be associated with bilaterally decreased hemodynamic activation in the posterior insula of parents ($p < .005$). Activity in the posterior insula has been associated with perceptions of other's pain, suggesting a role in empathetic reactions. The findings provide initial evidence for the neural basis of parents' empathetic reactions to their adolescents' costly errors and reveal how activity in the recruited regions relates to their child's perceptions of parental involvement.

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Poster

281. Adolescent Development: Human Imaging

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Program #/Poster #: 281.10/D2

Topic: A.09. Adolescent Development

Support: NIH Grant P20GM109097

Title: The relationship between brain activation during parent-child fMRI hyperscanning and symptoms of anxiety and depression

Authors: *K. T. COSGROVE[1,2], D. C. DEVILLE[1,2], K. L. KERR[3,1], E. L. RATLIFF[3,1], K. BURROWS[1], A. J. MOORE[1], S. F. TAPERT[4], M. MISAKI[1], J. BODURKA[1,5], R. L. AUPPERLE[1,2], W. K. SIMMONS[1,6], A. S. MORRIS[1,3]
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Abstract: A reciprocal relationship exists between children's emotion regulation (ER) abilities and those of their parents. A parent's ER and mental health symptoms can alter how a child learns to modulate their own distress. Conversely, children's mental health symptoms may lead to parent ER difficulties. The medial prefrontal cortex (mPFC) has been implicated in ER processes, including the appraisal of errors and receipt of negative feedback. However, it remains largely unknown how mPFC activity within parent-child dyads may relate to one another's mental health.

In an ongoing study, we use hyperscanning fMRI with parents (N = 22, mean age = 43, 91% female) and their adolescent children (N = 25, mean age = 15, 64% female). All subjects are psychiatrically healthy and right-handed. While undergoing simultaneous fMRI scans, the parent-adolescent dyads play the Testing Emotional Attachment and Mutuality task. In this task, subjects experience feigned error conditions in which it appears the other person made a mistake, costing the dyad five dollars. AFNI's 3dttest++ was used to examine adolescents' and parents' mPFC BOLD activation during feigned error conditions and how this related to the other dyad-member's mental health symptoms (voxelwise $p < 0.005$).

Decreased parent mPFC activity was associated with higher anxiety in adolescents. Greater adolescent mPFC activity was associated with higher depression in parents. Furthermore, measures of parent and adolescent mental health symptoms were not related. However, there was a significant negative correlation between parent and adolescent mPFC percent signal change during the feigned error condition.

These findings provide neurobiological support for the idea that ER is developed within a dyadic parent-child context. Parent ability to recruit mPFC regions when confronted with their child's

error may represent an adaptive brain response that contributes to decreased adolescent anxiety. Adolescents with more depressed parents exhibit increased mPFC activation when confronted with their parents' errors, potentially as a compensatory response to parent ER disruptions. Future longitudinal investigations could be used to identify causal relationships between parent-child neural responsivity and ER.

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Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.11/D3

Topic: A.09. Adolescent Development

Support: NSF GRFP

Title: Developmental, cognitive, and gender correlates of dynamic functional brain connectivity

Authors: *B. ROSENBERG, E. MENNIGEN, R. KAISER
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Abstract: BACKGROUND: Resting-state functional connectivity (rsFC) has traditionally identified *static* properties of brain networks over long periods of time. Prior research has showed that magnitude or spatial extent of static networks correspond with individual differences in development or cognitive functioning. Recently, scientists have become interested in how patterns of network connectivity exhibit *dynamic* changes on a shorter timescale. As these measures have a unique capacity to highlight network integration and coordination, they may provide novel insights into brain network functioning. Given that individuals consistently exhibit differences in static rsFC as a function of age, gender, and task performance, the present study assessed if these variables also relate to dynamic rsFC. METHODS: This study used resting-state data on 26 subjects (ages 8-75) from the Human Connectome Project. Data were analyzed using the Group ICA of fMRI Toolbox. This approach yielded spatially distinct components that covaried in their levels of activation over time. Next, the timeseries was separated into sliding windows, and patterns of rsFC among these components for each sliding window were estimated. Finally, patterns were clustered into network states and mean dwell time (MDT; average time in each state before switching to another state) was estimated. Group-level analyses were performed on all five states to explore differences in MDT based on gender, age, and working memory (WM) task performance. RESULTS: Analysis yielded five brain connectivity states; group-level analyses revealed significant effects for States 2 and 5. State 2 was defined by

positive rsFC among regions of the prototypical default network, including the precuneus and angular gyrus, and negative rsFC between bilateral insula and both the precuneus and angular gyrus. State 5 was defined by positive rsFC among regions involved in visual processing, including occipital regions, bilateral lingual gyrus, and bilateral fusiform gyrus; positive rsFC between occipital regions and areas of superior parietal lobule; and negative rsFC between occipital regions and inferior frontal gyrus. Group-level analyses revealed a main effect of gender on MDT for State 2 (male > female), which was moderated by both age and WM task performance. Analyses did not detect gender or age differences in State 5 MDT, but there was a main effect of task performance in which greater N-Back accuracy predicted lower MDT. DISCUSSION: These results suggest that dynamic rsFC may underlie or reflect individual differences in cognitive functioning, as well as sex-specific differences in the development of functional brain networks.

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Poster

281. Adolescent Development: Human Imaging

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.12/D4

Topic: A.09. Adolescent Development

Support: JSPS KAKENHI 16H06396
JSPS KAKENHI 16H06398
JSPS KAKENHI 16H06399

Title: Sex-dependent effects of child-parent relationships on resting-state functional connections in early adolescence

Authors: *T. ITAHASHI[1], N. OKADA[2], S. ANDO[2,5], S. YAMASAKI[5], D. KOSHIYAMA[3], K. MORITA[2], N. YAHATA[6], S. KOIKE[7,2], A. NISHIDA[5], K. KASAI[4], R.-I. HASHIMOTO[1,8]
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Abstract: Boys and girls exhibit different trajectories of brain development especially during adolescence. Prior studies have mainly examined sex-related differences in intrinsic functional

connections (FCs) and its interaction with age. Although the child-parent relationship plays critical roles in the child's brain development, no studies have investigated how the child-parent relationships influence on boy's and girl's brain differentially in adolescence. Furthermore, relationships with father and mother may impact on the child's brain differently. To investigate sex-dependent effects of mother- and father-child relationship on child's FCs we analyzed a cohort dataset of early adolescence that included resting-state fMRI data and questionnaires. For the evaluation of child-parent relationship, we used part of the Network Relationships of Inventory (NRI) that assessed child's positive relationships with his/her father and mother separately. In addition, the Child Behavior Checklist (CBCL) was used to assess child's behavioral symptoms. After data quality control, we used 93 children (52 girls; age [mean ± SD]: 11.96 ± 0.79). For each child, FC matrix was created using a 273 whole brain atlas. To examine the effect of NRI and its interaction effect with sex separately for father and mother, we fitted a general linear model that included NRI score, sex, interaction term of NRI and sex, and other nuisance covariates. Statistical analyses revealed that the child-father relationship was associated with FCs between right fronto-parietal (FP) and default mode networks (DMN), while the child-mother relationship was associated with FCs between the limbic and primary sensorimotor networks (P &lt 0.05, corrected). Furthermore, the interaction effects were observed mainly in FCs between right FP and other networks such as DMN and orbitofrontal network.Using the identified FCs, we built a connectome-based predictive model (CPM) with leave-one-out cross validation for the severity of behavioral symptoms. CPM revealed a separate pattern of correlations with subscales of CBCL for boys and girls: boy-specific correlations were found in rule-breaking behavior ($r = 0.36$, $P = 0.01$), aggressive behavior ($r = 0.43$, $P = 0.002$), and externalizing problems ($r = 0.41$, $P = 0.004$), whereas girl-specific correlations were found in anxious/depressed ($r = 0.32$, $P = 0.01$) and internalizing problems ($r = 0.32$, $P = 0.01$). These results suggest that the father- and mother-child relationships differentially affect FCs and identified FCs have a potential for predicting the severity of externalizing problems for boys and that of internalizing problems for girls differentially.

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Poster

281. Adolescent Development: Human Imaging

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Program #/Poster #: 281.13/D5

Topic: A.09. Adolescent Development

Support: R37MH101495

Title: Differential effects of pubertal development on changes in white matter microstructure in adolescent boys and girls

Authors: *T. C. HO[1], K. OSKIRKO[1], N. L. COLICH[3], J. K. LEONG[2], I. H. GOTLIB[1]
[1]Psychology, [2]Stanford Univ., Stanford, CA; [3]Psychology, Univ. of Washington, Seattle, WA

Abstract: Adolescence is the transition between childhood and adulthood; it is a key developmental window during which significant psychosocial and biological changes occur. There is rapid brain development during adolescence that is attributed, in part, to surges in gonadal hormones (Dahl & Spear, 2004; Spear, 2010). Data from animal studies suggest that these hormones affect axonal myelination and the growth of astrocytes (Yates & Juraska, 2008; Chowen et al., 2000). Further, recent work has documented sex-specific effects in long-range white matter tracts terminating in frontal cortex (Herting, 2011; Tamnes, 2017). To date, however, there have been no longitudinal investigations of the effects of sex hormones and white matter tract development. Here, we acquired T1-weighted MRI, diffusion-weighted MRI (60 directions) at two timepoints from 52 females (11.05±1.03 years at Time 1; 12.77±1.31 years at Time 2) and 31 males (ages 12.01±0.87 years at Time 1; 13.9±0.92 years at Time 2) who were matched on pubertal development at Time 1. On the morning of each participants' scans, we also collected saliva samples to assay levels of testosterone (in males) and estradiol (in feamles). All data were preprocessed according to standard protocols (Ho et al., 2017). We used Automated Fiber Quantification (AFQ) to segment 8 major white matter tracts and to estimate diffusivity metrics for each tract (Yeatman et al., 2012). We conducted separate linear regressions to predict the rate of change in fractional anisotropy (FA) of each white matter tract from the rate of change in gonadal hormone levels and age at Time 1. We found, in females only, that increases in estradiol were significantly associated with changes in FA of tracts terminating in frontal cortex (all t's>1.78, p's<0.01); changes in estradiol were not significantly associated with FA of posterior tracts (all t's<0.79, p's>0.44). There were no associations between changes in testosterone and changes in FA of any of the 8 tracts (all t's<0.10, p's>0.9). Our findings suggest that there are sex-specific effects of FA on white matter development in tracts terminating in frontal cortex during adolescence that may be explained by changes in levels of estradiol.

Effects of change in estradiol (accounting for age and Tanner) on FA in females

	B ± SE	t(df)	p-value
Callosum Forceps Minor	0.017 ± 0.006	t(37)=2.78	p=0.009**
Left IFOF	0.017 ± 0.006	t(37)=1.72	p=0.01*
Right IFOF	0.018 ± 0.005	t(38)=3.22	p=0.002***
Left Uncinate	0.016 ± 0.005	t(33)=3.19	p=0.003***
Right Uncinate	0.006 ± 0.004	t(38)=1.57	p=0.126
Left Cingulum	0.021 ± 0.007	t(31)=2.80	p=0.009***
Right Cingulum	0.029 ± 0.01	t(31)=2.81	p=0.008***
Callosum Forceps Major	0.008 ± 0.009	t(35)=0.79	p=0.44

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Poster

281. Adolescent Development: Human Imaging

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.14/D6

Topic: A.09. Adolescent Development

Support: William T. Grant Foundation
National Science Foundation Graduate Research Fellowship Program

Title: Representational differentiation in the amygdala to faces relates to trustworthy judgments in adolescents

Authors: *S. M. TASHJIAN, J. F. GUASSI MOREIRA, A. GALVÁN
UCLA, Los Angeles, CA

Abstract: Judgments of trustworthiness are a common aspect of social interaction and are important for determining approach and avoidance behavior. During adolescence, socioemotional skills undergo significant development due to structural and functional changes in the brain. Although prior human neuroimaging work identifies the amygdala as an important neural region underpinning the evaluation of facial expressions, less is known about the evaluation of trustworthiness during the developmental period of adolescence. Prior work suggests impaired trust learning may be associated with risk of assault in adolescents (Lenow et al., 2014), highlighting the importance of understanding neural systems that contribute to trustworthy judgments.

Using representational similarity analyses (RSA; Kriegeskorte et al., 2008; Lee et al., 2017), we assessed individual differences in amygdala differentiation of faces at poles of a trustworthy continuum and examined how this differentiation related to judgments of trustworthiness for ambiguous faces at the middle of the continuum. During functional magnetic resonance imaging, 46 adolescents (M_{age} = 15.85, 26 female) made binary judgments (trustworthy, not trustworthy) for each face image presented in a randomized series. Faces varied along established dimensions of trust (Todorov et al., 2008) yielding stimuli ranging in trustworthy valence from 1-7 (least to most trustworthy).

Behavioral discrimination index scores were calculated for each participant representing one's tendency to classify faces as trustworthy or not during the task. Higher scores indicated a greater propensity to judge faces as trustworthy. Discrimination scores for faces at the low end of the continuum were significantly lower than scores at the high end of the continuum, $p < .001$.

We examined individual differences in amygdala sensitivity during evaluation of diametric faces and subsequently related those differences to discrimination scores of ambiguous faces. RSA was conducted for voxel-wise bilateral amygdala (anatomically defined) activation to faces at the poles of the trustworthy continuum using CoSMoMVPA (Oosterhof et al., 2016). Participants with greater similarity (e.g., less differentiation) to faces ranked as low and high on the trustworthy continuum rated ambiguous faces in the middle of the continuum as more trustworthy, $p < .05$. These findings indicate that a lack of amygdala differentiation to subtle changes in trustworthiness is associated with more positively biased judgments in response to social ambiguity during adolescence.

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Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.15/D7

Topic: A.09. Adolescent Development

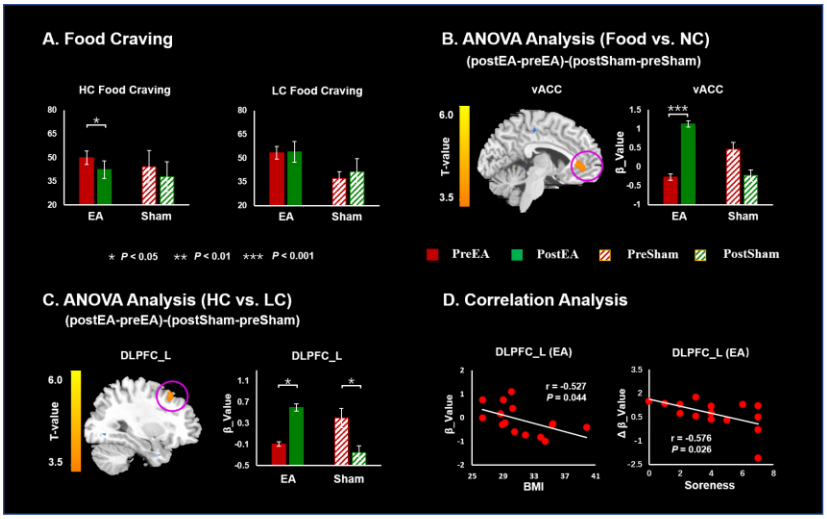
Support: NSFC Grant 81501543

Title: Acute electroacupuncture modulates the fronto-limbic system in overweight/obese patients during food and neutral cues fMRI task

Authors: Y. REN†[1], M. XU†[2], X. LI[1], W. ZHANG[1], *Y. ZHANG[2], K. VON DENEEN*[2]
[1]Xi'an Traditional Chinese Med. Hosp., Shaanxi Univ. of Chinese Med., Xi'an, China; [2]Sch. of Life Sci. and Technol., Xidian Univ., Shaanxi, China

Abstract: Electroacupuncture (EA) affects the neurophysiology in overweight/obese populations, curbing appetite and decreasing cravings. Our study evaluated overweight/obese Chinese patients' responses to a food-cue functional-magnetic-resonance-imaging (fMRI) task after receiving standard weight-loss EA (n = 15, 5M/10F) and Sham stimulation (n = 7, 3M/4F) using clinical measures (YFAS, SDS, SAS, STAI (SAI, TAI)) and high-calorie (HC)/low-calorie (LC) food-cue stimuli which consisted of 88 unique HC, 88 LC food pictures and 88 neutral pictures selected from IAPS and others. The stimulation consisted of 3 HC, 3 LC and 3 neutral pictures blocks presented in a pseudorandom order. Each block lasted 30 seconds, during which 10 pictures were presented for 3 seconds each without inter-trial interval. There were 30 seconds between blocks. At baseline, there were no significant differences in these demographic/clinical measures between EA/Sham groups. ANOVA showed significant time effect only for HC food-craving ($F = 8.89$, $P = 0.007$) (Fig 1). There was only significant reduction in HC food-craving in EA group ($t = -2.25$, $P = 0.041$). There were significant interaction effects (group × time) on brain responses to food vs. neutral (NC) cues in the ventral anterior cingulate cortex (vACC) (*P*

< 0.001) due to significant increased activation in EA group (t = 5.31, *P* < 0.001), and HC vs. LC food cues in the left DLPFC (*P* < 0.001) due to significant increased activation in EA group (t = 2.83, *P* < 0.05) and reduction in Sham group (t = -3.49, *P* < 0.05). At baseline, there were significant negative correlations between DLPFC activation and BMI (*P* = 0.044, r = -0.53), and soreness (*De-qi*) was negatively correlated with changes in DLPFC activation (*P* = 0.026, r = -0.58) in EA group. Psycho-physiological interaction analysis was further employed to depict the regional connectivity, but we did not obtain any significant results. Most importantly, this study revealed the neuromechanism how EA is associated with food craving via the fronto-limbic system.



Disclosures: Y. Ren†: None. **M. Xu†:** None. **X. Li:** None. **W. Zhang:** None. **Y. Zhang:** None. **K. von Deneen*:** None.

Poster

281. Adolescent Development: Human Imaging

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Program #/Poster #: 281.16/D8

Topic: A.09. Adolescent Development

Support: NSFC Grant 81501543

Title: Acute electroacupuncture modulates the somatosensory and mesocorticolimbic dopamine systems in overweight/obese patients during resting state

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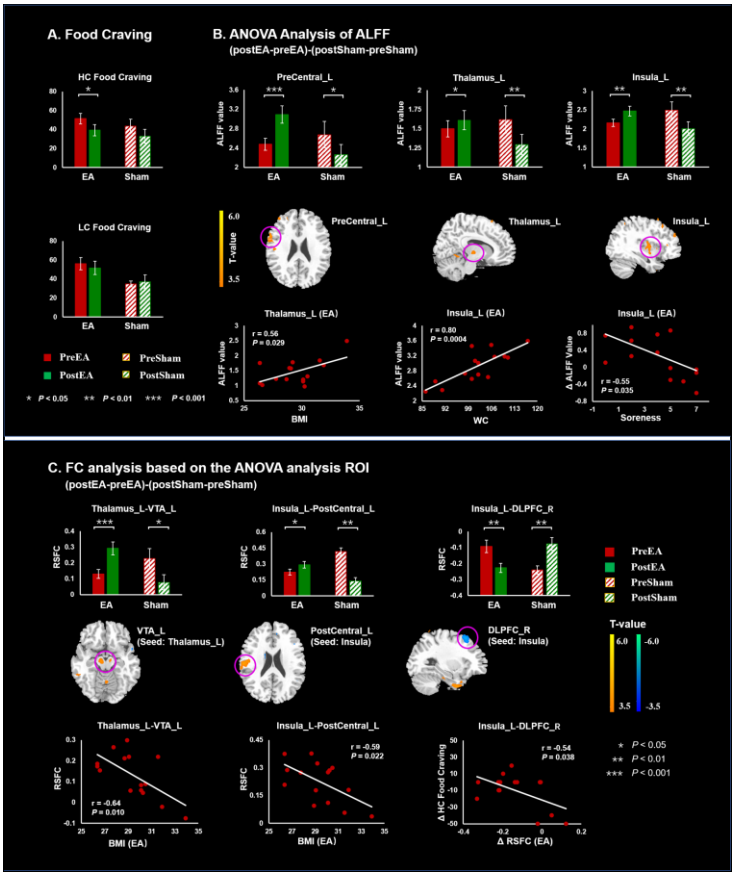
Abstract: Obesity is a worldwide epidemic with few alternative treatment methods, but electroacupuncture (EA) is effective in managing it. We compared acute effects during resting-state functional magnetic resonance imaging (fMRI) between overweight/obese patients who received weight-loss EA (n=15, 5M) and Sham stimulation (n=7, 3M) using amplitude of low-frequency fluctuation (ALFF) and clinical measures (YFAS, SDS, SAS, STAI). At baseline, there were no differences in these clinical measures between EA/Sham groups. De-qi sensations were all significant between EA/Sham groups (P<0.05) except for coolness/sharp pain (P>0.05). Hunger was not significant between EA/Sham groups (P=0.18). Significant difference existed in food craving in response to high-calorie (HC) food cues post-EA (t=-2.26, P=0.041) (Fig 1). Significant interaction effects (group × time) for ALFF were in left precentral gyrus, thalamus and insula (P<0.001). EA increased and sham decreased ALFF in these three regions. At baseline, BMI correlated with ALFF in thalamus (P=0.029, r=0.56); same for waist circumference (WC) and ALFF in left insula (P<0.001, r=0.80); and soreness (*De-qi*) was negatively correlated with change in ALFF in left insula (P=0.035, r=-0.55). Significant (group × time) interaction effects on resting-state functional connectivity (RSFC) existed between left thalamus seed and ventral tegmental area (VTA), and between left insula seed and postcentral/dorsolateral prefrontal cortex (DLPFC) (P<0.001). Post-hoc test showed EA increased thalamus-VTA and insula-postcentral gyrus connectivity and decreased the insula-DLPFC connection. At baseline, BMI was significantly negatively correlated with thalamus-VTA connectivity (P=0.010, r=-0.64) and insula-postcentral gyrus connectivity (P=0.022, r=-0.59), and changes in craving for HC food were negatively correlated with insula-DLPFC (P=0.038, r=-0.54). These results depict the neuromechanism that EA modulates the insula/thalamus via somatosensory connections along with VTA via the mesocorticolimbic dopamine system.



Disclosures: M. Xu: None. **Y. Ren†:** None. **W. Zhang:** None. **X. Li:** None. **Y. Zhang:** None. **K. von Deneen*:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.17/D9

Topic: A.09. Adolescent Development

Support: EEF Grant Ref. 2681

Title: Physical health and active lifestyle in 12-year-old children is linked with brain measures

Authors: *P. SALVAN[1], T. WASSENAAR[1], C. WHEATLEY[1], N. BEALE[2], H. DAWES[2], H. JOHANSEN-BERG[1]
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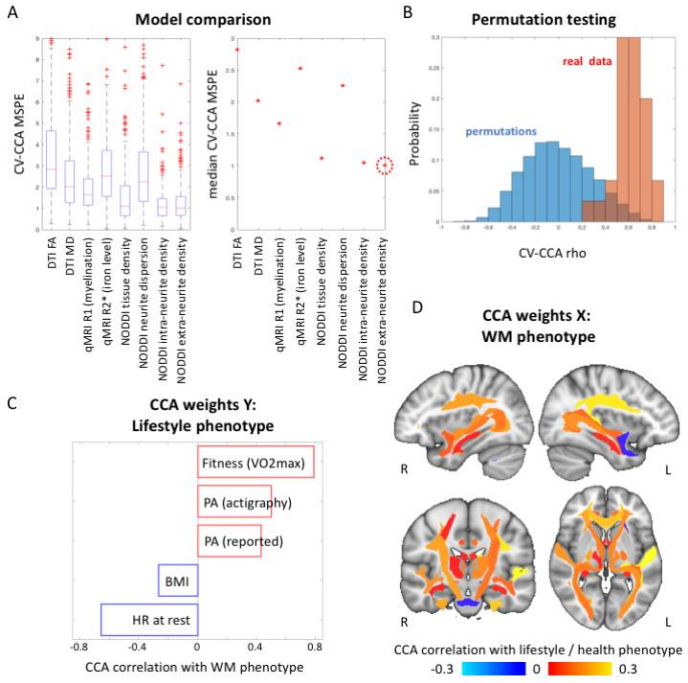
Abstract: Current research suggests that regular physical activity (PA) and aerobic fitness are associated with better cognitive performance and variation in brain measures. However, in children the cross-sectional brain correlates of physical activity and fitness are still poorly characterized. Here we tested the hypothesis that physical activity and fitness in 12-years-old children co-vary with white-matter (WM) microstructure. In 50 pupils, we acquired measures of fitness (via VO2max testing); objective week-day PA (via wrist-worn accelerometers); reported number of days performing at least 60min of moderate-to-vigorous PA; body mass index (BMI); heart rate (HR) at rest; together with multimodal-MRI. We performed automatic probabilistic tractography to reconstruct 29 major WM tracts and quantified distinct microstructural parameters. WM parameters and lifestyle measures were adjusted for age; sex; pubertal developmental level; socioeconomic score; whole-brain volume. Model comparison of the association between each WM parameter and lifestyle/health measures was carried out using cross-validated canonical correlation analysis (CV-CCA) and Monte Carlo repetitions (MCR). The model with lowest mean squared prediction error (MSPE; median value across MCR) was then selected (Fig. 1A) and tested against permutations in order to assess statistical significance (Fig. 1B). We found that the best model significantly linked WM microstructure with a positive lifestyle/health phenotype (CV-CCA results: rho = 0.64; p-value = 0.0115; MSPE = 1.0146; p-value = 0.0080; median values across MCR and compared against 1,000 permutations). In this covariation mode, higher fitness, regular exercise, lower BMI and lower HR at rest (Fig. 1C), were associated with greater WM extra-neurite density (Fig. 1D). These findings provide novel insight into the relationship between variation in lifestyle and physical health and measures of WM microstructure. This work may inform future intervention and rehabilitation studies aimed to foster healthy neurodevelopment throughout the life-span.



Disclosures: P. Salvan: None. **T. Wassenaar:** None. **C. Wheatley:** None. **N. Beale:** None. **H. Dawes:** None. **H. Johansen-Berg:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.18/D10

Topic: A.09. Adolescent Development

Support: NIH 5U01DA041022-04 (SRI)
NIH U01DA041028 (Pittsburgh)

Title: Typical total sleep time is associated with intra- and inter- resting-state network functional connectivity in 9-10 year olds

Authors: *A. GOLDSTONE[1], S. A. CLAUDATOS[1], L. ROSAS[1], V. ALSCHULER[1], Y. LIM[1], M. GIL[1], M. DE ZAMBOTTI[1], D. B. CLARK[2], B. P. HASLER[2], D. E. PROUTY[1], I. M. COLRAIN[1,3], F. C. BAKER[1,4]
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Abstract: The brain undergoes substantial developmental changes during childhood and adolescence, the full extent of which remains unknown. Sleep has been associated with waking resting-state network (RSN) functional connectivity (FC) strength in adults, but it remains to be seen how sleep may affect RSN FC in youth. Here we used data from the first year of The Adolescent Brain Cognitive Development (ABCD) study, which is the largest multi-site, longitudinal study of brain development to date. Baseline data from 3947 participants (1892 female, aged 9-10 years) are included in this analysis. All participants underwent an MRI session, using either a GE, Siemens or Philips scanner (depending on study site). The scanning protocol was the same across sites and included up to four ~5-minute resting-state fMRI scans, from which FC measures were derived. A seed-based approach calculated FC between each region-of-interest pair, derived from a number of cortical networks. FC was then averaged across pairs within (intra) and between (inter) networks to create average network FC measures. A measure of 'typical' total sleep time (TST) (i.e. number of hours slept on most nights in the past six months) was obtained from the Parent Sleep Disturbance Scale. We identified that shorter sleepers (<7 h sleep per night) had significantly weaker intra-RSN FC for default-mode (DMN), cingulo-opercular (CO), dorsal attention (DAN), retrosplenial temporal (RST), ventral attention (VA), visual and motor networks compared to longer sleepers (9-11 h sleep per night). Similarly, shorter sleepers exhibited weaker salience (SN)-DMN and SN-fronto-parietal (FPN) inter-network FC. Follow-up regression models identified that shorter TST significantly predicted

lower RSN FC, after controlling for ethnicity, sex, race, scanner, and parent's highest level of education. Models accounted for 2-17% of the variance in RSN FC, depending on the network investigated. We provide evidence that typical night-time TST, assessed by parent-report, predicts RSN FC in 9-10 year olds, with shorter TST associated with weaker FC. Notably, the association between TST and RSN FC was network-specific, rather than brain wide, suggesting that sleep is important for maintaining connectivity within specific cortical networks. Furthermore, sleep may be particularly important for maintaining coherence between the SN and other cortical regions. Future longitudinal analysis of ABCD data will allow investigation of whether TST and other sleep characteristics mediate RSN development across adolescence.

Disclosures: A. Goldstone: None. **S.A. Claudatos:** None. **L. Rosas:** None. **V. Alschuler:** None. **Y. Lim:** None. **M. Gil:** None. **M. de Zambotti:** None. **D.B. Clark:** None. **B.P. Hasler:** None. **D.E. Prouty:** None. **I.M. Colrain:** None. **F.C. Baker:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.19/D11

Topic: A.09. Adolescent Development

Support: CONACyT 619683/330142

Title: Inverse relationship between homotopic and intra-hemispheric asymmetry of intrinsic brain functional connectivity in school-age children

Authors: *Z. GRACIA TABUENCA[1], M. B. MORENO[2], F. A. BARRIOS[2], S. ALCAUTER[2]
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Abstract: Hemispheric specialization is a dynamic process along age and unbalanced functional asymmetries are related with developmental disorders such as dyslexia. In order to improve the better understanding of normal and atypical development, this study focuses on characterizing the relationship between inter-hemispheric and intra-hemispheric functional connectivity in healthy school-age children.The sample consisted in 60 typically developing children (6-10 years old, 35 girls; mean age = 8.46, sd = 0.77 years old) with resting state functional MRI scans (TR=2s; 150 volumes). After standard preprocessing, five noise-based components (aCompCor) and movement-affected volumes (relative RMS &gt 0.25mm) were regressed out, and corregistered to a symmetric standard space.Functional connectivity (FC) was defined as the the Pearson correlation (R) between two voxels fMRI timeseries. For each subject, inter-hemispheric connectivity was computed as the FC between all possible pairs of ipsilateral voxels (i.e., homotopic FC). While intra-hemispheric asymmetry was calculated as the absolute asymmetry

index (ASI) of intra-hemispheric weighted degree (WD) for every pair of mirrored voxels. WD is a basic graph theory measure that computes the sum of connections above a threshold (R &gt 0.3 in this case), and ASI was computed as: (rWD-lWD)/(rWD+lWD); where rWD accounts for WD in right hemisphere and lWD for the left hemisphere. The relationship between both measures was assessed by the voxelwise correlation and the slope of the linear fit between asymmetry and homotopy, in both cases regressing out average head motion. Significance was defined as p-value &lt 0.05 after correction for multiple comparison, estimated with a permutation test with 5000 permutations.A widespread significant negative correlation was found between homotopy and asymmetry covering every area of the brain. Moreover, the averaged linear slope of this relationship was -1.00 (sd = 0.56).This study showed an inverse and significant relationship between inter-hemispheric and intra-hemispheric asymmetry of brain FC in the rest condition. These results emphasize that homotopic and inter-hemisperic asymmetry of FC interact in an opposite direction, suggesting that both processes may consolidate hemispheric specialization during development, and even work as a compensatory mechanism for any developmental disruption. These results will contribute to the better understanding of typical development.This research was supported by CONACyT 619683/330142.

Disclosures: Z. Gracia Tabuenca: None. **M.B. Moreno:** None. **F.A. Barrios:** None. **S. Alcauter:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.20/D12

Topic: A.09. Adolescent Development

Title: Preliminary evidence of the maturation of cortical inhibition from a TMS-evoked potential study

Authors: *C. P. WALKER[1], N. MURPHY[2], N. RAMAKRISHNAN[2], D. FRAHER[2], R. Y. CHO[3]
[1]Grad. Sch. of Biomed. Sci., Univ. Of Texas Hlth. Sci. Ctr. At Houst, Houston, TX; [3]Psychiatry, [2]Baylor Col. of Med., Houston, TX

Abstract: Background: Adolescence is a distinct developmental period marked by rapid changes in affective and motivational systems and comparatively slower maturation of higher-order cognition with adult levels reached around 25 years. Much of this slower development is attributed to the protracted course of inhibitory maturation in the prefrontal cortex. To measure this trajectory *in vivo*, we recorded electroencephalography (EEG) data from children and adolescents during transcranial magnetic stimulation (TMS) of the left prefrontal (PFC) and motor (MT) cortices. **Methods:** High density 64-channel EEG recordings were collected from a

sample of healthy children (n=2; 10-11 yrs) and adolescents (n=3; 15-17 yrs) during biphasic single pulse TMS. The stimulation intensity was set to 120% of resting motor threshold, determined by motor evoked potentials recorded from the first dorsal interosseous. This scalp location was set as the MT stimulation site. PFC stimulation was applied to the left dorsolateral prefrontal cortex by co-registering an MNI template to fiducial head locations. For both sites, the TMS coil was oriented tangential to the scalp at ~45 degrees from the mid-sagittal line. Artifacts were removed via 2-stage independent component analysis. Artifact free TMS-evoked potentials (TEP) were extracted from the cluster of electrodes immediately surrounding the stimulation sites. **Results:** Preliminary evidence suggests a fundamental restructuring of early TEP components with age. As recently reported (Määttä, et al., 2017), the N100 to MT was substantially reduced in adolescents compared to children. Nevertheless, the morphology of the TEP was largely intact. In the PFC, the N45 was found to be absent in children and present in adolescents. Furthermore, the latency of the N120 was found to peak later in children (~140ms) and a positive frontal potential with a peak at 100 ms was present when compared to adolescents. **Conclusions:** The emergence of the classic PFC TEP component structure is notable in this sample. The N45 and N100/N120 are associated with GABA-A and GABA-B neurotransmission, respectively (Premoli et al., 2014). In non-human primates, GABA-A receptors have been shown to shift from a predominance of α2 to α1 subunit compositions which supports faster inhibitory kinetics and high-frequency cortical oscillations. The N45 has been shown to be particularly sensitive to GABA-A agonists selective for the α1 subunit suggesting the a similar subunit shift may be occurring in humans. To our knowledge, this is the first study of its kind to investigate the EEG response to prefrontal TMS in children or adolescents.

Disclosures: C.P. Walker: None. **N. Murphy:** None. **N. Ramakrishnan:** None. **D. Fraher:** None. **R.Y. Cho:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.21/D13

Topic: A.09. Adolescent Development

Support: NIH Grant 3R01HD061414
NIH Grant RC2DA029475

Title: Developmental trajectories of MR diffusion parameters in major brain fiber tracts: A longitudinal study with multiple measurements from ages 5 to 12

Authors: *W. ZHAO[1], W. K. THOMPSON[3], N. AKSHOOMOFF[4], T. T. BROWN[2], A. M. DALE[5], T. L. JERNIGAN[2]
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Publ. Hlth., [4]Dept. of Psychiatry, [5]Ctr. for Multimodal Imaging and Genet., Univ. of California, San Diego Sch. of Med., La Jolla, CA

Abstract: Strong age dependence of diffusion MRI parameters in brain fiber tracts during postnatal development is well established in previous research. Tamnes et al (2017) reviewed longitudinal studies measuring white matter microstructure in pediatric samples. Among these, only two studies followed young school-aged children, one which included only 2 observations for each participant (Krogsrud et al., 2016), and the other included more observations in a only a handful of children (Lebel & Beaulieu et al., 2011), limiting the ability to model the nonlinearity of developmental trajectories. In this study, we examined the within-subject, nonparametric, age-related trajectories in white matter FA and MD in children studied at approximately 1-year intervals.

Longitudinal DTI data were acquired in the Pediatric Longitudinal Imaging, Neurocognition, and Genetics (PLING) study from 126 participants aged 5-12 years old, who were scanned annually between 2 and 5 times. Repeated measure of white matter diffusion parameters allows the identification of any curvilinear pattern of maturation in these tracts. FA and MD measures were computed for major white matter tracts that may exhibit different maturation rates during development, including the corticospinal tract, anterior thalamic radiations, corpus callosum, superior and inferior longitudinal fasciculi, inferior frontal-occipital fasciculus, uncinate, and cingulum.

Nonparametric statistical analyses of age effects on FA and MD of white matter tracts were performed with generalized additive mixed models (GAMM4) with a smooth age term (with sex and scanner as covariates) to allow different shapes of curvilinear age trends for different white matter tracts. GAMM4 results of smooth and linear age models for FA and MD were compared with model selection statistics. The results of these comparisons and the best fitting age function will be presented, illustrating the tract variability in the apparent underlying developmental trajectories. Results will be compared with previous observations and possible explanations for apparent differences will be discussed.

Reference:

Lebel & Beaulieu. *J. Neurosci*. 2011, 31, 30

Krogsrud et al. *NeuroImage*. 2016, 124.

Tamnes et al. *Dev Cogn Neurosci*. 2017 Dec 7.

Disclosures: W.K. Thompson: None. **N. Akshoomoff:** None. **T.T. Brown:** None. **A.M. Dale:** None. **T.L. Jernigan:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.22/D14

Topic: A.09. Adolescent Development

Support: NSF BCS 0963750
William T. Grant Foundation
Jeffrey/Wenzel Chair in Behavioral Neuroscience

Title: White matter microstructure relates to reward-seeking behavior under stress in adolescents and adults

Authors: *J. P. UY[1], A. GALVAN[2]
[1]Psychology, UCLA, Northridge, CA; [2]Psychology, UCLA, Los Angeles, CA

Abstract: Adolescence is characterized by increases in risky behavior, heightened physiological response to stress relative to other age groups, and ongoing white matter development in long-range association tracts that connect the prefrontal cortex (PFC) to other cortical and subcortical regions. Previous research suggests that protracted development of the PFC during adolescence renders the PFC susceptible to the effects of stress, potentially amplifying adolescents' proclivity toward reward-motivated risky behavior. Research relating white matter microstructure and risky decision-making during adolescence has been limited, and no study has examined the associations between white matter microstructure and risky decision-making in the context of stress in adolescents. In the current study, daily self-reports of stress were documented in adolescents (n=19, 12 females; ages 15-17 years) and adults (n=19, 12 females; ages 25-30 years). Participants completed two visits - once each when they endorsed a high and low level of stress - during which they completed a risky decision-making task about monetary gains and losses with varying expected values (EV). DTI scans were acquired from participants at one of the visits and fractional anisotropy (FA) values were used as an index of white matter coherence. Results revealed that adults evinced greater FA in long-range association tracts (e.g., inferior fronto-occipital fasciculus) compared to adolescents. Controlling for age and gender, greater FA in long-range association tracts were associated with fewer gain-related risks with EV that was equal to and/or disadvantageous to the certain decision under high stress, but not low stress. FA was not associated with gain-related risks with advantageous EV or loss-related risks across levels of EV. These findings suggest that, rather than relating to general increases in risky decisions across contexts, developing white matter tracts might specifically underlie increases in gain-motivated risky decisions under stress during adolescence.

Disclosures: J.P. Uy: None. **A. Galvan:** None.

Poster

281. Adolescent Development: Human Imaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 281.23/D15

Topic: A.09. Adolescent Development

Support: NINDS K23-NS092923

Title: Focal abnormalities in white matter microstructure correspond to neuropsychological comorbidities in BECTS

Authors: *L. OSTROWSKI[1,2], D. Y. SONG[2], E. L. THORN[2], S. M. STOYELL[2], G. XIAO[2], M. PARNES[2], M. A. KRAMER[3], S. M. STUFFLEBEAM[4], A. K. MORGAN[5], B. C. EMERTON[5], C. J. CHU[2,6]
[1]Brown Univ., Providence, RI; [2]Neurol., Massachusetts Gen. Hosp., Boston, MA; [3]Dept. of Mathematics and Statistics, Boston Univ., Boston, MA; [4]MGH NMR Ctr., Charlestown, MA; [5]Psychological Assessment Center, Massachusetts Gen. Hosp., Boston, MA; [6]Harvard Med. Sch., Boston, MA

Abstract: Benign epilepsy with centrotemporal spikes (BECTS) is a common childhood epilepsy syndrome with a male-predominance, characterized by seizures arising from the sensorimotor and temporal cortices and neurocognitive difficulties associated with these anatomic regions. The coincident maturation of association fibers during childhood provides a structural substrate that could contribute to the neurodevelopmental aspects of this disease. To investigate this relationship, we use an *a priori* region of interest (ROI) based approach to evaluate specifically for focal white matter abnormalities contiguous to the seizure onset zone (SOZ) in children with BECTS compared to healthy control (HC) children. We analyze the characteristics of the peri-rolandic u-fibers and termination zones of the superior longitudinal fasciculus (SLF) in relation to fine motor performance and phonological awareness, respectively. We also evaluate the relationship of white matter features in these regions to gender. Children with BECTS (n=22) and age-matched HCs (n=18) underwent multimodal testing with high resolution MRI including DTI sequences and targeted neuropsychological assessment. In the peri-rolandic region, children with BECTS had increased FA ($p=0.017$). Consistent with abnormal crossing u-fiber development, increased FA correlate with inferior fine motor performance ($p=0.029$). As with the peri-rolandic SOZ, children with BECTS had increased FA in the terminal zones of the SLF($p=0.044$). Phonological awareness was found to be impaired in BECTS subjects ($p=0.041$), though this did not directly correspond with FA. In the peri-rolandic region, we found gender-specific differences in white matter microstructure such that all BECTS subjects and HC males have higher FA values than HC females ($p\leq0.035$ for all measures), suggesting that the typical male pattern of white matter development may predispose boys to BECTS. Global exploration revealed that the FA abnormalities we observed were specific to the superficial white matter and the SOZ. These data provide evidence that focal atypical maturation of white matter microstructure is a basic feature in BECTS and may contribute to the neurodevelopmental comorbidities observed in this disorder.

Disclosures: L. Ostrowski: None. **D.Y. Song:** None. **E.L. Thorn:** None. **S.M. Stoyell:** None. **G. Xiao:** None. **M. Parnes:** None. **M.A. Kramer:** None. **S.M. Stufflebeam:** None. **A.K. Morgan:** None. **B.C. Emerton:** None. **C.J. Chu:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.01/D16

Topic: A.10. Development and Evolution

Support: National Research Foundation- Third World Academy of Science African Renaissance Doctoral Fellowship (AI)
South African National Research Foundation (PRM)

Title: Chemical neuroanatomy of the olfactory system of the nocturnal tree pangolin (Manis tricuspis)

Authors: *A. IMAM[1,3], M. S. AJAO[3], A. BHAGWANDIN[2], M. A. SPOCTER[4], I. O. AMADI[2], P. R. MANGER[2]
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Abstract: The tree pangolin is one of the eight extant species of Pholidota, with conflicting phylogeny. Despite the expanded olfactory gene family, it is unknown if the structural and neurochemical architecture of the pangolin olfactory system support its behavioural preference for olfactory cues. We used a range of neuroanatomical stains (Nissl; Myeline; Anti-NeuN, PV, CR, CB, ChAT, vGlut2, SMI-32, TH and DCX) to determine the organization of the main and accessory olfactory systems within the brain of the tree pangolin. The tree pangolin has a typically mammalian olfactory system, but minor variations were observed. The main olfactory system is comprised of the layered main olfactory bulb (MOB), the anterior olfactory nucleus (AON), the rostral olfactory cortex (including the taenia tecta, anterior hippocampal continuation and induseum griseum), the olfactory tubercle (Tu), the lateral olfactory tract (lot) and the olfactory limb of the anterior commissure, the nucleus of the lateral olfactory tract (NLOT), the piriform cortex (PIR) and a typically mammalian rostral migratory stream (RMS). The accessory olfactory system included the layered accessory olfactory bulb (AOB), the bed nucleus of the stria terminalis (BNST), and the nucleus of the accessory olfactory tract (NAOT). Volumetric analysis of the relative size of the MOB and PIR indicate that the tree pangolin has an olfactory system that occupies a proportion of the brain typical for the majority of mammals. Within the MOB, the glomeruli of the tree pangolin, at 200 µm diameter are larger than observed in most other mammalian species, and the MOB lacks a distinct internal plexiform layer. In addition, the laminate appearance of the NLOT was not observed in the tree pangolin. The accessory olfactory system appears to lack the posterior compartment of the accessory olfactory bulb. These observations are contextualized in relation to olfactory-mediated behaviours in pangolins.

Disclosures: A. Imam: None. **M.S. Ajao:** None. **A. Bhagwandin:** None. **M.A. Spocter:** None. **I.O. Amadi:** None. **P.R. Manger:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

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Program #/Poster #: 282.02/D17

Topic: A.10. Development and Evolution

Support: JSPS Grant-in-Aid for Challenging Exploratory Research #22657066, to AM
JSPS Research Fellowships for Young Scientists, #21- 3916, to TS
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JSPS KAKENHI Grant for Young Scientists (B) #17K18097 to TS
JSPS Postdoctoral Fellowships for Research Abroad, # 490 to T.S
MEXT KAKENHI Grant, 16002001, 20002001, and 2400001, to TM

Title: Development of the brain structures in chimpanzees and database of mri data

Authors: *A. MIKAMI[1], T. SAKAI[2], Y. HAMADA[3], J. SUZUKI[3], T. MIYABE-NISHIWAKI[3], M. MATSUI[4], K. OISHI[5], T. MATSUZAWA[3], M. TANAKA[3], M. HAYASHI[3], M. TOMONAGA[3]
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Abstract: Chimpanzees have the closest evolutionary kinship with humans. Their brain sizes are about three times smaller than the brain sizes of humans. However, the brain sizes of chimpanzees are almost same as the ancient hominoid *Australopithecus africanus*. The macro-anatomical structures and shapes are similar between chimpanzees and humans. Thus, in order to reveal the evolutional progress of human brains, it must be helpful to comprehend the brain development in chimpanzee and to compare this with the brain development in human. We used magnetic resonance imaging (MRI) technique to study the brains of four chimpanzees (one male and three females), whose ages (ranged from 1.8 to 60 months) were longitudinally evaluated during development from infancy to the juvenile stage. Ages of adult chimpanzees (3 males and 7 females) were ranged 23 to 42 years old. All subjects lived within a social group of 14 individuals in an enriched environment at the Primate Research Institute, Kyoto University (KUPRI). The brain size almost doubled from 1.8 to 36 months after birth. Among 4 lobes of cortices, volume increase in the frontal cortex was largest. These developmental processes were similar to those of the humans although the relative sizes of human brains were about 3 times

larger than those of chimpanzees. In the initial 36 months of infancy, the relative volume of the high intensity portion that corresponds to the mielinated white matter was smaller compared with the adult level. These data resemble the age-related volumetric changes of the mielinated white matter in human. To facilitate scientific discoveries in the field of primate comparative neuroanatomy, we launched a collaborative project to develop a database of growing chimpanzee brain images as an open resource. As an initial attempt, we will release a collection of structural MRI obtained from all 14 chimpanzees including growing chimpanzees at KUPRI in near future. The expected significant contributions of this database include (1) resources for comparative neuroscience research and (2) preservation of chimpanzee brains as endangered species, in a permanent digital form. User-initiated research projects beyond these contributions are also anticipated.

Disclosures: A. Mikami: None. **T. Sakai:** None. **Y. Hamada:** None. **J. Suzuki:** None. **T. Miyabe-Nishiwaki:** None. **M. Matsui:** None. **K. Oishi:** None. **T. Matsuzawa:** None. **M. Tanaka:** None. **M. Hayashi:** None. **M. Tomonaga:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.03/D18

Topic: A.10. Development and Evolution

Support: NSERC
FONDECYT

Title: Organization of telencephalic inputs to the medial spiriform nucleus, a pretectal cerebellar relay nucleus in birds

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Abstract: Birds, like mammals, have relatively large telencephala and cerebella. In mammals, one of the largest circuits in the brain involves a projection from the cerebral cortex to the cerebellum through the pontine nuclei, a group of neurons in the base of the caudal brainstem. Inputs to the pontine nuclei arise from all parts of the cortex, and these inputs are organized in discrete, non-overlapping areas. As in mammals, the telencephalon of birds sends descending projections to several nuclei that in turn project to the cerebellum, but the organization of these efferents has not been studied extensively. Birds possess a medial and lateral pontine nuclei at the base of the brainstem that receive projections from the telencephalon and project to the cerebellum and are thought to be homologous to the pontine nuclei of mammals. Additionally,

birds are unique in that they have a pretectal nucleus, the medial spiriform nucleus (SpM), that receives projections from the telencephalon and projects to the cerebellum. Here we used injections of anterograde tracers in the two main output regions of the pallium of birds, the Wulst and the arcopallium, to show the organization of these inputs to the SpM. We found that the anterior somatomotor and more posterior visual wulst project upon two separate and non-overlapping regions of the medial SpM. Additionally, we show that the visual arcopallium projects to more lateral regions of the SpM. Our results suggest that the organization of telencephalic inputs to SpM in birds parallels that of the projection to the pontine nuclei in mammals, and supports the notion that SpM can be considered a "displaced" pontine nuclei. Combined with our previous work, showing segregated projections from different regions of SpM to different zones of the cerebellum, this study helps to understand the organization of telencephalo-cerebellar pathways in birds.

Disclosures: C. Gutierrez-Ibanez: None. **M.D. Fernández:** None. **G.J. Marín:** None. **D.R. Wylie:** None.

Poster

282. Comparative Anatomy and Brain Evolution

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Program #/Poster #: 282.04/D19

Topic: A.10. Development and Evolution

Support: CURAS Faculty Research Fund

Title: The role of grp and grpr in the extinction of cued fear memory in zebrafish

Authors: *L. L. BRUCE[1], E. A. DORCHUCK[2], B. N. HASSMAN[2], A. W. MEZHER[1], O. OCHUBA[1], K. L. KRAMER[1]
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Abstract: The amygdala is the anatomical core of an emotional learning circuit. In particular, the amygdalar basolateral complex (BLC) is a critical site for sensory convergence for conditioned stimuli (e.g., light), unconditioned stimuli (e.g., shock), and for extinction retention and learning. Gastrin-releasing peptide (Grp or bombesin) is a neurotransmitter that is highly expressed in excitatory pyramidal neurons in the rodent BLC and may be co-released with glutamate. Gastrin-releasing peptide receptor (Grpr) is expressed in GABAergic inhibitory interneurons, which then exert negative feedback on BLC pyramidal neurons. Studies in mice have shown that Grp and Grpr regulate memory formation and retention related to behavioral and stress responses to emotional stimuli. We have previously demonstrated that *grp* mRNA is highly expressed in the dorsomedial region of the zebrafish *(Danio rerio*) forebrain, the proposed homologue of the mammalian BLC that contains *grp*- and *grpr*-expressing neurons. To determine if Grp and Grpr

function is conserved across species, we examined chronic anxiety, cued fear conditioning, and extinction of conditioning using *grp* and *grpr* mutant zebrafish.
Measures of chronic anxiety behavior in young fish aged 12-15 days post-fertilization showed no significant differences between zebrafish with wildtype (TL) and *grp*- or *grpr*-mutant genotypes. A second task, a cued fear conditioning assay that tested amygdalar memory, used freezing as an index of fear. Adult *grp*-mutant, *grp*-heterozygote, and wildtype fish rarely froze after exposure to an 8 sec red light stimulus in adaptation trials. When the last second of the red light was paired with a shock (learning trials), all groups responded similarly with increased average freezing ratios. During the subsequent retention and extinction trials, the red light was presented without shock. Wildtype and *grp*-heterozygote fish approached normal freezing times after 6 trials, whereas the mutant *grp* fish reached normal freezing times after only 1 trial. Trials using *grpr*-mutant fish are underway.
Our results suggest that *grp*- and *grpr*-mutant zebrafish responded and adapted to chronic anxiety situations similar to wildtype fish. Although mutation of *grp* had little effect on chronic anxiety, the *grp*-mutant zebrafish exhibited selective impairment of cued fear memory retention, consistent with most previous studies in mice. Furthermore, our data support the observations that a region homologous to the mammalian BLC has a similar role in the formation and expression of emotional memories in zebrafish.

Disclosures: L.L. Bruce: None. **E.A. Dorchuck:** None. **B.N. Hassman:** None. **A.W. Mezher:** None. **O. Ochuba:** None. **K.L. Kramer:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

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Program #/Poster #: 282.05/D20

Topic: A.10. Development and Evolution

Title: Carnivores and rodents evolved different patterns of proportional brain structures than other taxa

Authors: S. GRETA[1], W. TOMITA[2], A. BURRE[4], D. ROSTAMIAN[3], N. SCHOTTLER[3], *W. E. GRISHAM[3]
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Abstract: Examining the proportion of brain devoted to various neuroanatomical structures across taxa provides an interesting lens into how mammalian orders diverged through evolution. By using proportions, all brain regions are on the same scale, which allows us to compare the pattern of relationships across various taxa. This will enable us to determine whether the same

pattern of brain evolution occurred across taxa or if they have diverged. We examined each of the following regions as proportions of the whole brain: isocortex, subcortical structures (striatum, thalamus and hippocampus), and cerebellum. Images were obtained from the Comparative Mammalian Brain Collection (http://neurosciencelibrary.org/).
Considering all of the animals together, the proportional subcortical structures were all positively and significantly correlated with each other. The proportional isocortex, however, was significantly inversely correlated with all other structures. The proportional cerebellum was significantly correlated with the proportional hippocampus and thalamus but inversely correlated with the isocortex. We then sought to see if this pattern was uniformly present in the various taxa. We examined these brain regions across primates (n =11), carnivores (n=17), artiodactyls (n = 8), rodents (n = 7) and "others" (n=18).
Some notable exceptions to the overall pattern appeared. Given that the proportional isocortices are fairly large are in carnivores, we expected an inverse relationship between proportional isocortex and subcortical structures. However, this inverse relationship was largely lost, although the proportional subcortical structures stayed fairly well correlated in carnivores. The pattern of relationships in carnivores suggest that the subcortical features evolved in concert but independent of proportion of brain devoted to isocortex.
The relationships among the proportional subcortical structures among rodents are essentially absent. Rodents have a relatively large proportional hippocampus, striatum, and thalamus compared to other taxa. Whereas these structures seem to evolve in concert in other taxa, they don't seem to do so in rodents.
Finally, the relationships between the proportional cerebellum and any other structure are largely lost when we examine the individual taxa. The cerebellum appears to be subject to very different sets of evolutionary pressures both across and within taxa than are the other structures.
Clearly brains evolve in different patterns across taxa—most particularly carnivores and rodents, which are on very different paths in brain evolution.

Disclosures: S. Greta: None. **W. Tomita:** None. **A. Burre:** None. **D. Rostamian:** None. **N. Schottler:** None. **W.E. Grisham:** None.

Poster

282. Comparative Anatomy and Brain Evolution

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Program #/Poster #: 282.06/D21

Topic: A.10. Development and Evolution

Title: An overview of adult neurogenesis in the forebrain of domestic pigeons

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University of Düsseldorf, Germany; [3]Inst. of Neurosci. and Med. INM-1, Res. Ctr. Jülich, Jülich, Germany

Abstract: Adult neurogenesis in the avian brain has been detected in the telencephalon of several species of song birds, food caching birds and poultry. Only a few studies reported on generation and proliferation of neurons in the domestic pigeon and up to now there is no overall overview about adult neurogenesis particularly in pigeons or birds in general that includes different stages of cell proliferation in the telencephalon. Here, the comparison between pallial and subpallial structures will give new insights in functional consequences of adult neurogenesis and brain plasticity in general. In this study, free flying homing pigeons (*Columba livia* f.d.) were treated with 5-bromo-deoxyuridine (BrdU) to label dividing cells and sacrificed about three months after injection. Brains were dissected and immunohistochemically processed with several markers to examine different stages of cell proliferation in a quantitative and qualitative way. We used SOX2, GFAP and PCNA for precursor cell stages, doublecortin (DCX), Prox1, Tbr2, NeuN, S100β and Calbindin for intermediate progenitor cells and postmitotic stages. BrdU-positive (BrdU-ir) and DCX-positive (DCX-ir) neurons were widely distributed in the telencephalon. The number of DCX-ir cells was higher compared to BrdU-ir cells and comparable to SOX2-positive cells. Next to the olfactory bulb and the ventricular zone, the ventrolateral part of the V-complex and the ventral dorsolateral subdivision of the hippocampal formation exhibit high numbers of proliferating cells. Pallial, most of the proliferating cells are detected in the intercalated hyperpallium, while subpallial the highest numbers were found in the basal ganglia. The used markers allowed a differentiation between the different cell stages and cell types, revealing a highly plastic nature of structures in the pigeon's telencephalon. Our findings provide detailed insights into adult neurogenesis in pigeons and complete the knowledge about this dynamic process in birds. The high number of immature neurons indicate a wide range in plasticity. Now, it is possible to link our knowledge about brain structure and function under the influence of brain plasticity.

Disclosures: J. Mehlhorn: None. **E. Schreivogel:** None. **K. Amunts:** None. **C. Herold:** None.

Poster

282. Comparative Anatomy and Brain Evolution

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Topic: A.10. Development and Evolution

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Title: The Japan Monkey Centre primates brain imaging repository for comparative neuroscience: an archive of digital records including records for endangered species

Authors: *T. SAKAI[1], J. HATA[2], H. OHTA[3], Y. SHINTAKU[4], N. KIMURA[6], Y. OGAWA[3], K. SOKABE[7], S. MORI[8,9], H. J. OKANO[3], Y. HAMADA[5], S. SHIBATA[1], H. OKANO[1], K. OISHI[8]
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Abstract: Advances in magnetic resonance imaging (MRI) and computational analysis technology enable comparisons among various primate brains in a three-dimensional electronic format. Results from comparative studies provide information about common features across primates and species-specific features of neuroanatomy. Investigation of various species of non-human primates is important for understanding such features, but the majority of comparative MRI studies are based on experimental primates, such as common marmoset, macaques, and chimpanzee. A major obstacle has been the lack of a database that includes non-experimental primates' brain MRIs. To facilitate scientific discoveries in the field of comparative neuroanatomy and brain evolution, we launched a collaborative project to develop a repository of non-human primate brain images using *ex vivo* MRI as an open resource. As an initial attempt, we released a collection of structural MRI and diffusion tensor imaging obtained from 12 species: pygmy marmoset (*Cebuella pygmaea*), owl monkey (*Aotus trivirgatus*), white-fronted capuchin (*Cebus albifrons*), long-tail macaque (*Macaca fascicularis*), Japanese macaque (*Macaca fuscata*), bonnet macaque (*Macaca radiata*), toque macaque (*Macaca sinica*), Sykes's monkey (*Cercopithecus albogularis*), red-tailed monkeyt (*Cercopithecus ascanius*), Schmidt's monkey (*Cercopithecus ascanius schmidti*), de Brazza's guenon (*Cercopithecus neglectus*), and lar gibbon (*Hylobates lar*), 16 postmortem brain samples from the 12 species, stored in the Japan Monkey Centre (JMC), were scanned using a 9.4 T MRI scanner and made available through the JMC collaborative research program. The expected significant contributions of the JMC Primates Brain Imaging Repository include (1) resources for comparative neuroscience research, (2) preservation of various primate brains, including those of endangered species, in a permanent digital form, (3) resources for optimizing methods of scanning large fixed brains, and (4) references for veterinary neuroradiology. User-initiated research projects beyond these contributions are also anticipated. We encourage its use by not only neuroscientists but also

researchers that belong to research fields outside traditional neuroscience, such as computer science, mathematical modeling, and medicine.

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Poster

282. Comparative Anatomy and Brain Evolution

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Topic: A.10. Development and Evolution

Support: NSF Grant BCS-0921079
NSF Grant BCS-1316829
NIH Grant RR000166

Title: Differential serotonergic innervation at the amygdala among macaque species that differ in social style

Authors: *D. N. JONES[1], C. C. SHERWOOD[2], P. R. HOF[3], J. M. ERWIN[2], M. RAGHANTI[1]
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Abstract: Among the 23 macaque species that constitute the genus *Macaca*, a high level of behavioral diversity has been observed, particularly related to aggressiveness. To investigate the neural underpinnings of variation in aggressiveness among species, we compared serotonergic innervation of the amygdala among four species. The amygdala plays a prominent role in emotional processing and social intelligence. Additionally, central serotonin (5HT) availability and aggressive behavior have been found to be inversely related in humans and nonhuman primates. Our study sample included left hemisphere brain sections containing the amygdala from 19 individuals of the following species: rhesus (*M. mulatta*) n = 6, Japanese (*M. fuscata*) n = 2, pigtailed (*M. nemestrina*) n = 6, and moor (*M. maura*) n = 5. Four amygdaloid nuclei were examined: the lateral, basal, accessory basal, and central nuclei. We used immunohistochemical methods to stain for the 5HT transporter (SERT) and quantified SERT-immunoreactive axon density using a stereological approach. Based on evidence that suggests increased central serotonergic signaling functions to inhibit aggressive behavior, we hypothesized that the greatest amount of innervation would exist in the least aggressive, most egalitarian species, the moor macaque. However, in contrast to this prediction, our results reveled a significantly greater amount of innervation in the more aggressive, hierarchical species, the Japanese and pigtailed macaques, relative to the moor macaque. These findings suggest that, unlike what has been

reported in a similar comparative study on the more aggressive chimpanzee and the relatively tolerant bonobo, increased serotonergic innervation of the amygdala in macaques may not be associated with more affiliative, egalitarian social styles. The implications of our findings are discussed in a larger evolutionary framework.

Disclosures: D.N. Jones: None. **C.C. Sherwood:** None. **P.R. Hof:** None. **J.M. Erwin:** None. **M. Raghanti:** None.

Poster

282. Comparative Anatomy and Brain Evolution

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Topic: A.10. Development and Evolution

Support: Guerrieri Undergraduate Endowment Summer Research Program

Title: Neural scaling of auditory nuclei with overall brain size in passeriformes

Authors: *P. MILLER[1], J. CORFIELD, 21804[2]
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Abstract: Generally, neural scaling follows the rule that the larger the brain is, the larger individual brain regions are. Although, after more detailed analyses, we know that exceptions to this rule are frequent. Auditory regions in Galliformes, for example, do not scale in the same way that mammals do. In Galliformes, as brain size increases neuron density decreases. Whether this applies to other avian orders or to other brain regions is not known. Passeriformes (songbirds) are a highly derived order of birds that have a well-developed auditory system, complex communication system and vary in body sizes, making them excellent candidates for examining neural scaling relationships. This study investigated neural properties in two auditory nuclei, nucleus magnocellularis and nucleus laminaris, in ~20 different species of songbird. Neuronal sizes, neuronal number and the volume of each region was measured using stereological techniques. Regression models were used to assess how the volumes of auditory nuclei scaled in songbirds and how this compared to other species of birds. Interestingly, results suggests that the relative size of auditory regions in songbirds scale differently to that of other birds, and were significantly smaller than that predicted based on their brain size. This decrease in size in these auditory regions appears to be associated with an increase in neuronal density, rather than a reduction in the relative number of neurons or neuronal size. Neuronal size showed a strong correlation with overall brain size, with the largest species having the largest neurons and also the largest range of neuronal sizes. This research will help us better understand the general rules that determine how neural structures scale across vertebrates.

Disclosures: P. Miller: None. **J. Corfield:** None.

Poster

282. Comparative Anatomy and Brain Evolution

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National Chimpanzee Brain Resource - NIH NINDS NS092988
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Netherlands Organization for Scientific Research NWO [452-13-015]

Title: A white matter atlas of the chimpanzee brain and quantitative comparison with the human and macaque

Authors: *K. L. BRYANT[1], L. LI[2], R. B. MARS[3]
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Abstract: Determining the unique specializations of the human brain requires an anatomically informed understanding of how the neocortex has been modified and reorganized since our evolutionary divergence from other primates. The chimpanzee brain is arguably the least understood of the three. Therefore, in this project we create a comprehensive atlas of the major white matter fibers of the chimpanzee brain, based on diffusion MRI tractography data, similar to maps created previously for the human and macaque (Mars et al., 2018; Thiebaut de Schotten et al., 2012). In addition to comparing fascicular anatomy, we also produce cortical projection maps in chimpanzees. We can then use these projection maps with similar maps in the other species to create a formal comparison between the organization of the three different brains, following techniques recently developed in a direct human/macaque comparison (cf. Mars et al., 2018). We produced the chimpanzee white matter atlas using probabilistic diffusion tractography on *in vivo* HARDI scans of 29 chimpanzees from Yerkes Primate Center available through the US-based National Chimpanzee Brain Resource. Protocols seeding in the bodies of over 20 major white matter tracts, derived from protocols designed for human and macaque tractography (De Groot et al., 2013; Mars et al., 2018), were adapted and in some cases refined using additional information from previous investigations in chimpanzee (Hecht et al., 2015), human (Dejerine and Dejerine-Klumpke, 1895; Catani and Thiebaut de Schotten, 2008), and macaque (Schmahmann and Pandya 2006) fascicular anatomy. Tractography was carried out in native space for each individual chimpanzee and then averaged and thresholded to produce a

chimpanzee fascicular atlas. Next, tracts were projected to the surface by multiplying the tracts with a matrix describing the tractography of cortical grey/white matter boundary to the whole brain (O'Muircheartaigh & Jbabdi, 2017), allowing us to create a map of each tract's cortical termination points. Our results suggest modifications to the organization of the superior longitudinal fasciculi (SLF), middle longitudinal fasciculus, and inferior longitudinal fasciculus (ILF) have occurred in the hominoid lineage. The second branch of the SLF seems to project more ventrally than expected based on the human brain, while the ILF contains a branch in the human and chimpanzee that is not observed in the macaque.

Disclosures: K.L. Bryant: None. **L. Li:** None. **R.B. Mars:** None.

Poster

282. Comparative Anatomy and Brain Evolution

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Program #/Poster #: 282.11/D26

Topic: A.10. Development and Evolution

Support: EY002686

Title: Expansion of primary areas occurs without a change in the relative distribution of cortical neurons

Authors: *M. GABI[1], E. C. TURNER[2], J. KAAS[1]
[1]Vanderbilt Univ., Nashville, TN; [2]The Biodesign Inst., ASU-Banner Neurodegenerative Res. Ctr., Tempe, AZ

Abstract: Across primate species, the cerebral cortex shows a similar neuronal distribution along the anterior-posterior axis, with lower densities in the frontal areas that increases towards the occipital areas. Previous studies have shown that the primary motor cortex, primary visual cortex, and primary auditory cortex, occupy a similar percentage of the cortical surface and also contains a similar percentage of all neurons across nonhuman primates. However, these studies did not address how these areas scale in relative number of neurons with the cerebral cortex. Here we aim to understand what are the cellular scaling rules of the primary motor cortex(M1), primary visual cortex (V1), primary auditory cortex (A1) and primary somatosensory cortex (S1) of 44 individuals from 10 primate species (*Aotus trivirgatus, Saimiri sciureus, Callicebus moloch, Otolemur garnettii*, *Macaca mulatta*, *Macaca radiata, Pan troglodytes*, *Papio cynocephalus, Callitrix jacchus*, *Macaca nemestrina).* In all species, the neocortex was separated from the underlying white matter, manually flattened and then the locations of primary areas were estimated as seen previously. Each area had its number of neurons determined using the Isotropic Fractionator, a method which transforms a tissue into a nuclei suspension. Across all ten species, the surface area scales with similar power functions of the number of neurons in all

four primary areas (A1, M1, S1 and V1). The neuron density (Neurons/area) remain constant with the surface area in M1 suggesting that the relative neuron size remains the same in this region. Also, V1 scales slowly as the number of neurons in the cerebral cortex increases in all primates analyzed, while S1 and M1 have similar power functions that are close to the linearity with exponents 0.885 and 0.903 respectively. Most importantly, we find that the number of neurons in primary motor cortex and the neurons in the primary somatosensory cortex varies linearly in all species analyzed. These findings indicate that the expansion of primary areas occurred with no particular increase in the relative distribution of cortical neurons across primate species, which shows to vary in a similar manner in all four areas as seen previously. Still, primary motor cortex and primary somatosensory cortex vary proportionally in its number of neurons in all species, from the smallest New world monkey to the Chimpanzee, suggesting a functional relationship among these areas.

Disclosures: M. Gabi: None. **E.C. Turner:** None. **J. Kaas:** None.

Poster

282. Comparative Anatomy and Brain Evolution

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Program #/Poster #: 282.12/D27

Topic: A.10. Development and Evolution

Title: Longevity and sexual maturity scale with number of cortical neurons across birds and mammals, and humans are no different

Authors: *S. HERCULANO-HOUZEL
Dept. of Psychology, Vanderbilt Univ., Nashville, TN

Abstract: Maximal longevity of endotherms has long been considered to increase with decreasing specific metabolic rate, and thus with increasing body mass. Using a dataset of over 700 species, here I show that maximal longevity, age at sexual maturity and post-maturity longevity across bird and mammalian species instead correlate primarily, and universally, with the number of pallial brain neurons. Correlations with metabolic rate and body mass are entirely explained by clade-specific relationships between these variables and numbers of pallial neurons across species. Importantly, humans reach sexual maturity and subsequently live just as long as expected for their number of cortical neurons. Longevity might increase together with numbers of pallial neurons through their impact on three main factors: delay of sexual maturity, which postpones the onset of aging; lengthening of the period of viable physiological integration and adaptation; and improved cognitive capabilities that benefit survival of the self and of longer-lived progeny.

Disclosures: S. Herculano-Houzel: None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.13/D28

Topic: A.10. Development and Evolution

Title: Analysis of astrocyte densities across the cerebral cortex of primate species

Authors: *L. GLASSBURN[1], S. E. DOS SANTOS[2], S. HERCULANO-HOUZEL[2]
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Abstract: Across the evolution of mammalian brains, the scaling of neuronal size and density in the cerebral cortex varies between mammalian orders, with a clade-specific neuronal scaling rule and density for primates. In contrast, non-neuronal cell size and densities indicate that non-neuronal cells do not scale differently between mammalian orders. Mammals share a common and unique non-neuronal scaling rule and have a constant density and invariant average non-neuronal cell size across species and brain structures, including cerebral cortex. These non-neuronal cells are glial cells and vasculature-associated cells, and more research is needed to understand if each of these cell-types are themselves invariant in density across mammals. Alternatively, their densities may be inversely correlated such that variation in the cell-types is not evident in analyzing overall non-neuronal cell density. This research investigates how astrocyte density scales across the cerebral cortex of 8 primate species, including human. We used the isotropic fractionator method to quantify astrocyte numbers in the grey and white matter of coronal sections of the cerebral cortex, for which total, neuronal, and non-neuronal cell numbers were previously reported. Astrocyte nuclei were immunocytochemically labeled with the astrocyte-specific marker S100β. Astrocytes quantification was done in every fourth section (*M. fascicularis* N = 18, *M. nemestrina* N = 29, *P. cynocephalus* N = 27, *H. sapiens* N = 75), every second section (*A. trivirgatus* N = 19), or the entire cerebral cortex (*C. apella* N = 82, *S. midas* N = 22, *O. garnetti* N = 27), depending on the overall size of the brain. In total, 299 samples were analyzed. Results indicate that astrocyte densities have similar relationships to structure mass and neuronal density across species and cortical regions, where within cortex structure mass is related to astrocyte numbers by a power function with an exponent of 0.761 ± 0.028 ($p < 0.0001$). Astrocyte density varies with neuronal density within the cortex of primates ($\alpha = 0.512 \pm 0.054$, $p < 0.0001$), and the astrocyte to neuron ratio decreases with increasing neuronal density ($\alpha = -0.488 \pm 0.054$, $p < 0.0001$) in the cortical grey matter, giving interesting functional implications for neurons with varying numbers of supporting astrocytes. However, the cortex of *M. fascicularis* and the human hippocampus appear to have higher astrocyte densities than other primate cortical tissue with similar neuronal density. Overall, primates have evolved with one rule for adding astrocytes into cortical tissue, and this similar scaling rule indicates that primates of varying brain size have similar sized astrocytes.

Disclosures: L. Glassburn: None. **S.E. Dos Santos:** None. **S. Herculano-Houzel:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.14/D29

Topic: A.10. Development and Evolution

Support: Enigma Grant U54 EB020403

Title: MicroRNAs associated with neurogenesis in the developing human cerebral cortex

Authors: *M. J. LAFFERTY[1], D. H. GESCHWIND[2], L. DE LA TORRE-UBIETA[2], J. L. STEIN[1]
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Abstract: Gene regulation is critical to fate decisions during differentiation. Previous work has shown transcription factors, broad orchestrators of gene regulation, can guide fate decisions during neurogenesis. MicroRNAs (miRNAs) also have broad effects on transcriptional programs, yet their impact on human neurogenesis is relatively understudied. Mouse knockout models, of the key miRNA processing gene Dicer, have shown that miRNAs play a critical role in neural progenitor proliferation, neuronal differentiation, and cortical wall development. Additionally, expression of miR-124 is greatly upregulated in neurons in culture, and overexpression of this miRNA can promote differentiation of progenitors into neurons. Here, we sought to identify specific miRNAs involved in human neurogenesis. We profiled miRNA expression levels within dissected germinal zone and cortical plate fetal cortex tissue from 3 donors ranging from gestation weeks 17-19. After standard pre-processing and correcting for confounding effects, we identified 95 miRNAs that are significantly upregulated in germinal zone tissue and 76 miRNAs significantly upregulated in cortical plate tissue. Consistent with previous work in cultured neurons, miR-124 is upregulated in cortical plate. We performed miRNA target prediction analyses and assessed regulatory relationships with key neurogenesis genes to identify molecular processes driving cortical neurogenesis. Profiling miRNAs associated with human neurogenesis will lead to a more complete understanding of gene regulation influencing proliferative or neurogenic fate decisions and may lead to the development of higher fidelity neuronal trans-differentiation tools.

Disclosures: M.J. Lafferty: None. **D.H. Geschwind:** None. **L. De La Torre-Ubieta:** None. **J.L. Stein:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.15/D30

Topic: A.10. Development and Evolution

Support: NIH Intramural Research

Title: Secretory cells in the digestive epithelium of Trichoplax adhaerens, an animal that feeds by external digestion

Authors: *T. D. MAYOROVA, C. L. SMITH, T. S. REESE
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Abstract: *Trichoplax adhaerens*, a tiny marine animal, locomotes by ciliary gliding to feed upon algae and bacteria. It has only six cell types (1) and represents an early branch of the metazoan tree (2). It lacks an internal gut but, instead, feeds by external digestion on its lower surface, which contains several cell types resembling those in the digestive epithelia of Eumetazoa. When the animal crawls over a patch of food, it ceases gliding (3). Pausing is thought to be elicited by an endomorphin-like peptide (ELP) secreted by cells that express proteins involved in regulated secretion in neurons and neuroendocrine cells (1, 4, 5). Then a different type of secretory cell secretes a large granule whose contents lyse nearby algae/bacteria (3). The lysate is endocytosed by the ciliated cells, which, like enterocytes, bear microvilli. Here we examine the structures and distributions of *Trichoplax* secretory cells in more detail and provide evidence of another type of secretory cell, mucus cells. Analysis of serial sections obtained from an ATUM microtome with backscatter SEM revealed ciliated cells with large electron dense granules (Type 1). These cells were most prevalent around the edge and correspond to the neuropeptidergic cells described previously. Another type of secretory cell (Type 2) was distributed sparsely but widely in the lower epithelium, had microvilli, but no cilium and contained smaller, clear granules. Because the granules were clear, we supposed they might contain mucus (6). We applied various fluorescent lectins and discovered that one, wheat germ agglutinin (WGA), labeled the mucus trails left by migrating animals and the rings of mucus that appear around animals during feeding. Labeling of fixed animals revealed WGA-labelled cells, including many that co-labeled for endomorphin, distributed widely in the lower epithelium and around its edge. Electron microscopic analysis of animals labeled with HRP- or nanogold-labeled lectins confirmed that the clear secretory granules of Type 2 cells contained mucins. However, we are left with a puzzle because, as yet, no lectin label has been detected by EM in Type 1 cells. The presence of mucus cells in the digestive epithelium of *Trichoplax* reinforces its similarity to digestive epithelia of more complex animals and is consistent with the idea the gut evolved by invagination of a tissue originally used for external digestion (7). 1. Smith et al 2014 Current Biology 2. Srivastava et al

2008 Nature 3. Smith et al 2015 PLOS One 4. Smith et al. 2017 Journal of General Physiology 5. Senatore et al 2017 Journal of Experimental Biology 6. Harrison, Microscopic Anatomy of the Invertebrates, Vol. 2 7. Schierwater et al. 2009 PLOS Biology

Disclosures: T.D. Mayorova: None. **C.L. Smith:** None. **T.S. Reese:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.16/D31

Topic: A.10. Development and Evolution

Title: Exploring the evolutionary origin of small-molecule neurotransmission through the Hydra nervous system

Authors: *H. MAHMOOD, Y. NORO, H. SHIMIZU, K. MINETA, P. MAGISTRETTI, T. GOJOBORI
King Abdullah Univ. of Sci. & Technol., Thuwal, Saudi Arabia

Abstract: *Hydra* is a fresh water metazoan of the phylum Cnidaria which is among the first phylum to develop a nervous system. The primitive organisms of this phylum are known to use peptides as neurotransmitters. However, the presence of neurotransmission through small molecules like glutamate and glycine in *Hydra* is debatable. The purpose of this study is to elucidate the evolutionary origin of small molecule-mediated neurotransmission in animals by studying it in *Hydra*. Using the genome sequence of *Hydra*, we performed phylogenetic tree analyses, revealing that there are genes of sequence homology to mammalian glutamate and acetylcholine receptors. We also found that there is conservation of sequences pertaining to the ligand binding domains of these receptors in *Hydra*. In order to explore whether these receptors are functional in *Hydra* and whether they are localized in neurons, we created transgenic actin-GCAMP *Hydra* to study their response to treatment with small molecular weight neurotransmitters. GCaMP6s is a calcium sensor, allowing us to monitor neuronal activity *in vivo* on stimulation with neurotransmitters. The stimulations were carried out by bath application of the small molecules into *Hydra* media and recording changes in the firing of neurons. Our initial experiments suggest that *Hydra* do not respond to stimulation by glutamate and glycine by mere bath application. Although, the other possibilities are not ruled out. For example, these receptors are localized in epithelial cells rather than neurons in *Hydra.* Including this possibility, it is of particular interest to examine, in the near future, if glutamate and other small molecules may have served merely as metabolites in Cnidarians and evolved as neuronal signaling molecules later in the animal kingdom.

Disclosures: H. Mahmood: None. **Y. Noro:** None. **H. Shimizu:** None. **K. Mineta:** None. **P. Magistretti:** None. **T. Gojobori:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.17/D32

Topic: A.10. Development and Evolution

Support: MRC PhD studenship

Title: Comparative development of the cerebellum in reptiles reveals different strategies for morphogenesis

Authors: T. VARELA[1], *R. J. WINGATE[2]
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Abstract: The cerebellum is composed of only a few cell types whose stratification within the organ has remained fairly conserved throughout evolution. The classic image of a cerebellum is that of a highly folded structure, though in truth, the complexity of foliation various quite dramatically between species. Reptiles, for example, exhibit a wide range of cerebellar shapes ranging from the simple, relatively flat structures of snakes and turtles, to the larger, multiply folded cerebella of alligators and birds. The contoured appearance of brain tissue is due to the division of different nerve cell progenitors that combine to generate folds and bends. How these differences are generated are likely to be due to the genes that control patterns of cell division. By comparing the development of different reptile and bird cerebella, we have found that different degrees of foliation correspond to observable differences in proliferation in the transient external granule cell layer. These patterns also correlate with the maturation of Purkinje cells underlying the external granule layer, which serve as a source of signalling factors that influence the behaviour of granule cell precursors. We have also examined the expression of *Atonal1*, *NeuroD1* and *SHH* through immunohistochemistry and *in situ* hybridisation. Our results suggest that precocious expression of NeuroD1 in granule cell precursors is a key factor in attenuating cell division in unfoliated cerebella, and I have knocked down NeuroD1 in turtles by electroporation of shRNA constructs into cultured cerebellar explants to further investigate the function of this gene.

Disclosures: T. Varela: None. **R.J. Wingate:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.18/D33

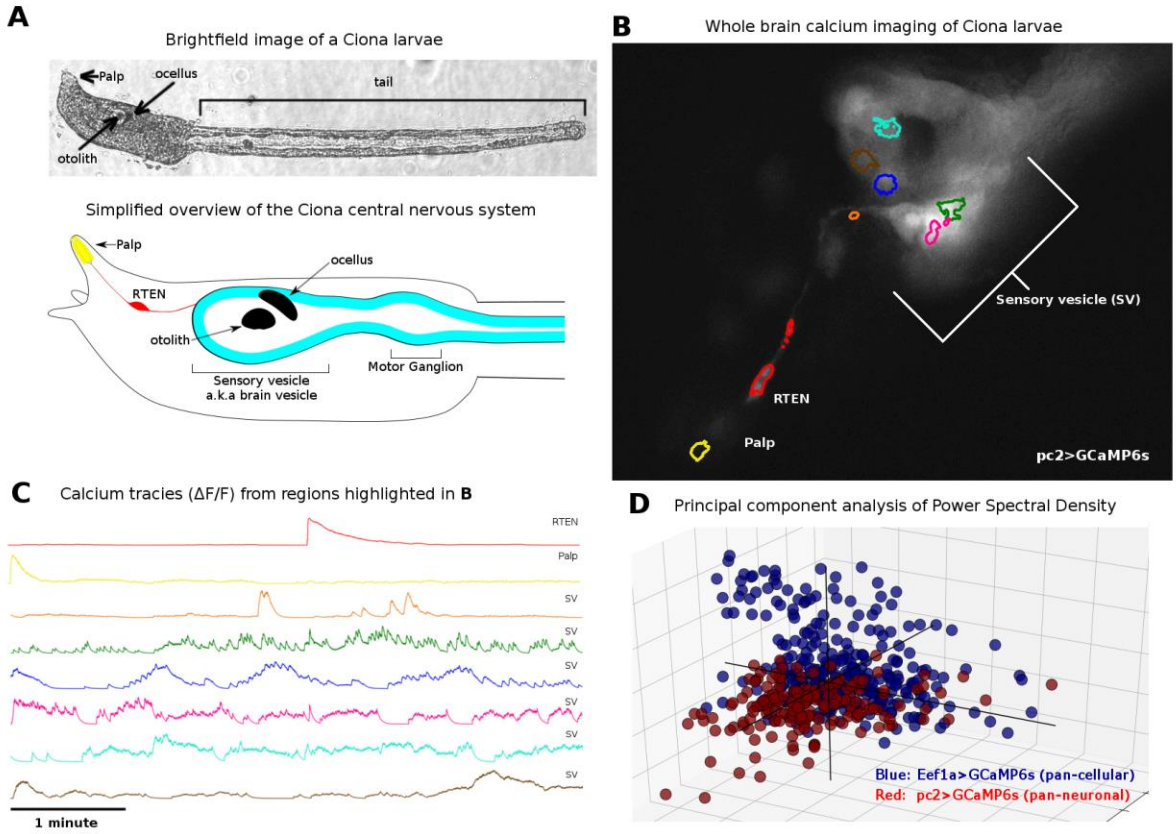
Topic: A.10. Development and Evolution

Support: Sars Centre core budget

Title: Whole brain imaging of neuronal activity in ciona intestinalis, an early branching chordate

Authors: *K. KOLAR, M. CHATZIGEORGIOU
Sars Intl. Ctr. For Marine Mol. Bio, Bergen, Norway

Abstract: The vast majority of functional studies in systems neuroscience are performed in a limited number of model species. Over the past few decades these studies have provided us with a very detailed understanding of these nervous systems, but we still lack an understanding of how nervous system function is altered for adaptation and evolution.
Here we aim to incorporate an evolutionary perspective into modern neuroscience by presenting whole brain imaging in *C. intestinalis* larvae, an early branching chordate. The *C. intestinalis* CNS consists of only about 330 cells (connectome by Ryan *et al.* 2016), but possesses presumptive integration centers and specialized sensory structures. These merits and the ability to induce transgenesis in wild-caught animals are key reasons for introducing *C. intestinalis* to the broader neuroscience community.
To record spontaneous activity, larvae expressing GCaMP6 under the pan-neuronal promoter pc2 (proprotein-convertase 2) were embedded in low melting point agarose and imaged for 300 sec at 10Hz. Movies were motion corrected and calcium traces extracted using CNMFE (Giovannucci *et al.* 2017). We show diverse patterns of calcium activity in the sensory vesicle, a brain-like structure and low activity in an RTEN and Palp neuron that are presumed to be part of an olfactory system (Fig C). In order to classify and cluster neurons to interpret the diverse activity patterns, we first differentiate neuronal and non-neuronal calcium dynamics using animals that express pan-cellular GCaMP6. Our results suggest a neuronal cluster which is a subset of the pan-cellular cluster (Fig D). We will classify all neuronal subtypes to determine if their activity patterns form cluster domains, and interpret how domains in the *multidimensional calcium dynamics space* shift in response to sensory cues. We speculate that these domains may represent a language or repertoire of vocabulary that these neurons are able to employ. We will soon expand our methodology to other species to understand how they explore and utilize the *calcium dynamics space*, and examine how their languages vary.



Disclosures: K. Kolar: None. **M. Chatzigeorgiou:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.19/D34

Topic: A.10. Development and Evolution

Support: NIH GRANT T32

Title: Duplicated genes and their role in human neurological development and disease

Authors: *A. SEKAR[1], J. WANG[2], E. HA[2], K. HINO[3], G. KAYA[2], S. SIMO[3], M. DENNIS[4]
[2]Genome Center, Dept. of Biochem. & Mol. Medicine, MIND Inst., [3]Dept. of Human Anat. & Cell Biology, UC Davis, Davis, CA 95616, [4]Genome Center, Dept. of Biochem. & Mol. Med., [1]Univ. of California Davis, Davis, CA

Abstract: The human brain exhibits radically different anatomical and cognitive features relative to closely ape related species. Gene duplications have long been identified as drivers of speciation. Duplications arising uniquely on the human lineage ("human-specific segmental duplications" or HSDs) are enriched for genes implicated in neurological function—relative to nonhuman great apes—and have the propensity to contribute to novel phenotypes by creating gene copies that may be truncated, fused with other genes or expressed in alternative tissues. One example is *SRGAP2C*, a HSD gene implicated in neuronal migration and synaptogenesis, that is co-expressed, translated and heterodimerizes with its ancestral paralog, *SRGAP2A*, in mammalian cell lines. In mice, expression of *SRGAP2C* was found to result in altered neuronal migration and neoteny of synaptogenesis reminiscent of human neurodevelopment. Another HSD gene, *ARHGAP11B*, has been implicated in the promotion of basal progenitor amplification and neocortex expansion in mice. Here, to further understand the roles of both *SRGAP2* and *ARHGAP11* paralogs during cortex development, we have reanalyzed RNA-seq data of human fetal tissue and embryonic stem cells and overexpressed these genes in mammalian cell lines and mice. Using two existing RNA-seq datasets, (1) distinct cortical layers of human fetal tissues and (2) differentiated embryonic stem cells (hESC)-derived cortical neurons at varied time points, we have assessed for regional differences and temporal changes between human-specific and ancestral paralogs during corticogenesis. Since actin dynamics play an important role in neuronal migration and both ancestral *SRGAP2A* and *ARHGAP11A* are implicated in signaling pathways affecting the cytoskeleton, we have overexpressed the aforementioned HSD genes in monkey kidney and rat neuronal cells (COS-7 and PC12) and assayed for changes affecting cell membrane physiology, such as outgrowth of filopodia/lamellipodia and molecular activation/inactivation of myosin phosphatase. In mice, we have expressed these HSD paralogs using in utero electroporation in developing embryos and assessed for differences in neuronal migration and polarization. We have preliminary results that suggest *SRGAP2C* expression leads to different outcomes in neuronal cell fate and *ARHGAP11B* causes alterations in neuronal migration within the developing mouse cortex, both novel findings. Overall, our results continue to support previous research that human-specific paralogs of *SRGAP2* and *ARHGAP11* have distinct impacts on cortex development relative to their ancestral paralogs.

Disclosures: A. Sekar: None. **J. Wang:** None. **E. Ha:** None. **K. Hino:** None. **G. Kaya:** None. **S. Simo:** None. **M. Dennis:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.20/D35

Topic: A.10. Development and Evolution

Support: NSF CAREER AWARD 1149446

NIH grant R01 NS047557

Title: Characterization of diminished diffusion in the brain extracellular space of the naked mole-rat harboring unique high-molecular-mass hyaluronan

Authors: *D. THEVALINGAM[1,2], S. HRABETOVA[3], D. P. MCCLOSKEY[4,2]
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Abstract: Hyaluronan (HA; Hyaluronic Acid), a primary scaffolding component of the brain extracellular matrix, serves as an integral structural component to the brain extracellular space (ECS). The fossorial African naked mole-rat (Heterocephalus glaber), a mammal demonstrated to have protracted brain development and remarkable longevity, has been shown to synthesize and sustain a unique high-molecular-mass variant of hyaluronan macromolecule (HMM-HA). Thus the naked mole-rat serves as a unique model to observe the role of the extracellular matrix in maintaining brain microstructure and regulating diffusion in the brain ECS. In the present study, we utilized Integrative Optical Imaging to quantify the diffusion of fluorescently labeled dextran (~3,000 MW) in naked mole-rat cortical slices (400 μm). The average tortuosity, which is a measure of the hindrance to a diffusing molecule in the ECS, was significantly higher in naked mole-rat cortical slices than in mouse. These results are indicative of a significant role for the extracellular matrix, particularly HMM-HA, in regulating the behavior of diffusing molecules in the brain ECS of the naked mole-rat. This study provides additional insight into how the composition of the brain extracellular matrix ultimately affects brain physiology and behavior.

Disclosures: D. Thevalingam: None. **S. Hrabetova:** None. **D.P. McCloskey:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.21/D36

Topic: A.10. Development and Evolution

Title: Homology in Gyf gene maintains neuron cell homeostasis in *Drosophila melanogaster* and *Drosophila* eugracilis

Authors: *L. A. NEAL, J. LARIMORE, S. ROBIC
Agnes Scott Col., Decatur, GA

Abstract: The Drosophila 4th chromosome, the Muller F Element, or the 'Dot' Chromosome is a unique feature of the Drosophila genome (Leung et. al., 2015). This region of the genome is of particular interest due to the fact that even though it is almost entirely heterochromatic, it still contains a number of active proteins, which are not characteristic of heterochromatin (Leung et. al., 2015). The Genomics Education Partnership (GEP), based at Washington University in St. Louis, MO, has organized a study based on comparative genomics of the 'Dot' chromosome in all Drosophila. This study examines the conservation of the genes found on this chromosome across D. eugracilis and D. melanogaster species using various bioinformatics softwares such as FlyBase BLAST, NCBI BLAST, Gene Record Finder, and the UCSC Genome Browser. In particular, we focused on contig25, a 50kb stretch of DNA in the D. eugracilis genome, where the ortholog of the D. melanogaster 'Gyf' gene lies. According to FlyBase, the Gyf gene is found to be involved in three terms or groups of functions: muscle cell cellular homeostasis, neuron cellular homeostasis, and regulation of autophagy (Gramates et. al., 2017). Our results concluded that there is between 68.5% and 68.8% identity between the genes found in both species, with an E value of 0. These results indicate that there is a relatively high conservation of this gene in the various species. Further analysis of this gene reveals that it plays an important role in the reduction of protein aggregates and organelle dysfunction that have implications in the onset of Parkinson's disease (Kim et. al., 2015). In conclusion, understanding the differences in the gene in these species is important to our understanding of neurodevelopment, neurodegeneration and the use of Drosophila as a model species.

Disclosures: J. Larimore: None. **S. Robic:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.22/D37

Topic: A.10. Development and Evolution

Title: The miR-183/-96/-182 cluster - A key player in the ontogeny of neuronal asymmetries?

Authors: *S. LOR[1], V. THEIS[2], D. MOSER[3], R. KUMSTA[3,4], C. THEISS[2,4], O. GUNTURKUN[1,4]
[1]Inst. of Cognitive Neuroscience, Dept. Biopsychology, [2]Dept. Cytology, Med. Fac., [3]Genet. Psychology, [4]Intl. Grad. Sch. of Neurosci., Ruhr-University Bochum, Bochum, Germany

Abstract: The asymmetrical organization of the nervous system (or *lateralization*) is a fundamental organizational principle of the brain which means that the left and the right hemisphere differ in cognition, perception, and motor control. Atypical lateralization in humans has been linked to various types of neurological disorders while lateralized brain functions in non-human animals have been shown to allow for higher cognitive capacities and therefore,

benefit survival. One of the animals, in which the ontogenesis of lateralization has been studied, are pigeons that display left/right differences in their visual system. Owing to the embryo's asymmetrical body position inside the egg, the resulting uneven light input onto the eyes shortly before hatch induces left/right differences of neural wiring in their visual system. Consequently, one side of the brain develops bigger neurons and more fibers, resulting in a higher computational system than the other. This is also observable in behavioral tasks, in which the right eye/left hemisphere excels in visual discrimination of fine patterns, whereas the left eye/right hemisphere is specialized on spatial attention. The fact that the modulation of the brain can be regulated at such a precise point in time suggests a tightly regulated mechanism. So, what are the cellular cascades triggered by this light stimulation to shape the brain into its lateralized system?
In the recent years, miRNAs have emerged as an important class of small non-coding RNAs, which are involved in a subset of biological processes such as developmental timing. They regulate gene expression on the post-transcriptional level and entire pathways, and thus, are considered as master regulators of gene expression. Therefore, our study aims to uncover the cellular mechanisms of the retino-tectal system during embryonic development via miRNA analyses. Whereas on retinal level, miRNAs were symmetrically expressed and therefore, might not be required for the ontogeny of lateralization, the cluster of miR-183/-96/-182 showed higher expression in the right tectum opticum compared to the left side. Dark incubated pigeon embryos displayed a symmetrical expression pattern of this cluster while their overall expression was significantly diminished compared to normal incubated embryos. Interestingly, other studies in humans have reported an involvement of the miR-183/-96/-182 cluster in the ontogenesis of handedness, and potentially in dyspraxia. Further investigations will unravel the anatomical localization of the miR-183/-96/-182 cluster within the tectum opticum, and to investigate their effects on the targeted mRNA and protein output.

Disclosures: V. Theis: None. **D. Moser:** None. **R. Kumsta:** None. **C. Theiss:** None. **O. Gunturkun:** None.

Poster

282. Comparative Anatomy and Brain Evolution

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 282.23/D38

Topic: A.10. Development and Evolution

Support: R00MH102357-04

Title: Dynamic changes of chromatin accessibility during human telencephalic neuronal differentiation

Authors: *D. LIANG[1], A. E. ELWELL[1], O. KRUPA[1], K. E. CHEEK[1], K. P. COURTNEY[1], L. DE LA TORRE-UBIETA[2], D. H. GESCHWIND[2], J. L. STEIN[1]
[1]Neuronscience Ctr. & Genet., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [2]UCLA, Los Angeles, CA

Abstract: Cortical neurogenesis occurs prenatally, when neural progenitor cells differentiate into neurons. Neurogenic or proliferative fate decisions are determined, in part, by regulatory elements modulating the expression of proliferative or neurogenic genes. Previous work has recently identified neurogenesis-associated regulatory elements from dissected fetal tissue laminae in humans, and found that genetically mediated alterations in these elements impact risk for a variety of neuropsychiatric illnesses. This previous work was unable to dissect cell-type specific effects, however, as laminae contain heterogeneous populations of cells. Here, we extend this work by profiling chromatin accessibility in a cell-type specific manner using a large population of human neural progenitor cells. In this study, we cultured neural progenitor cells derived from 92 human fetal brain donors (61 males and 31 females, gestation weeks 14-21). We differentiated cells for 8 weeks and sorted virally labeled neurons (AAV2-hSyn1-EGFP). We then then generated open chromatin profiles for both neural progenitor cells and sorted neurons using the Assay for Transposase Accessible Chromatin followed by sequencing (ATAC-seq). We found global chromatin accessibility profiles are strongly different based on cell-type. Differential chromatin accessibility peaks at gene promoters were enriched in gene ontology terms related to neurogenesis (progenitor > neuron peaks) or synapses (neuron > progenitor peaks), as expected. A differential motif enrichment analysis identified transcription factors (TFs) driving neuronal differentiation, including NEUROG1 and CUX1/2. Similarly, well-known TFs involved in neural progenitor proliferation and maintenance including SOX2 had binding sites more often accessible in progenitors. We found common genetic variants within differentially accessible peaks are enriched in heritability explained for several human neuropsychiatric illnesses and cognitive traits, most notably IQ, neuroticism, schizophrenia, and ADHD. This provides further evidence linking functional alterations in neurogenesis to risk for these illnesses and traits. Chromatin accessibility profiles from in vitro neural progenitor differentiation show largely consistent findings to previous in vivo profiling of fetal cortical laminae, providing further validation of both our culture system and genetic risk factors for neuropsychiatric diseases impacting neurogenesis. These data may also be used to prioritize transcription factors that can be modulated to induce neurogenesis in human culture systems.

Disclosures: D. Liang: None. **A.E. Elwell:** None. **O. Krupa:** None. **K.E. Cheek:** None. **K.P. Courtney:** None. **L. De La Torre-Ubieta:** None. **D.H. Geschwind:** None. **J.L. Stein:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.01/D39

Topic: B.02. Ligand-Gated Ion Channels

Support: Welch Foundation, Departmental Grant No. BC-0022 (to A. V. K.)
Houston-Louis Stokes Alliance for Minority Participation (H-LSAMP), undergraduate fellowship (to M. F. M.)

Title: Binding of noncompetitive inhibitors to the extracellular domain of neuronal nAChRs: Molecular docking with anticonvulsant α-substituted acetamides and lactams

Authors: *A. V. KRIVOSHEIN, J. L. GUEVARA, M. F. MERIANO
Physical and Applied Sci., Univ. of Houston - Clear Lake, Houston, TX

Abstract: We have recently discovered that α-substituted acetamides and lactams noncompetitively inhibit neuronal nAChRs (Krivoshein, 2016, *ACS Chem. Neurosci.* 7: 316-326). Importantly, their inhibitory affinities toward the receptor *in vitro* (in patch clamp measurements) show excellent correlation with their anticonvulsant potency *in vivo* (in MES tests in mice). We are thus interested in developing a framework for rapid *in vitro* (patch clamp) and *in silico* (molecular docking) testing of the newly synthesized derivatives. In this study, we used molecular docking simulations with AutoDock VINA and EADock DSS to pinpoint binding sites and estimate affinities for neuronal nAChRs (α2, α4β2) and the acetylcholine-binding protein (AChBP) for a series of α-substituted acetamides and lactams. Notably, despite the different algorithms employed in these two programs, the docking results were similar. However, when docking the same inhibitor to different intersubunit interfaces, substantial differences were found. Even more profound differences were found between the binding sites on the different target proteins. The predicted affinities follow about the same rank order as those observed in patch-clamp experiments with a heterologously expressed neuronal nAChR. Our results (*i*) underline the importance of conducting molecular docking simulations with multiple receptor structures and (*ii*) demonstrate the potential of molecular docking in screening of novel noncompetitive inhibitors of the nAChR *in silico*.

Disclosures: A.V. Krivoshein: None. **J.L. Guevara:** None. **M.F. Meriano:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.02/D40

Topic: B.02. Ligand-Gated Ion Channels

Support: Funding from SRF for 2013-2017 (KK, TF, MM, SO)
Grant-in Aid for Scientific Research (15K07969) from the Ministry of Education, Science, Sports and Culture (C) of Japan (KK, TF, MM)

Title: Regulation of antigen-presenting cell (APC)-dependent $CD4^+$ T cell differentiation by α7 nicotinic acetylcholine receptors on both APC and $CD4^+$ T cells

Authors: *K. KAWASHIMA[1], M. MASHIMO[2], T. FUJII[3], Y. MORIWAKI[4], H. MISAWA[5], S. ONO[6]
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Abstract: Immune cells including T and B cells, dendritic cells and macrophages have the ability to synthesize acetylcholine (ACh) by choline acetyltransferase (ChAT). Activation of these immune cells up-regulates ChAT expression and ACh synthesis. Furthermore, immune cells express various subtypes of both muscarinic and nicotinic ACh receptors (mAChRs and nAChRs, respectively) including α7 nAChRs. These findings suggest that ACh synthesized and released from immune cells during antigen presentation between $CD4^+$ T cells and antigen-presenting cells (APCs) plays a role in regulation of immune function by acting on their mAChRs and nAChRs. In fact, by immunization with ovalbumin (OVA), we found a significant elevation of anti-OVA-specific IgG_1 in α7 nAChR-deficient (α7-KO) mice compared to the wild-type C57BL/6J (WT). Furthermore, OVA-activated spleen cells from α7-KO mice produced more TNF-α, IFN-γ and IL-6 than those from WT mice. These findings support a notion that α7 nAChRs in immune cells are involved in regulation of immune function.
We investigated whether α7 nAChRs play roles in $CD4^+$ T cell differentiation into $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells (Tregs) and effector T cells (Th1, Th2 and Th17) using spleen cells from OVA-TCR transgenic BALB/c (DO.11.10) mice. The spleen cells containing $CD4^+$ T cells were activated using OVA or OVA-peptide$_{323-339}$ (OVA-P) and cultured in the presence or absence of GTS-21 (3-30 μM), a partial α7 nAChR agonist, for 5 days in 96-well plate. For activation of $CD4^+$ T cell differentiation, OVA is required to be endocytosed into APCs and processed to OVA-P and then coupled to MHC class II before presentation on the surface of the APCs. On the other hand, OVA-P binds directly to MHC class II expressed on the surface of APCs. At the end of the culture, we performed flow cytometric analysis of the expression of a number of Treg and effector T cell markers.
GTS-21 down-regulated the OVA-activated $CD4^+$ T cell differentiation into Tregs and effector T cells significantly. However, GTS-21 up-regulated the OVA-P-activated $CD4^+$ T cell differentiation into Tregs and effector T cells significantly. The results suggest that activation of α7 nAChRs in APCs inhibits antigen presentation via suppression of antigen processing leading to down-regulation of $CD4^+$ T cell differentiation, and that activation of α7 nAChRs in $CD4^+$ T cells facilitates differentiation into Tregs and effector T cells. In conclusion, these findings demonstrate that α7 nAChRs in both APCs and $CD4^+$ T cells play roles in regulation of $CD4^+$ T cell differentiation.

Disclosures: M. Mashimo: None. **T. Fujii:** None. **Y. Moriwaki:** None. **H. Misawa:** None. **S. Ono:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.03/D41

Topic: B.02. Ligand-Gated Ion Channels

Title: Effect of new modulator compounds on the activity of human α7-acetylcholine receptors using an automated patch clamp system

Authors: *T. SEEGER[1], C. SCHEFFEL[1], S. RAPPENGLUECK[1], F. WOREK[1], H. THIERMANN[1], K. T. WANNER[2], K. V. NIESSEN[1]
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Abstract: Nicotinic acetylcholine receptors (nAChRs) were described to be implicated in a series of pathological disorders in the CNS and in the PNS. Furthermore, these receptors are interesting therapeutic targets for the treatment of intoxications by organophosphorus compounds (OPCs). OPCs inhibit the enzyme acetylcholinesterase (AChE) resulting in accumulation of the transmitter acetylcholine in the synaptic cleft. Thereby, the function of postsynaptic nAChRs is impaired by desensitization. Consequently, identification of drugs acting as positive allosteric modulators (PAMs) and reducing or reversing nAChR desensitization may be regarded as rational therapeutic approach. A series of structurally-related bispyridinium non-oxime (BP) compounds was tested for their ability to prevent desensitization. For this purpose, whole-cell currents of human α7-nAChRs stably expressed in a CHO cell line (CHO/RIC-3/hα7-nAChR) were recorded under voltage-clamping conditions (-70 mV) performed with planar electrodes in an automatic setup (Patchliner®, Nanion Technologies GmbH, Munich).
Cholinergic currents of hα7-nAChRs induced by nicotine (1–100 µM) increased concentration-dependently up to approx. 500 pA at 100 µM nicotine. However, at higher concentrations (> 100 µM) currents decayed reflecting desensitization of hα7-nAChRs.
Incubation of BP compounds carrying a *tert*-butyl- methoxy- or a dimethylamino-group at both pyridinium moieties in presence of 100 µM nicotine produced an amplification of nicotine-induced peak current amplitudes and a prolonged duration of these currents. Regarding that the effect of these compounds is induced only when co-administered with nicotine, it can be considered as a positive allosteric modulation. At high concentrations of these BP compounds (≥ 30 – 70 µM), dose-response relations revealed a concentration-dependent current decay.
These results are valuable basics for the development of potent PAMs for hα7-nAChRs, allowing initial structure-activity relationships requested for predictive drug design.

Disclosures: T. Seeger: None. **C. Scheffel:** None. **S. Rappenglueck:** None. **F. Worek:** None. **H. Thiermann:** None. **K.T. Wanner:** None. **K.V. Niessen:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.04/D42

Topic: B.02. Ligand-Gated Ion Channels

Title: Functional analysis of muscle-type nicotinic acetylcholine receptors using SSM-based electrophysiology - Detection of novel "resensitizers"

Authors: *K. V. NIESSEN[1], S. RAPPENGLUECK[1], W. SCHMEISSER[1], T. WEIN[2], S. SICHLER[1], G. HOEFNER[2], K. T. WANNER[2], H. THIERMANN[1], F. WOREK[1], T. SEEGER[1]
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Abstract: Transmission in neuromuscular synapses may be impaired by various toxic substances, e.g. organophosphorus compounds (OPC). In OPC poisoning, acetylcholinesterase (AChE) is inhibited, resulting in accumulation of acetylcholine in the synaptic cleft. Thus, the desensitization of nicotinic acetylcholine receptors (nAChRs) in the postsynaptic membrane is provoked. Direct targeting of nAChRs to recover their activity from desensitization (i.e. “resensitizing”) might be a promising therapeutic approach. Screening of several novel substances interacting with the receptor needs to be performed for identifying active compounds. In addition to the affinity of such ligands towards the nAChRs[1], their functional properties have to be considered. Bilayer methods (so-called “cell-free electrophysiology“) based on solid supported membranes (SSM) are suitable for investigation of activity of electrogenic membrane proteins (e.g. ligand-gated ion channels like nAChRs) which are not accessible for patch clamp methods. Using native plasma membrane fractions prepared from *Torpedo californica* electroplax, functional measurements of muscle-type nAChRs were performed. Rapid exchange of differently composed buffers forced the receptor to shift into the conformations of resting, activated and desensitized states[2]. Especially, the interaction of ligands with the receptor in a desensitized state and their ability to “resensitize” the blocked receptor was topic of interest. To enhance the screening capacities, the recently developed method was transferred to the fully parallel 96 well-based platform SURFE^{2}R 96SE (Nanion Technologies, Munich), the first marketed instrument featuring the SSM-technology in a high-throughput manner. The upscaling allowed repetitive measurements of differently substituted bispyridinium propanes including positive and negative controls as well as multiple ligand concentrations within one single run. Depending on their substitution pattern, several bispyridinium propanes interact as positive allosteric modulatos (PAMs) and revealed “resensitizing” activity after desensitizing nAChRs by excess carbamoylcholine (> 1 mM). The results demonstrate that SSM-based electrophysiology is well suited to allow detailed functional screening of nAChR-active compounds and has great potential for drug discovery, because of its robustness und scalability.

[1] K.V. Niessen et al., *Chem. Biol. Interact*. **206** (2013), 545-554
[2] K.V. Niessen et al., *Toxicol. Lett*. **247** (2016), 1-10

Disclosures: S. Rappenglueck: None. **W. Schmeisser:** None. **T. Wein:** None. **S. Sichler:** None. **G. Hoefner:** None. **K.T. Wanner:** None. **H. Thiermann:** None. **F. Worek:** None. **T. Seeger:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.05/D43

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant DA038817

Title: Evaluation of nicotinic acetylcholine receptor expression and plasticity following chronic nicotine exposure in alpha 4-GFP and WT C57Bl/6 mice

Authors: *J. R. PAULY[1], C. L. RICHARDS[2], P. MORAN[1]
[1]Pharmaceut. Sci., [2]Chem., Univ. of Kentucky, Lexington, KY

Abstract: Many studies have previously shown that neuronal nicotinic acetylcholine receptors (nAChRs) respond uniquely to chronic agonist treatment with a paradoxical increase in the level of receptor protein expression. The process of nAChR “up-regulation” seems to involve multiple post-translational processes that have been difficult to fully characterize. The purpose of this study was to compare the responsiveness of α4 and α7 nAChRs to chronic nicotine treatment in wild type C57BL/6 mice and mice with a green fluorescent protein expressed on the α4 subunit (α4-GFP mice). Adult male wildtype C57BL/6 and α4-GFP mice were randomized to the following treatment groups: 1) 2% saccharin (Sigma Chemical Company, St Louis, Mo., USA) in tap water for 7 days, 2) 200 µg/mL nicotine in 2% saccharin for 3 days, or 3) 200 µg/mL nicotine (free base; Sigma) in 2% saccharin for 7 days (n=5 per group). Brain sections were prepared for an autoradiographic analysis of [^{3}H]-Epibatidine and [^{125}I]-alpha bungarotoxin to alpha 4-containing and alpha 7 nAChRs respectively. In saccharin treated mice there was a 30-50% decrease in the baseline expression of [^{3}H]-Epibatidine in the α4-GFP mice in some (motor cortex, dentate gyrus of the hippocampus) but not all brain regions. The decreased α4β2 nAChR baseline expression was selective since there were no strain differences seen in α7 nAChR expression in similar brain regions. There were also no strain differences in cytisine resistant [^{3}H]-Epibatidine binding to non-β2 containing nAChR's. In spite of the decreased baseline number of α4-containing nAChRs in the GFP mice, the plasticity of the expression was similar following chronic nicotine treatment. Chronic nicotine treatment via the drinking solution increased [^{3}H]-Epibatidine binding by 20-30% in both strains of mice. These studies reveal for

the first time that tagging the α4 subunit with GFP may significantly decrease the level of α4β2 baseline receptor expression, which could have functional impacts on cellular and behavioral studies performed with these animals.

Disclosures: J.R. Pauly: None. **C.L. Richards:** None. **P. Moran:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.06/D44

Topic: B.02. Ligand-Gated Ion Channels

Title: Evaluating commercially-available antibodies for RIC3

Authors: *R. H. LORING, S. SUKUMARAN, J. P. THUMMAPUDI, Z. WANG
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Abstract: α7 nicotinic acetylcholine receptors (nAChRs) depend on chaperone proteins that allow folding, assembly and transport to the cell surface membrane. Resistance to Inhibitors of Cholinesterase 3 (RIC3) is one known chaperone for α7 nAChRs. Antibodies validated to cross-react with human, mouse and rat RIC3 would be very useful, but currently, only antibodies raised against human RIC3 epitopes are commercially available. Also, RIC3 has alternate splice variants, including an alternate extra serine (S+) or not (S-) encoded at the boundary between exons 4 and 5. Mutations due to single nucleotide polymorphisms (SNPs) are also common. We tested existing antibodies that might cross-react between species and whether SNPs and splice variants make any difference. DNA encoding either human or S+mouse RIC3 (S+mRIC3 from Genescript) was linked to a Flag (DDK) epitope to allow detection by anti-DDK antibodies. Human RIC3 (S-hRIC3-YN) purchased from Origene had SNPs C130Y and D352N present in one version without the serine but with a DDK tag, while S-hRIC3-HF, also from Origene, had SNPs P57H and I165F and a DDK tag. Western Blotting detected anti-hRIC3 or anti-DDK antibodies that bound to protein from hRIC3 or mRIC3 constructs transiently expressed in human embryonic kidney (HEK) cells and blotted onto nitrocellulose following electrophoresis. Rat RIC3 (S-rRIC3) expressed without an extra serine or a DDK tag was also tested as an antigen. Four rabbit anti-human RIC3 antibodies (two antibodies from ThermoFisher Scientific and one each from Abcam and Santa Cruz Biotechnology) were tested. Three of these antibodies recognized only hRIC3-YN and hRIC3-HF, while one antibody strongly reacted with S+mRIC3 at a dilution of 1:5000 and showed weak reactions with both S-hRIC3 isoforms and with S-rRIC3. An antibody that recognizes mouse or rat RIC3 will allow us to evaluate whether RIC3 protein is expressed in animal tissues that expresses surface α7 nAChRs in the presence or absence of other known α7 nAChR chaperones. Further experiments are planned to evaluate the

effects of the serine splice variants in cross-reactions between species, and whether this antibody also detects Xenopus RIC3.

Disclosures: R.H. Loring: None. **S. Sukumaran:** None. **J.P. Thummapudi:** None. **Z. Wang:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.07/D45

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH grant 5R01NS077114

Title: Bupropion modulation of 5-HT_{3AB}receptors

Authors: *M. JANSEN[1], A. STUEBLER[1], F. OMORUYI[2]
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Abstract: The FDA-approved drug bupropion has been prescribed as an antidepressant (Wellbutrin) for over three decades, and more recently as a smoking cessation aid (Zyban). The presumed mechanism of action of bupropion was inhibition of norephinephrine and dopamine reuptake by their respective transporters. Subsequently, its non-competitive antagonistic effect was demonstrated in nicotinic acetylcholine receptors (α1βεδ, Torpedo, α1βγδ, α3β4α5±β2, α3β2, α4β2, α7) of the Cys-loop superfamily providing an alternate pharmacological pathway. Recently, our laboratory has shown that another cation-selective member of the Cys-loop superfamily, the serotonin type 3 receptor (5-HT3-R), is modulated by bupropion at clinically relevant concentrations. Specifically, we determined that bupropion acts as a non-competitive antagonist at 5-HT_{3A}subunits. 5-HT3-Rs are found pre- and postsynaptically, and are currently targeted by anti-emetics and irritable bowel syndrome treatments. They also hold promise as potential future targets for multiple neurological disorders, such as Alzheimer's disease, schizophrenia, and bipolar disorder.The 5-HT3-R family consists of five different subunits (A-E) but the assembly of this receptor requires the 3A subunit, yielding either a homomer or heteromer with another subunit. To date, only the interaction of bupropion with the 3A subunit has been studied. Here, we extend our investigations to heteromeric 5-HT_{3AB}-Rs, which are known to frequently show different responses to non-competitive antagonists as compared to homomeric 5-HT_{3A}-Rs. 5-HT_{3AB}-Rs are found in the central and peripheral nervous system, predominantly in the amygdala, caudate nucleus, and hippocampus. The functional interaction of bupropion with 5-$HT_{3AB}$was characterized in *Xenopus*oocytes using two-electrode voltage clamp

and patch clamp techniques. Further studies, including docking studies and site-directed mutagenesis, will be used to identify the binding site/s in 5-HT_3-R.

Disclosures: M. Jansen: None. **A. Stuebler:** None. **F. Omoruyi:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.08/D46

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01-GM57481
NIH Grant R01-EY024717

Title: Macroscopic and microscopic activation of α7 nicotinic acetylcholine receptors by the structurally unrelated ago-PAMs B-973B and GAT107

Authors: *M. QUADRI[1], S. GARAI[3], G. A. THAKUR[3], C. STOKES[1], A. GULSEVIN[2], N. A. HORENSTEIN[2], R. L. PAPKE[1]
[1]Dept. of Pharmacol. and Therapeut., [2]Dept. of Chem., Univ. of Florida, Gainesville, FL; [3]Dept. of Pharmaceut. Sci., Northeastern Univ., Boston, MA

Abstract: We report the profiles of two α7 nicotinic acetylcholine receptor (nAChR) ago-PAMs, GAT107 and B-973B, in both two-electrode and patch-clamp experiments. α7 positive allosteric modulators (PAMs) are able to potentiate channel activation by binding to a site in the transmembrane domain (TMD). By binding to additional allosteric sites in the extracellular domain, ago-PAMs act as allosteric agonists, inducing activation in the absence of a typical orthosteric agonist. By also acting at the α7 TMD PAM site, this activation results in large macroscopic currents and protracted bursts of channel opening. Both compounds showed the typical ago-PAM profile but with several significant differences. Specifically, allosteric activation by B-973B appeared more protracted than that produced by GAT107, and B-973B responses were relatively insensitive to the noncompetitive neuronal nAChR antagonist mecamylamine compared to GAT107 responses. Detailed patch-clamp analyses indicated differences in open times, closed times, and burst durations, together with different patterns of full and subconductance states. In single-channel studies we saw that for B-973B, mecamylamine was able to completely block full conductances of the receptor, but was permissive of a single subconductance. Mecamylamine's activity for this subconductance state was consistent with sequential block of the open channels, such that, while individual openings were shorter, burst durations were longer, so that the total open time within a burst was unchanged. In the case of GAT107, however, full conductances were not completely abolished even if profoundly affected in open durations. *In silico* analyses suggested that B-973B bound in

the TMD PAM site might distort the channel, preventing mecamylamine access to binding sites deeper in the pore. Our results demonstrate that, although similar in some ways, the two agents have different balances in their activities at the two allosteric sites and subsequent coupling to the orthosteric site and the ion channel of the receptor. These differences may have further implications as to how the intracellular domains couple to the interactome and subsequent signal transduction associated with the cholinergic control of inflammation.

Disclosures: M. Quadri: None. **S. Garai:** None. **G.A. Thakur:** None. **C. Stokes:** None. **A. Gulsevin:** None. **N.A. Horenstein:** None. **R.L. Papke:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

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Program #/Poster #: 283.09/D47

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant DA040047
Marshall University Research Corporation

Title: Upregulation of α4* and α4α6* nAChRs on VTA dopamine neurons is correlated with nicotine reward-related behavior

Authors: *B. J. HENDERSON, A. T. AKERS, Z. J. BAUMGARD, A. J. AVELAR
Biomed. Sci., Joan C Edwards Sch. of Med. at Marshall Univ., Huntington, WV

Abstract: Nicotine is the primary addictive component of tobacco products. Previous reports indicate that nicotine reward is mediated through α4β2*, α6β2*, and α4α6β2* nicotinic acetylcholine receptors (nAChRs) (*, indicates that additional nAChR subunits may be present). Little is known about α4α6β2* nAChR involvement due to a lack of methods that allow the direct investigation of this particular nAChR subtype. Here we use mice that contain α4-mCherry and α6-GFP nAChR subunits to show that concentrations of nicotine sufficient to evoke reward-related behavior (in a conditioned place preference assay) robustly upregulate α4* and α4α6* nAChRs on midbrain dopamine and GABA neurons. Furthermore, the extent of α4* and α4α6* nAChR upregulation on ventral tegmental area (VTA) dopamine neurons correlates to the magnitude of nicotine reward-related behavior. We also show that the upregulation of α4α6* nAChRs in VTA dopamine neurons is accompanied by a change in nAChR stoichiometry that is dependent on the concentration of nicotine in our long-term exposure paradigms. Together, these data highlight the importance of nAChRs that contain both the α4 and α6 nAChR subunit and suggest that α4α6β2* nAChRs on VTA DA neurons play a significant role in the cellular changes that mediate the addiction to nicotine.

Disclosures: B.J. Henderson: None. **A.T. Akers:** None. **Z.J. Baumgard:** None. **A.J. Avelar:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.10/D48

Topic: B.02. Ligand-Gated Ion Channels

Support: Marshall University Research Corporation and National Institutes of Health: DA040047 (BJH).

Title: Green apple tobacco flavorant farnesol enhances nicotine reward-related behavior

Authors: *A. J. AVELAR, A. T. AKERS, Z. J. BAUMGARD, B. J. HENDERSON
Biomed. Sci., Marshall Univ., Huntington, WV

Abstract: Previous investigations have shown that menthol, the most popular tobacco flavorant, can enhance nicotine reward and reinforcement. With the growing popularity of electronic nicotine delivery systems, more flavors are available to smokers and there is a critical need to understand how these flavorants may alter nicotine's actions. The need to know the abuse liability of flavorants is especially urgent considering that it is generally assumed that flavorants are harmless and they are, therefore, used without caution. In this study we examined the green apple flavorant and odorant farnesol for its ability to alter nicotine reward-related behavior and nicotinic acetylcholine receptor (nAChR) upregulation.
Using a conditioned place preference assay we found that farnesol enhanced nicotine reward-related behavior to a degree that is similar to menthol. We then used confocal microscopy and α4-mCherryα6-GFP mice to examine the upregulation of α4-containing (α4*), α6*, and α4α6* nAChRs in ventral tegmental area (VTA) dopamine neurons. Here, we observed that farnesol, combined with nicotine, enhanced the upregulation of α6* nAChRs but had little effect on α4* and α4α6* nAChRs.
Together, these data show that farnesol alters nicotine reward-related behavior. This is most likely accomplished by its ability to enhance α6* nAChR upregulation. These data highlight the need to study how tobacco flavorants alter nicotine reward and reinforcement.

Disclosures: A.J. Avelar: None. **A.T. Akers:** None. **Z.J. Baumgard:** None. **B.J. Henderson:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.11/D49

Topic: B.02. Ligand-Gated Ion Channels

Support: Texas A&M University

Title: Building extracellular domain α4β2 nicotinic acetylcholine receptors on stilts for making water-soluble receptors

Authors: *G. B. WELLS, A. M. PERSON
Mol. & Cell. Med., Texas A&M Univ. Col. of Med., College Station, TX

Abstract: Background: Extracellular domain (ECD) receptors from α7, α4, α3, β2, and β3 nicotinic receptor subunits that are truncated after the first transmembrane domain (M1) have functional and structural similarity to full-length nicotinic acetylcholine receptors (nAChRs). Their smaller size and reduced transmembrane sequence might allow structural studies at higher resolution and lead to better understanding of structural and functional roles of extracellular and transmembrane domains. The conserved Cys-loop of the ECD interacts with proximal residues of M1 in crystallographic structures of full-length Cys-loop receptors. This interaction guides the design of site-specific protease sites at the ECD-M1 interface that might liberate water-soluble ECD nicotinic receptors *in vitro*. Properties of interfacially-inserted residues, figuratively called "stilts", that facilitate expression of ECD nicotinic receptors, however, are poorly understood.
Objective: Determine whether extending the ECD with proximal residues from M1 functionally unlinks the two domains and guides a strategy for inserting a site-specific protease site at the interface in ECD α4β2 nAChRs.
Methods: Human α4 and β2 cDNAs were truncated after M1 (α4M1 and β2M1). Five to 11 residues were inserted at the interface between the ECD and M1 by mutagenesis, producing an extended ECD followed by native M1. Subunits were expressed in *Xenopus laevis* oocytes. Immunoblotting and immunoisolated [^{3}H]epibatidine binding sites assessed expression of subunits and ECD α4β2 nAChRs.
Results: Excluding the conserved proline at the N-terminus of M1 from its juxtaposition with the ECD and extending the ECD with residues SGMH (from DNA restriction sites) adversely affected expression. Extending the ECD with the first six M1 residues PLFYTI maintained expression. In contrast, extending the ECD with 6 PAGSAG residues for increased interfacial flexibility adversely affected expression. Extending α4 ECD with 11 M1-derived residues PLFYTILFYTI maintained expression of ECD α4β2 nAChRs when combined with β2M1. Extending both α4 and β2 ECD with these 11 M1-derived residues, however, adversely affected expression.

Conclusions: Interaction between the Cys-loop and proximal M1 residues likely is important for expressing ECD α4β2 nAChRs. Success of functionally unlinking the ECD from M1 by inserting residues at the interface may be limited by increased orientational flexibility that inserted residues permit for the ECD of each subunit. A site-specific protease site inserted at the interface may need to include proximal residues from M1, be as short as possible, and have low overall hydrophobicity.

Disclosures: G.B. Wells: A. Employment/Salary (full or part-time):; Texas A&M University. **A.M. Person:** A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.12/D50

Topic: B.02. Ligand-Gated Ion Channels

Title: Mechanism of alpha7 nicotinic acetylcholine receptor upregulation by Bcl2 family proteins

Authors: *B. DAWE[1], H. YU[1], S. GU[1], A. N. BLACKLER[1], E. R. SIUDA[2], J. A. MATTA[1], E. B. REX[3], D. S. BREDT[1]
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Abstract: Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels that modulate synaptic transmission throughout the brain. Accordingly, nAChR dysfunction has been implicated in a variety of neurological disorders, including Alzheimer's disease and schizophrenia, as well as drug addiction. Though neuronal nAChRs have long been considered promising targets for therapeutic compounds, relatively little was known, until recently, regarding the involvement of other, regulatory proteins in their biogenesis. Recent studies from our group have identified NACHO as an essential chaperone for the assembly of homomeric α7 nAChRs, in both recombinant expression systems and brain tissue (Gu et al., 2016; Matta et al., 2017). Additional high-throughput screening of α7 and NACHO, cotransfected with the Broad cDNA library in HEK293T cells, revealed that several anti-apoptotic members of the Bcl2 protein family further upregulated functional expression of this nAChR subtype. Though Bcl2 proteins are principally known to promote or inhibit apoptosis at the mitochondrial membrane, we found that α7 nAChRs possess a Bcl2-like binding motif that facilitates their interaction during biogenesis in the endoplasmic reticulum. Point mutations targeted to this motif strongly attenuate Bcl2-mediated effects on receptor assembly and expression, as assessed by immunostaining and patch-camp electrophysiology. Meanwhile, the same mutations did not affect receptor upregulation by NACHO and the previously reported nAChR chaperone RIC3.

Similarly, chemical inhibitors of Bcl2 proteins also diminished their ability to regulate α7 assembly. Other neuronal nAChR subtypes, including the α4β2 receptor did not appear to be regulated by Bcl2 overexpression. In summary, we characterized a subset of Bcl2 proteins as sufficient to upregulate recombinant α7 expression in HEK293T cells, through a distinct mechanism from other known nAChR protein chaperones.

Disclosures: **B. Dawe:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson. **H. Yu:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson. **S. Gu:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson. **A.N. Blackler:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson. **E.R. Siuda:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson. **J.A. Matta:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson. **E.B. Rex:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson. **D.S. Bredt:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson & Johnson.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.13/D51

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01DA036061

Title: Characterization of murine brain region-specific ^{3}H-epibatidine binding in response to chronic exposure to nicotine, (-) menthol, and nicotine co-administered with either (-)-menthol or (±)-menthol

Authors: *M. J. MULCAHY, S. M. HUARD, J. H. WANG, H. A. LESTER
Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Nicotinic acetylcholine receptors (nAChRs) are pentameric cation channels that are expressed in the mammalian central nervous system, the peripheral nervous system, and the neuromuscular junction. Eleven neuronal nAChR subunits have been identified in mammals (α2-7, α9-10, β2-4), and receptors containing α4β2, α3β4, and α7 subunits are the most abundant nAChR subtypes in the mammalian CNS. Chronic nicotine exposure upregulates total neuronal nAChR levels, as measured by ^{3}H-nicotine and ^{3}H-epibatidine binding. Epibatidine is a toxin that has high affinity for nAChRs and can be used to quantify nAChR levels. Chronic exposure of menthol, a cigarette flavorant, has been shown to upregulate specific nAChR subunits in

several brain regions. A systematic characterization of changes in receptor levels in response to chronic menthol or chronic nicotine + menthol had yet to be performed prior to this study. We investigated the effect of chronic nicotine, (-)-menthol, and nicotine co-administered with either (-)-menthol or (±)-menthol in fourteen murine brain regions for changes in ^{3}H-epibatidine binding. Total ^{3}H-epibatidine binding was further resolved through characterization of cytisine sensitive (mostly α4β2 nAChRs) and cytisine resistant (mostly non-α4β2 nAChRs) fractions. C57bl/6 mice were separated into five treatment groups: vehicle (ethanol), nicotine (2 mg/kg/hr), (-)-menthol (2 mg/kg/hr), nicotine + (±)-menthol (2 mg/kg/hr), or nicotine + (-)-menthol (2 mg/kg/hr). Osmotic minipumps were used for chronic treatment administration over 10-12 days. Our investigations identified region specific upregulation and downregulation of nAChR levels in response to the different chronic drug treatments tested. This comprehensive characterization of changes in nAChR levels in specific brain regions enhances our understanding of the effects of menthol on the mammalian CNS.

Disclosures: M.J. Mulcahy: None. **S.M. Huard:** None. **J.H. Wang:** None. **H.A. Lester:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.14/E1

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH NIGMS grants 1R01GM098343
COBRE NIEF 1P20GM103642
Research Initiative for Scientific Enhancement (RISE) 5R25GM061151-16

Title: Essential role of chs in the ion channel function and thermal stability of native muscle type nachr detergent complex

Authors: *R. MALDONADO-HERNÁNDEZ[1], C. MAYSONET[2], A. PASTRANA[2], C. SILVA[2], E. ALBINO[2], O. QUESADA[2], J. LASALDE[2]
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Abstract: Nicotinic acetylcholine receptors (nAChRs) play crucial roles in many cellular and physiological processes. The manner by which lipid composition affects the functionality and stability of solubilized nAChR is poorly understood. Lipid-protein interactions are of crucial importance for stability and correct function of transmembrane proteins.Cholesterol, which is a key lipid for maintaining the correct functionality of membrane proteins, has been found to alter the nAChR function. Our objective of this study is to understand how cholesteryl hemisuccinate (CHS) affects the thermal stability and functionally the nAChR-detergent complex (nAChR-DC). The nAChRs was extracted from the electric organ tissue of *Torpedo californica,* using

LysoFos Choline 16 as a lipid-analogous detergent (LFC-16), followed by affinity purification, size exclusion, and ionic exchange chromatography. We used circular dichroism spectroscopy, dynamic light scattering, and a two voltage-clamp assay to examine the functionality and stability of the nAChR-DC prepared with different concentrations of CHS and LFC-16. The present results suggest that the CHS preserves the secondary structure of the nAChR making it more thermo-stable in the thermal unfolding experiment. Also, the addition of CHS increases the yields of the nAChR-DC in the affinity purification assay and preserves the functionality in oocytes. This research was supported by the NIH NIGMS grants 1R01GM098343 (JALD); COBRE NIEF 1P20GM103642 (J.R and JALD) and Research Initiative for Scientific Enhancement (RISE) 5R25GM061151-16.

Disclosures: R. Maldonado-Hernández: None. **C. Maysonet:** None. **A. Pastrana:** None. **C. Silva:** None. **E. Albino:** None. **O. Quesada:** None. **J. Lasalde:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.15/E2

Topic: B.02. Ligand-Gated Ion Channels

Title: Anti-apoptotic bcl2 proteins upregulate α7Nicotinic acetylcholine receptorsin neurons

Authors: *H. YU[1], G. B. DAWE[1], A. N. BLACKLER[1], S. GU[1], E. SIUDA[1,2], J. MATTA[1], E. REX[1,3], D. BREDT[1]
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Abstract: Until the discovery of NACHO, α7 nicotinic acetylcholine receptors (nAChRs) were known to not express well in recombinant cell systems. To identify additional partners that can modulate α7 nAChR expression in the presence of NACHO, we conducted a high throughput screen of the Broad cDNA library using surface Bungarotoxin (Bgt) staining and Opera Phenix high content, high throughput imaging system. A group of Bcl2 proteins showed synergy with NACHO to further enhance surface Bgt staining. Systematic study of all Bcl2 proteins indicated that only anti-apoptotic Bcl2 proteins exert this effect. In cultured hippocampal neurons, treatment with inhibitors of Bcl-xl and MCL1 reduced surface Bgt staining, while surface GluA1 labeling was not changed. The inhibitor concentrations were optimized to cause minimal cell death. Only healthy neurons were used in quantification of the Bgt and GluA1 surface stain. Lentiviral-mediated MCL1 overexpression in cultured hippocampal neurons increased Bgt staining but didn't affect GluA1 surface labeling. These results indicate that these anti-apoptotic Bcl2 proteins regulate α7 nAChR surface expression in a manner that is not related to apoptosis.

Disclosures: **H. Yu:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **G.B. Dawe:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **A.N. Blackler:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **S. Gu:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **E. Siuda:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **J. Matta:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **E. Rex:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **D. Bredt:** A. Employment/Salary (full or part-time):; Johnson and Johnson.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.16/E3

Topic: B.02. Ligand-Gated Ion Channels

Support: NSF 1745823
NIH DA032464
NIH DA043567
Danish Research Foundation 109639
Lehigh University CAS
Lehigh University Biological Sciences

Title: Uncovering cholinergic mechanisms of anxiety regulation through the nicotinic receptor protein modulator, lynx2, in mice and humans

Authors: *K. R. ANDERSON[1], H. WANG[1], A. HUPBACH[2], J. M. MIWA[1]
[1]Biol. Sci., [2]Psychology, Lehigh Univ., Bethlehem, PA

Abstract: Anxiety is an adaptive response to a threatening situation, but if not regulated properly can lead to the development of anxiety disorders. The exact etiology of anxiety disorders are unknown. Due to this gap in full understanding, current treatments only provide temporary symptomatic relief and are not effective in all anxiety disorder sufferers. A novel therapeutic approach is through the nicotinic acetylcholine receptors (nAChRs) of the cholinergic system. Nicotinic acetylcholine receptors (nAChRs) have been shown to regulate amygdalar activity but the discovery of their exact roles is still under investigation due to the complexity of nAChR subtypes and varied responses to antagonism. Additionally, anxiety disorders are thought to develop from a complex interaction between genetic, psychological, and environmental factors. To study the role of amygdalar nAChRs and a possible genetic underpinning of anxiety we are using the candidate gene, lynx2. The lynx2 gene is expressed in the amygdala, where the protein product binds to and suppresses nAChR activity. Additionally, heightened anxiety-like behavior have been reported in the lynx2 knockout mouse. Here we further characterize the role of lynx2 in anxiety-like behaviors and responses to different environmental conditions in the knockout

mouse model. We also identify a role of the lynx2 gene in human behavior through human gene sequence analysis and human anxiety behavior correlations.
We hypothesize that lynx2 modulators act to properly regulate amygdala nAChR activity and thus proper anxiety responses in both mice and humans. We are investigating associations between human lynx2 gene sequences and human anxiety levels. To investigate the biological and cellular mechanisms underlying behavioral differences observed in lynx2KO mice, we are pairing behavioral pharmacology assays to further characterize the extent of the anxiety phenotype with electrophysiology studies. We have found that anxiety behaviors such as fear learning are altered in lynx2 knockout mice and that deficits in fear learning could be restored with cholinergic blockade and pharmacology targeted at learning mechanisms. Further studies into the lynx2 knockout mouse model could identify biological mechanisms of anxiety and inform a pharmacogenetic approach to treatment of anxiety disorders.

Disclosures: K.R. Anderson: None. **H. Wang:** None. **A. Hupbach:** None. **J.M. Miwa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ophidion, Inc..

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.17/E4

Topic: B.02. Ligand-Gated Ion Channels

Title: Effects of positive allosteric modulators on the human α4β2 receptor desensitization

Authors: *S. BERTRAND[1], T. SCHAER[1], D. BERTRAND[1], M. ACKERMAN[2], J. NAU[2]
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Abstract: Neuronal nicotinic acetylcholine receptors display a high degree of desensitization upon sustained exposure to an agonist. While onset and recovery of desensitization was characterized for acetylcholine at the human α4β2 receptors, much less is known about the effects of other agonists.
In this work, we examined the desensitization and recovery to a sustained exposure for the full agonist OC-02 (Oyster Point Pharma, Inc, formerly TC-6499) and the partial agonist varenicline at the human α4β2 receptors. Whereas almost full recovery of the response was observed for OC-02, inhibition caused by varenicline was more profound and long lasting.
The discovery that several substances such as Br-PBTC or NS-9283 act as positive allosteric modulators at neuronal nicotinic receptors offers additional possibilities to tackle the mechanisms underlying receptor desensitization. Experiments conducted at the human α4β2 receptors expressed in *Xenopus* oocytes confirmed that Br-PBTC and NS-9283 are powerful positive allosteric modulators at these receptor subtypes. A difference was, however, observed

between these two compounds when comparing their activity at the responses evoked by OC-002. Namely, while Br-PBTC significantly increase the maximal evoked currents, exposure to NS-9283 caused no increase of the current amplitude.
Effects of Br-PBTC and/or NS-9283 were next examined on the desensitization caused by sustained exposure to OC-02 or varenicline and if co-exposure with a modulator could prevent varenicline desensitization. A major difference was observed in presence of BrPBTC. Namely coexposure with this modulator was able to reverse desensitization caused by varenicline within 3 hours. Conversely, NS9283 caused no significant modification of recovery from desensitization. While these modulators had little or no effect at recovery from desensitization caused by OC-02
These data illustrate the importance of allosteric modulation on the functional properties of neuronal nicotinic acetylcholine receptors and highlight the possibility to minimize desensitization effects caused by sustained exposure to an agonist.

Disclosures: S. Bertrand: A. Employment/Salary (full or part-time):; HiQScreen Sàrl. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Contracted Research, Oyster Point Pharma Inc. **T. Schaer:** A. Employment/Salary (full or part-time):; HiQScreen Sàrl. **D. Bertrand:** A. Employment/Salary (full or part-time):; HiScreen Sàrl. F. Consulting Fees (e.g., advisory boards); Oyster Point Pharma Inc. **M. Ackerman:** A. Employment/Salary (full or part-time):; Oyster Point Pharm. Inc. **J. Nau:** A. Employment/Salary (full or part-time):; Oyster Point Pharm. Inc..

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.18/E5

Topic: B.02. Ligand-Gated Ion Channels

Support: NINDS 1R15NS090368-01
Deutsche Forschungsgemeinschaft (DE 1165/2-3)

Title: Properties of novel alpha7 nicotinic acetylcholine receptor ligands for predicting performance as PET tracers

Authors: *M. M. LEVANDOSKI[1], A. KOZJEK[1], Y. LIU[1], W. TEAGLE[1], D. PETERS[2], W. DEUTHER-CONRAD[3], M. SCHEUNEMANN[3], P. BRUST[3]
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Abstract: The nicotinic acetylcholine receptors (nAChRs), especially the α7 homomeric subtype, have been implicated in several neuropsychiatric disorders, such as Alzheimer's disease, Parkinson's disease, and schizophrenia. Although monitoring the activity of nAChRs *in vivo* can be achieved with positron emission tomography (PET), an optimal tracer for the α7 subtype with a high affinity, specificity and sensitivity has yet to be discovered. We aim to develop a correlative model to predict the *in vivo* performance of potential α7 nAChR PET ligands with *in vitro* methods. After expressing the receptor in *Xenopus* oocytes, we performed two-electrode voltage-clamp experiments to examine the pharmacological properties of six compounds (DBT-10, DBT-38, NS6784, NS10743, NS14490, and NS14492), including their potencies and efficacies, modes of modulation, and desensitization properties.
We have found that the compounds of the NS series are agonists with EC_{50}s ranging between 0.3 ± 0.1 and 2.5 ± 1.5 μM and efficacies in the range of that for acetylcholine (ACh). In contrast, the DBT compounds are weak partial agonists, but they modulate ACh responses in co-application experiments. We found a biphasic response, with the DBT compounds potentiating at low concentrations but inhibiting the response at higher concentrations. DBT-10, recently characterized as a suitable PET tracer, can achieve complete inhibition with an IC_{50} of 100 ± 25 nM, but DBT-38 only reached 40% inhibition. Modes of modulation vary, notably with DBT-10 being a non-competitive inhibitor.
Due to the importance of desensitization of α7 nAChRs, we studied the effects of the novel ligands on these properties. We studied the time course of recovery back to the control response following exposure to each compound in several ways. We found that recovery from desensitization is a function of time, frequency of receptor activation, and amount of exposure to the drug, and all vary depending on the compounds used. Responses in oocytes exposed to NS14490, DBT-10, and DBT-38 take longer to recover, whereas those for the other NS compounds recover at a rate comparable to ACh.
Future research will include the examination of the PET tracer [^{18}F]ASEM, a structural analog of DBT-10, and further derivatives in order to establish a link between function and structure. We have started developing a single-channel approach to address the complication in predicting the performance of α7 nAChR potential PET ligands regarding desensitization properties. Finally, we have begun developing an initial model correlating these parameters and ligand effectiveness *in vivo.*

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Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.19/E6

Topic: B.02. Ligand-Gated Ion Channels

Support: ANR JCJC-Nicopto
NARSAD
Fondation pour la recherche médicale

Title: *In vivo* optical control of brain nicotinic acetylcholine receptors

Authors: *A. MOUROT, R. DURAND-DE CUTTOLI, S. MONDOLONI, J. JEHL, P. FAURE
Neurosci. Paris Seine, Sorbonne Univ., Paris, France

Abstract: Acetylcholine (ACh) provides a widespread and diffuse signal in the brain. It alters neurotransmitter release and affects neuronal integration and network activity, notably by acting through ionotropic nicotinic ACh receptors (nAChRs). nAChRs consist of hetero- and homo-pentameric arrangements of α and β subunits (9 and 3 genes, respectively), yielding a high combinatorial diversity of channel composition, localization and function. Nicotinic neuromodulation controls learning, memory and attention, and has been associated with the development of numerous neurological and psychiatric disorders, including epilepsy, schizophrenia, anxiety and nicotine addiction. To understand how nAChRs mediate such diverse functions, we developed an opto-chemical-genetic strategy for acutely and reversibly manipulating these receptors in the mammalian brain in vivo (1). We have notably developed light-inhibitable nAChRs (LinAChRs) of the β2 and β4 subtypes, that respond normally to ACh or nicotine in darkness, but are rapidly antagonized upon illumination with 380 nm light (2, 3). This strategy relies on the covalent attachment of a photoswitchable tethered antagonist onto a genetically-encoded, cysteine-ready receptor mutant. We used lentiviruses to demonstrate rapid and specific control of nicotinic transmission in the ventral tegmental area (VTA) and the interpeduncular nucleus (IPN), two brain regions expressing high densities of nAChRs and strongly implicated in nicotine addiction. Using in-vivo electrophysiological recordings coupled to photocontrol of specific nAChRs, we provide direct evidence that the ACh tone fine-tunes the firing properties of VTA dopamine and IPN neurons through somatic nAChRs. Furthermore, locally photo-antagonizing β2-containing receptors in the VTA was sufficient to reversibly switch nicotine reinforcement on and off. By enabling control of nicotinic transmission in targeted brain circuits, this technology will help unravel the various physiological functions of nAChRs and may assist in the design of novel therapies relevant to neuropsychiatric disorders.
Refs: (1) Durand-de Cuttoli R. et al., bioRxiv, 266163 (2) Tochitsky I. et al., Nat. Chem. 4 (2), 105-111 (3) Lemoine D. et al., Optogenetics: Methods and Protocols, 177-193.

Disclosures: A. Mourot: None. **R. Durand-de Cuttoli:** None. **S. Mondoloni:** None. **J. Jehl:** None. **P. Faure:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

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Program #/Poster #: 283.20/E7

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01 DA042749
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Barrow Neurological Foundation

Title: Screening of alpha-Conotoxins with activity at the alpha3beta2* nicotinic acetylcholine receptor subtype

Authors: *B. EATON[1], F. FISHER[3], F. HARARAH[3], C. HUIDOBRO[3], J. MCINTOSH[3,5,4], P. WHITEAKER[2]
[1]Neurobio., [2]Div. Neurobiol, Barrow Neurolog. Inst., Phoenix, AZ; [3]Dept. of Biol., [4]Dept. of Psychiatry, Univ. of Utah, Salt Lake City, UT; [5]George E. Whalen Veterans Affairs Med. Ctr., Salt Lake City, UT

Abstract: α-Conotoxin MII (α-CtxMII) selectively antagonizes α3β2*- and α6β2*-nAChR. We have previously developed α6β2*-nAChR-selective α-Ctxs to define mesolimbic α6β2*-nAChR contributions to nicotine and other drug abuse phenotypes. A lack of selective compounds, and lethality in α3-nAChR subunit-null mutant mice, means virtually no studies of native α3β2*-nAChR have been performed. The medial habenula (MH) and interpeduncular nucleus (IPN) contain the densest CNS α3β2*-nAChR populations (outnumbering MH and IPN α6β2*-nAChR). MH & IPN α3β4*- and α5*-nAChR are already known to support nicotine dependence, but ganglionic α3β4*-nAChR expression and a lack of α5 subunits in orthosteric binding sites may make these problematic anti-smoking targets. These potential difficulties motivate us to assess the contributions of additional MH and IPN subtypes such as α3β2*- and α6β2*-nAChR to nicotine abuse and addiction phenotype. Here, we describe screening of a panel of 372 α-Ctx ligands, to discover leads with α3β2*-nAChR selectivity. Preliminary screens were performed utilizing the $^{86}Rb^{+}$ efflux assay. Fifteen ligands in the panel have been found to be highly potent at α6/3β2β3-nAChR, having IC_{50} values less than 100nM. Included in those fifteen ligands are ten α-Ctxs that have multiple variants represented in the screen. Potency is highly sensitive to amino acid substitutions. Point mutations have weakened or completely eliminated activity of related α-Ctxs, and have also rendered inactive α-Ctxs highly potent at α6β2*-nAChR. As of the submission of this abstract our previously-created stably-transfected α3β2-nAChR mammalian cell line has lost function over multiple passages in cell culture. Because of this, we have been unable to screen with $^{86}Rb^{+}$ efflux assays. We are, instead, currently screening the α-Ctx panel for activity at α3β2-nAChR utilizing *Xenopus laevis* oocytes and two electrode voltage clamp

(TEVC) electrophysiology. Lead peptides will be identified as those with selectivity for α3β2- over α6β2*-nAChR. Following identification of such lead α-Ctxs, we will compare their sequences and use this information to drive a positional scanning mutagenesis approach. Our goal is to develop and validate a panel of α-Ctxs with greater than 100-fold α3β2-nAChR selectivity across human, mouse, and rat nAChR. This will be sufficient to identify and characterize the potential of α3β2*-nAChR, as well as refine our understanding of α6β2*-nAChR viability, as novel pharmacotherapeutic targets for smoking cessation.

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Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

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Program #/Poster #: 283.21/E8

Topic: B.02. Ligand-Gated Ion Channels

Support: Arizona Biomedical Research Commission (ADHS14-083003)
Barrow Neurological Foundation (BNF)

Title: Amyloid beta-induced alterations in basal forebrain cholinergic intrinsic excitability are mediated by α7 and α7β2-containing nicotinic acetylcholine receptors (nAChRs)

Authors: *A. A. GEORGE[1], H. A. BIMONTE-NELSON[2], R. J. LUKAS[1], P. WHITEAKER[1]
[1]Neurobio., Barrow Neurolog. Inst., Phoenix, AZ; [2]Arizona State Univ., Tempe, AZ

Abstract: Alzheimer's disease (AD), a progressive neurodegenerative disorder, is one of the most common causes of mental deterioration in the elderly. Hallmarks of AD pathology include alterations in brain regions associated with higher cognitive functions. Several studies have correlated the severity of cognitive decline in early AD with a loss of basal forebrain cholinergic neurons (BFCNs). Mechanisms underlying cholinergic neurodegeneration and subsequent memory impairments remain unknown. However, interactions between amyloid-beta (Aβ), a suspected etiopathogenic agent in AD, with a nicotinic acetylcholine receptor (nAChR) subtype containing α7 subunits trigger an increase in hippocampal neuronal excitability. Heteromeric α7β2-nAChRs have similar pharmacological properties to those of homomeric α7-nAChRs and are highly sensitive to functional modulation by Aβ. Toward understanding the roles played by nAChRs in BFCN function we used single-channel electrophysiology to explore the functional relationship between Aβ and α7 and α7β2-containing nAChRs. We demonstrate that oligomeric Aβ activates both α7 and α7β2-nAChRs and preferentially enhances α7β2-nAChR single-channel open dwell-times (representing a 3.5-fold increase), effects that can be abrogated using the known nAChR antagonists MLA or mecamylamine. Using organotypic slice cultures and

whole-cell patch clamp electrophysiology we demonstrate that chronic incubation with oligomeric Aβ increases BFCN firing rates in the medial septum and horizontal diagonal band (MSDB: 64 ± 8% and HDB: 25 ± 3.5%, respectively). BFCN firing rates were mirrored by 1) reduced afterhyperpolarization (AHP) magnitude (reduction of 44 ± 6.5% and 15 ± 2.5%, respectively), 2) attenuation in action potential amplitude (38 ± 6.5% reduction), 3) reduced spike-frequency adaptation (i.e. reduced interspike interval ratio) and 4) development of a hyperpolarization-activated cationic current (I_h), when compared to controls (scrambled Aβ). These Aβ-induced alterations were absent in the nucleus basalis (NB). Interestingly, regionally-specific changes in BFCN intrinsic excitability were normalized in β2 nAChR subunit knockout, suggesting that Aβ alters cholinergic intrinsic excitability by interacting with α7 and β2-containing nAChRs. These interactions may be specific to certain cholinergic circuits within the basal forebrain and suggest novel and potentially productive therapeutic strategies to combat neurodegeneration in a brain region affected early in AD. This work was supported by the Arizona Biomedical Research Commission (AAG; ADHS14-083003) and the Barrow Neurological Foundation (AAG).

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Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.22/E9

Topic: B.02. Ligand-Gated Ion Channels

Support: Michael J. Fox Foundation for Parkinson's Research (Grant #11728)

Title: AN6001: A subtype selective α6 nAChR PAM showing potentiation of dopamine release and protection of dopaminergic neurons

Authors: *T. DYHRING[1], D. T. BROWN[1], J. KLEIN[1], M. VAN HOUT[2], A. A. JENSEN[2], P. CHRISTOPHERSEN[1]
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Abstract: Dopamine (DA) release in the striatum is critical for regulation of movement and disruption of DA signaling underlie a variety of psychomotor disorders, including Parkinson's disease (PD). Pre-synaptic nicotinic acetylcholine receptors (nAChRs) are involved in the control of dopamine release and nAChRs containing the α6-subunit (α6* nAChRs) have gained interest as therapeutic targets in PD due to the restricted expression pattern of these receptors. Furthermore, parkinsonian animal models in which the nigrostriatal pathway has been selectively

damaged with dopaminergic neurotoxins such as 6-OHDA or MPTP, show a decreased α6* nAChR expression and function. Such lesions closely parallel the decline in dopaminergic terminal integrity seen in post mortem PD brains, which supports the involvement of nigrostriatal α6* nAChRs in PD.
By using a combination of fluorescence-based and electrophysiological assay techniques, we have identified small molecules acting as positive allosteric modulators (PAMs) of α6* nAChRs. Here we present data on AN6001, which has sub-micromolar potency at α6* nAChRs and demonstrates a high degree of selectivity for α6* nAChRs over other more widely expressed nAChR subtypes. When tested at native rodent receptors, AN6001 caused a significant potentiation of α6-stimulated synaptosomal DA. Furthermore, slice electrophysiological recordings on putative dopaminergic neurons from rat substantia nigra pars compacta, AN6001 displayed augmentation of cholinergic stimulated action potential firing. Additionally, we tested cell survival of dopaminergic neurons using rat primary mesencephalic cultures. By challenging the neurons with MPP+, we found that AN6001 elicited a significant enhancement of the neuroprotective effect mediated by nicotine.
These results provide the first evidence of positive allosteric modulation of α6* nAChRs and demonstrate that a nicotinic α6 PAM has the potential to strengthen acetylcholine-mediated dopaminergic signaling. An α6 PAM, as presented here, is expected to selectively enhance endogenous α6* nAChR-mediated signaling in a process that is not supposed to promote increased steady state desensitization of the receptors and thereby, is less likely to induce tolerance as compared to nicotinic receptor agonists.

Disclosures: D.T. Brown: None. **J. Klein:** None. **M. van Hout:** None. **A.A. Jensen:** None. **P. Christophersen:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.23/E10

Topic: B.02. Ligand-Gated Ion Channels

Title: SUVN-911 (potent and selective nicotitinicacetylcholine α4β2 receptor antagonist) - Safety, tolerability and pharmacokinetics in healthy subjects

Authors: *G. BHYRAPUNENI, K. MUDIGONDA, R. PALACHARLA, P. JAYARAJAN, R. SUBRAMANIAN, V. GOYAL, S. PANDEY, D. AJJALA, A. MOHAMMED, S. JETTA, R. NIROGI
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Abstract: SUVN-911 is a potent and selective α4β2 receptor antagonist with more than 300 fold selectivity (NovaScreen selectivity panel). SUVN-911 showed good oral bioavailability in all

preclinical species. It also showed good brain penetration and receptor occupancy following oral administration. It demonstrated antidepressant like effects in animal models of depression. Faster onset of action, no sexual dysfunction and procognitive potential in animal models are the differentiating features for SUVN-911. At behaviorally effective doses, SUVN-911 produced a significant increase in cortical serotonin and norepinephrine levels. SUVN-911 showed good margin of safety in toxicity studies and is non-mutagenic. SUVN-911 was studied in a single-center, multi-faceted, Phase 1 clinical trial (US IND) to evaluate its safety, tolerability, and pharmacokinetics after single and multiple ascending doses administered orally in healthy male subjects. For single dose evaluation, healthy human volunteers were once dosed with 0.5 mg, 6 mg, 15 mg, 30 mg and 60 mg of SUVN-911 tablets. For multiple ascending dose evaluation, once daily doses of 15, 30 and 45 mg SUVN-911 were administered orally for 14 days. SUVN-911 was quantified in plasma using a validated LC-MS/MS method. Safety and tolerability was evaluated throughout the study by assessing the incidence and severity of AEs, abnormalities in vital signs, ECG and clinical parameters.SUVN-911 was well tolerated up to the highest tested dose of 60 mg single dose or 45 mg/day multiple doses in healthy male subjects. There were no clinically relevant or serious adverse events reported. During single ascending dose studies, the absorption of SUVN-911 was rapid and exposures (C_{max} and AUC) were more than dose proportional at the tested doses between 0.5 mg to 60 mg. During multiple ascending dose studies, SUVN-911 achieved the projected efficacy concentrations. Additional Phase 1 clinical study (US IND) to evaluate the effect of food, gender and age on human pharmacokinetics is in progress.

Disclosures: G. Bhyrapuneni: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **D. Ajjala:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.24/E11

Topic: B.02. Ligand-Gated Ion Channels

Support: COGNITO (Innovation fund, Denmark)
Lundbeck Foundation

Title: The genes encoding the alpha7 nicotinic acetylcholine receptor subunit and the human truncated and duplicated form, dup alpha7, are expressed and regulated in microglia cells

Authors: *J. D. MIKKELSEN, S. ARPE, M. DINARZEHI, J. MENEZES, M. H. SØRENSEN, S. S. ARIPAKA
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Abstract: The penta-homomeric alpha7 nicotinic acetylcholine receptor (nAChR) is a ligand-gated ion-channel, and activation of the receptor leads to inward flow of calcium and natrium in neurons. Previous studies carried out in THP-1 or Jurkat cell lines, shows that the alpha7 nAChR conveys anti-inflammatory properties by reducing the inflammatory cytokine releases by a mechanism not involving ion flow. It is considered that the receptor signal involve other intracellular signalling pathways in microglia cells than in neurons. While agonists have no effect, a subset of low-efficacy partial or silent agonists such as NS6740 elicit anti-inflammatory effects. In this study, we compared the pharmacology and expression of the two genes (*chrna7* and c*hrfam7a*) encoding the alpha7 nAChR and the human truncated and duplicated form, dup-alpha7 nAChR in primary microglia and the microglia cell line, BV2. In all cells, NS6740 reduced lipopolysaccharide (LPS)-induced TNF-alpha release at concentrations of 30 uM, and full effect was achieved at 100 uM. Also, in rat microglia microglia NS6740 reduced interleukin-1b and TNFalpha gene expression in LPS-stimulated cells. Expression, of alpha7 nAChR mRNA was detected in non-human microglia, and the level up-regulated by LPS. In contrast, only dup-alpha7 nAChR mRNA was detected in human microglia. These data suggest that alpha7 nAChR is expressed in microglia and may exert an important role in control of inflammation in the brain, and that duplicated form may exert a role in human that may be different from other mammalian species.

Disclosures: J.D. Mikkelsen: None. **S. Arpe:** None. **M. Dinarzehi:** None. **J. Menezes:** None. **M.H. Sørensen:** None. **S.S. Aripaka:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.25/E12

Topic: B.02. Ligand-Gated Ion Channels

Support: CONACYT Grant 236719

Title: Modulation of glutamate release by nicotine in the rostromedial tegmental nucleus (RMTg)

Authors: *D. E. CASTILLO-ROLON, G. ARENAS-LÓPEZ, S. MIHAILESCU, O. HERNANDEZ-GONZALEZ, S. HERNÁNDEZ-LÓPEZ
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Abstract: The rostromedial tegmental nucleus (RMTg) is a bilateral structure localized in the midbrain. The RMTg is mainly constituted by GABAergic neurons which exert a strong tonic inhibition on the mesolimbic and the nigrostriatal dopamine systems (Barrot et al, 2012; Kaufling, 2009; Gonçalves, 2012). Accordingly, it has been reported that the inhibition or activation of the RMTg, increases or decreases the activity of midbrain dopamine neurons, respectively (Jhou et al, 2009b; Stamatakis & Stuber, 2012). The major excitatory input to the RMTg is glutamatergic projections from the lateral habenula (LHb). On the other hand, RMTg receives dense cholinergic inputs from the tegmental laterodorsal and pedunculopontine nuclei. Previous studies suggest the presence of nicotinic acetylcholine receptors (nAChRs) at glutamatergic terminals that establish contact with the RMTg cells (Lecca et al, 2012). The aim of this work was to investigate whether the activation of nAChRs modulates glutamate release in the RMTg nucleus. We used voltage clamp techniques in whole cell configuration to examine the effect of selective nicotinic drugs on the spontaneous glutamatergic excitatory postsynaptic currents (EPSCs) recorded from GABAergic RMTg neurons in rat midbrain slices. We found that the activation of nAChRs by nicotine or acetylcholine, increase the frequency of EPSCs in the RMTg neurons through α7 but not α4β2 nAChRs. This effect persisted for about 30-40 minutes after the washout of the drug. The effect was dependent on calcium release from intracellular calcium stores but independent on action potentials or the activation of voltage-gated calcium channels.

Disclosures: D.E. Castillo-Rolon: None. **G. Arenas-López:** None. **S. Mihailescu:** None. **O. Hernandez-Gonzalez:** None. **S. Hernández-López:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.26/E13

Topic: B.02. Ligand-Gated Ion Channels

Support: DGAPA PAPIIT grant-IN-216416

Title: Opposite effects of alpha7 and alpha4beta2 nicotinic acetylcholine receptors on dorsal raphe serotonergic neurons

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Abstract: The dorsal raphe nucleus (DRN) provides the serotonergic input for most of forebrain structures. Alpha7 and alpha4beta2 nicotinic acetylcholine receptors (nAChRs) are present on the soma of 5-HT DRN neurons an on intra-raphe noradrenergic, glutamatergic and GABAergic terminals. Previous studies from our laboratory indicated that nicotine increases the firing activity of 5- HT DRN neurons through stimulation of both postsynaptic and presynaptic nAChRs (Mihailescu et al, 1997; Galindo et al., 2008, Garduño et al, 2012). These studies did not however establish which type of presynaptic nAChR is responsible for the increase in 5-HT DRN neuron firing rate. The purpose of this study was to determine the effects on 5-HT DRN neuron firing rate, glutamate and GABA release of specific agonists of alpha7 and alpha4beta2 nAChRs. The experiments were performed in midbrain slices obtained from young (19-21 postnatal days) Wistar rats. The electrical activity of 5-DRN neurons was recorded using the whole cell voltage- and current clamp techniques. When bath administered in a concentration of 0.1 μM, the specific agonist at alpha4beta2 nAChRs E-N-methyl-4-(3-pyridinyl)-3-butene-1-amine (RJR-2403 oxalate, 0.1 μM), produced an increase in the firing rate of 5-HT DRN neurons by 37% and an increase of the frequency of spontaneous and miniature excitatory postsynaptic currents (sESPSCs and mEPSCs respectively). Surprisingly, mecamylamine (MCM, 3 μM), a non-specific and non-competitive antagonist at nAChR, produced similar effects as RJR-2403. The specific agonist at α7 nAChRs *N*-(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl-4-chlorobenzamide (PNU-282987,100 nM), induced a 64.8% decrease in 5-HT DRN neuron firing rate and an increase in the frequency of GABAergic sIPSCs and mIPSCs. These data indicate that the stimulatory effects of nicotine and mecamylamine on 5-HT DRN neurons are indirect, presynaptic, dependent on alpha4beta2 nAChRs-mediated increase of glutamate release in the DRN. The stimulation of DRN alpha7 nAChRs produces the inhibition of 5-HT DRN neurons by inducing presynaptic release of GABA from GABAergic terminals present in the DRN.

Disclosures: S.P. Mihailescu: None. **O. Hernandez:** None. **D. Castillo-Rolon:** None. **S. Hernandez-Lopez:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.27/E14

Topic: B.02. Ligand-Gated Ion Channels

Support: HHS-NIH-NIDA-SS-2016-251

R01-DA021274
NIH RL5GM118969
NIH TL4GM118971
NIH UL1GM118970

Title: Sex differences in gene expression of nicotinic acetylcholine receptor (nAChr) subunits in the interpeduncular nucleus of female and male rats experiencing nicotine withdrawal

Authors: *M. C. GARCIA ARREGUIN[1], V. L. CORREA[1], R. J. FLORES GARCIA[2], L. E. O'DELL[3]
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Abstract: Withdrawal from chronic nicotine elicits negative affective states that are modulated, in large part, via nAChRs in the medial habenula-interpeduncular nucleus (MHb-IPN) pathway of the brain. Previous research using knock-out mice has demonstrated that $alpha_4beta_2$ and $alpha_5$ nAChRs in MHb-IPN pathway are necessary for the expression of negative affective states produced by nicotine withdrawal. Despite the current knowledge of the role of nAChRs in nicotine withdrawal, there is little information regarding sex differences in the expression of these receptors during withdrawal in the IPN. To address this issue, the present study compared gene expression of $alpha_4$, $beta_2$, and $alpha_5$ receptor subunits in the IPN of female and male rats during nicotine withdrawal. Female and male rats were implanted with a pump that delivered nicotine for 14 days. The following day, the rats received an injection of saline or the nAChR antagonist, mecamylamine, to precipitate withdrawal. Twenty minutes later, rats were tested for anxiety-like behavior using the elevated plus maze (EPM) test. After testing, the IPN was dissected and $alpha_4beta_2$, and $alpha_5$ mRNA expression was assessed using RT-qPCR methods. The results from the EPM revealed that female rats displayed an increase in anxiety-like behavior during withdrawal that was larger than males. The molecular results revealed that female rats displayed an increase in the expression of $alpha_5$ mRNA, an effect that was absent in male rats experiencing withdrawal. In contrast, male rats displayed an increase in the expression of $apha_4$ and $beta_2$ mRNA, and this effect was absent in female rats. These data suggest that sex differences in anxiety-like behavior produced by nicotine withdrawal is related to a differential expression of $alpha_4beta_2$ and/or $alpha_5$ nAChRs in the IPN, and future studies are needed to explore the role of various nAChRs in the MHb-IPN pathway in modulating sex differences in the expression of the nicotine withdrawal syndrome.

Disclosures: M.C. Garcia Arreguin: None. **V.L. Correa:** None. **R.J. Flores Garcia:** None. **L.E. O'Dell:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.28/E15

Topic: B.02. Ligand-Gated Ion Channels

Title: Space clamp issues fail to confound estimates of nicotinic synaptic strength in rat sympathetic neurons

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Abstract: In recent experiments, we estimated the strength of individual nicotinic synapses on sympathetic neurons by whole-cell patch recording from the isolated intact rat superior cervical ganglion (SCG) at 36°C. To estimate synaptic size, we recorded EPSCs under voltage-clamp using minimal stimulation. We calibrated the excitatory strength of individual synapses in terms of threshold synaptic conductance (thresh-g_{syn}), measured using virtual EPSPs created by dynamic clamp. Given that nicotinic synapses are distributed over the cell body and dendrites, this raises an important methodological question. Do space clamp limitations invalidate our approach? To address this question, we took advantage of the fact that the strength of some nicotinic synapses straddles threshold when activated repeatedly at 1Hz. With minimal stimulation, we recorded trains of 100 straddling EPSPs and trains of 100 EPSCs from 10 synapses in 5 SCGs. In each case, we converted the EPSCs into a train of virtual EPSPs and used it to stimulate the same cell. To test our question, we then compared the number of action potentials evoked by the real EPSPs and the virtual EPSPs. The real EPSP trains triggered 3 to 87 spikes and the virtual EPSP trains triggered 3 to 88 spikes. The real and virtual spike numbers were well fit by linear regression (slope = 0.94, r^2=0.83, 95% confidence limits of slope = 0.60 to 1.29). Importantly, we also discovered that the excitatory strength of virtual EPSPs was very sensitive to the decay time constant of the EPSC, which was 4 ms in these experiments. This suggests that converting synaptic currents into corresponding virtual EPSPs can accurately mimic the excitatory strength of real EPSPs in these neurons. Although space clamp limitations may obscure synaptic events in distal dendrites, this hypothetical effect appears not to bias the mimcry produced by virtual EPSPs. These exploratory results provide the basis for a definitive confirmatory study. The approach described here also opens the door to detailed studies of postsynaptic integration of converging nicotinic EPSPs at synapses of known strength.

Disclosures: J.P. Horn: None. **P.H.M. Kullmann:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.29/E16

Topic: B.02. Ligand-Gated Ion Channels

Support: CIHR Grant MOP-89825 (EKL)
Canada Research Chair in Developmental Cortical Physiology (EKL)
NIH Award R01-DA035838 (EET)

Title: The elusive role of the alpha5 nicotinic receptor subunit in prefrontal responses to acetylcholine

Authors: *S. VENKATESAN[1,2], E. E. TURNER[5,6], E. K. LAMBE[2,3,4]
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Abstract: Layer 6 pyramidal neurons of the medial prefrontal cortex (mPFC) are excited robustly by acetylcholine (ACh) and are thought to be involved in top down cholinergic modulation of attention. The α5 nicotinic receptor subunit encoded by *Chrna5* is an accessory subunit that is heavily expressed in layer 6 of the PFC and is thought to affect receptor conductance and desensitization properties. Previous studies show that $\alpha5^{-/-}$ mice are impaired during demanding attentional tasks. Single nucleotide polymorphisms in *Chrna5* are also associated with increased risk of schizophrenia and smoking. However, the exact function of *Chrna5* in the cellular and network response to acetylcholine (ACh) is unknown. We performed whole cell recordings of layer 6 mPFC pyramidal neurons expressing *Chrna5* to measure responses to exogenous application of ACh in brain slices. BAC transgenic mice that express Cre from the *Chrna5* locus without the overexpression of the associated nicotinic receptor genes were generated and crossed with a ZsGreen reporter line (Ai6) to record from the labeled cells. Both male and female mice of postnatal day 36-40 were used. All labeled neurons were regular spiking, with input resistance 116 ± 11 MΩ, and resting membrane potential -86 ± 2 mV (mean ± SEM; N=16). The peak inward current elicited by bath application of 1mM ACh is twofold higher in *Chrna5* positive cells (-184 ± 17 pA, N=17 cells) compared to an unlabeled population of cells (-97 ± 7 pA, mean ± SEM; N=9 cells; p= 0.002, unpaired t test). Nonstationary fluctuation analysis of whole cell ACh currents will be used next to ascertain whether the higher response in *Chrna5* positive cells is due to increased single channel conductance of the nicotinic receptors. Our results show that there is a subpopulation of cells expressing *Chrna5* in layer 6 of the mPFC that have the highest responses to ACh. Further experiments will use *Chrna5* transgenic mice crossed with mice expressing Channelrhodopsin 2 in cholinergic neurons

(ChAT-ChR2 mice), to achieve optogenetic release of ACh. This will help understand the function of the Chrna5 expressing cells during endogenous release of ACh in the PFC. These experiments serve to elucidate the role of the α5 subunit in the cholinergic control of attention circuitry.

Disclosures: S. Venkatesan: None. **E.E. Turner:** None. **E.K. Lambe:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.30/E17

Topic: B.02. Ligand-Gated Ion Channels

Support: CIHR Award MOP-89825 (EKL)
Canadian Research Chair in Developmental Cortical Physiology (EKL)
Postdoctoral Fellowship from the Alzheimer's Society of Canada (DWS)
NIH Award R01-DA035838 (EET)
NIH Award R01-MN093667 (EET)

Title: The neurophysiological role of the interpeduncular nucleus in α5 subunit mediated nicotine responses

Authors: *S. SIVAKUMARAN[1,2], D. W. SPARKS[2], E. E. TURNER[5,6], E. K. LAMBE[2,3,4]
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Abstract: The interpeduncular nucleus (IP) is a well-known target for the effects of nicotine with potential repercussions regarding the initial physiological reaction to this addictive drug. The α5 nicotinic receptor subunit, encoded by the *Chrna5* gene, is highly expressed in the IP and potentially conveys aversive properties of the drug. Normal *Chrna5* expression appears to be protective against the development of nicotine addiction. In humans, a single nucleotide polymorphism in *Chrna5* that disrupts function of the α5 protein, has been identified among individuals who readily develop chronic nicotine dependence. The α5 subunit likely acts as an accessory subunit and does not appear to participate directly in the nicotinic receptor binding site. Yet, it alters the conductance and desensitization parameters of nicotinic receptors. Here, we probe the contribution of the α5 subunit to baseline properties and nicotine-elicited neuronal excitability in the IP. We further examine the plasticity of these neurons following prior *in vivo* nicotine priming. For these experiments, we use whole-cell patch clamp electrophysiology in brain slices from $\alpha5^{+/+}$ and $\alpha5^{-/-}$ mice together with a novel line of transgenic mice expressing Cre-recombinase from the *Chrna5* locus. These mice were created by BAC recombineering to

manipulate α5-expressing neurons to express fluorescent reporters or optogenetic proteins without mis-expressing the α3 and β4 nicotinic receptors encoded at the same locus. We find that responses to nicotine are attenuated in the IP of $\alpha5^{-/-}$ mice, with initial examination focused on the interneurons of the rostral IP (IPR). Ongoing work will examine the electrophysiological implications of *in vivo* exposure to systemic nicotine as measured in IPR neurons, as well as the relationship between these changes and mouse behavior.

Disclosures: S. Sivakumaran: None. **D.W. Sparks:** None. **E.E. Turner:** None. **E.K. Lambe:** None.

Poster

283. Structure and Function of Nicotinic Acetylcholine Receptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 283.31/E18

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant NS093590

Title: Pharmacological characterization of cmpi interaction with (A4)3(B2)2 neuronal nicotinic acetylcholine receptors

Authors: F. DEBA[1,2], K. MUNOZ[2], A. TAIRU[2], *A. K. HAMOUDA[1,2]
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Abstract: Positive allosteric modulators (PAMs) of neuronal nicotinic acetylcholine receptors (nAChRs) have emerged as a favorable pharmacological class to enhance brain ACh signaling for potential clinical applications. They enhance ACh potency and/or efficacy by binding at site(s) distinct from the ACh binding sites and thus potentially unique to a nAChR subtype. While a number of nAChR PAMs have been identified, CMPI and NS9283 are unique because they selectively potentiate (α4)3(β2)2 nAChR. CMPI and NS9283 potentiate responses of (α4)3(β2)2 but not (α4)2(β2)3 nAChR isoforms by binding to overlapping pockets at the "non-canonical" α4:α4 subunit interface which only exists in the (α4)3(β2)2 nAChR. NS9283 and CMPI potentiation of the (α4)3(β2)2 nAChR was characterized using ACh, a full agonist of (α4)3(β2)2 nAChR that binds with higher affinity at α4:β2 agonist binding sites and with lower affinity at the α4:α4 subunit interface. In addition, ACh binding site at the α4:α4 subunit interface overlaps with the NS9283 and CMPI binding sites. Here we extend these studies to characterize NS9283 and CMPI potentiation of a panel of (α4)3(β2)2 nAChR agonists including partial agonists and agonists that bind at the α4:β2 but not α4:α4 agonist binding site. Our results indicate that NS9283 and CMPI effect on the dose-response curve of a given nAChR agonist

(enhancing its potency, efficacy, or both) depends on the agonist's ability to bind at α4:α4 subunit interface.

Disclosures: F. Deba: None. **K. Munoz:** None. **A. Tairu:** None. **A.K. Hamouda:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.01/E19

Topic: B.06. Synaptic Transmission

Support: MH 84874

Title: Quantal fluctuation in transmitter release can be accounted for by fluctuations in presynaptic Ca^{2+} entry

Authors: *S. RODRIGUEZ[1], M. POTCOAVA[1], S. RAMACHANDRAN[2], S. T. ALFORD[3]
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Abstract: Neurotransmitter release is initiated by action potential-evoked Ca2+ influx through voltage-gated Ca2+ channels (VGCCs). Various spatio-temporal Ca2+ requirements for release have been proposed in different presynaptic terminals, by Ca2+ influx through many, or few open channels with varying structural relationships to the release machinery. In some cases, channels are tightly clustered in domains close to the release apparatus, in others clustering is more diffuse. The number of functional VGCCs in central synapses appears to as few as a dozen or less. This implies that variability of channel opening between individual action potentials is high. However, this variability is difficult to measure because channels and terminals are inaccessible to direct recording approaches and imaging lacks temporal and spatial resolution to determine Ca2+ entry at active zones. We have utilized the lamprey giant reticulospinal (RS) synapse, cell attached recordings and Lattice Light Sheet Microscopy at high sampling rates to overcome these limitations. Using an acute dissociation of axons from lamprey spinal cords we recorded from presynaptic terminals devoid of apposing postsynapses. Active zone VGCCs were characterized by single channel recordings. N-type, P/Q-type, and R-type were all present with mean P_{open} for each channel type at 0 mV of 0.26 ± 0.02, 0.29 ± 0.03 and 0.22 ± 0.02 and maximum numbers of channels at each synapse of 10, 9, and 32 respectively. With a mean of 33 channels and a very small number (3-6, mean 4) of Ca2+ channels opened on single stimuli, it is likely that variation in Ca2+ entry contributes to variation in transmitter release. We imaged Ca2+ entry to RS axons in the spinal cord, using high-speed imaging with either epifluorescence or Lattice Light Sheet imaging of single planes through axons labeled with Ca2+ sensitive dyes. This reveals a reliable signal throughout the axon. Rise times were fit with single exponentials

with time constants from 5 to 20ms and decays from 1.0 to 1.5 s. However, at high temporal resolutions, Ca2+ hotspots were recorded with rise times as fast as the imaging system (3ms) and decays fit with two exponentials. The first had an extremely short decay time of 14.0 ± 0.9 ms, the second identical to the entire axon. The fast component was readily separable from the slow component and varied substantially in intensity. At a small number of high intensity sites the fast component was seen following each action potential. At a larger number of low intensity sites it failed at each location in 44 ± 11 % of action potentials. We conclude that quantal fluctuation in transmitter release can be accounted for by fluctuations in presynaptic Ca2+ entry.

Disclosures: S. Rodriguez: None. **M. Potcoava:** None. **S. Ramachandran:** None. **S.T. Alford:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.02/E20

Topic: B.07. Synaptic Plasticity

Title: Probabilistic synaptic plasticity induction due to stochastic gating of synaptic receptors

Authors: *C. O'DONNELL[1], Y. RODRIGUES[2], H. MARIE[3], R. J. VELTZ[2]
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Abstract: When different synapses are stimulated with identical plasticity induction protocols, the magnitude and direction of plasticity typically varies from synapse to synapse. The origins of this variability are poorly understood, and its implications or possible functions for learning remain unknown.
We propose a new biophysical computational model of synaptic plasticity that depends on the dynamics of calcium signals local to the synapse. Unlike classic plasticity models that operate on the relative timing of pre- and post-synaptic action potentials, this model relies on entirely local variables: pre-synaptic glutamate pulses and dendritic spine voltage. When we simulate stochastic activation of AMPA, NMDA and VGCCs in response to glutamate pulses, we find highly variable levels of activation of calcium's downstream targets from trial to trial. We model two additional downstream pathways, Calcineurin / CamKII, using deterministic activation equations which shows high variability as consequence of stochastically-driven calcium dynamics.
We automatically fit the model's parameters to reproduce the mean activation of CaMKII and Calcineurin from Fujii et al, Cell Rep (2013) as averaged across multiple synapses. We then compare the model's prediction for the level of synapse-to- synapse variability with the same data. We are also able to capture the variability in the data with our simple model.

We then extended the model by adding a phenomenological stochastic rule that maps the activation of CaMKII and Calcineurin to synaptic strength change via addition or removal of AMPARs from the synapse. We automatically fit the parameters of this model to data from spike-timing-dependent plasticity experiments by Tigaret et al, Nat Comms (2016). We compare the predictions of the model for data from held-out plasticity protocols that it was not fit to, both for the mean outcome and the level of synapse-to- synapse variability.
The two advances from this work are: 1) a new local computational model of synaptic plasticity that is suitable for use in dendritic neuron models; 2) evidence that the variability of plasticity expression across synapses is due to stochastic gating of synaptic receptors and ion channels.

Disclosures: C. O'Donnell: None. **Y. Rodrigues:** None. **H. Marie:** None. **R.J. Veltz:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.03/E21

Topic: B.06. Synaptic Transmission

Support: NIH Grant MH106906
NIH Grant NS099691

Title: Contribution of single synapses on dendritic spines to electrical signaling in individual neurons

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Abstract: The objective of this study was to describe the contribution of individual excitatory, glutamatergic synapses on dendritic spines to electrical signalling in single neurons. The functional role of single synapses on individual dendritic spines is important because nonclustered, widely distributed spines are active *in vivo*, as documented repeatedly (see Chen, Rochefort, Sakmann and Konnerth, 2013). We carried out experiments using a combination of electrophysiology, pharmacological tests, 2-photon uncaging of glutamate, and voltage-sensitive dye recordings from dendritic spines in rat brain cortical slices. Our goal was to analyse temporal summation of excitatory postsynaptic potentials (EPSPs) at synaptic sites on dendritic spines. We first confirmed, in several classes of principal cortical neurons, our earlier result that optical recording of electrical signals has the adequate sensitivity and spatiotemporal resolution to monitor synaptic signals in individual dendritic spines. Using these techniques, we explored the temporal summation of glutamate uncaging evoked responses that mimic unitary EPSPs. The results showed that the excitatory postsynaptic currents (EPSCs) recorded electrically from the

soma as well as EPSP signals recorded optically at the site of origin (dendritic spines) do not exhibit temporal summation up to the frequency range of 50-100 Hz. This is because local EPSP signals in spines return to the baseline in 10-20 ms at different synapses. At common physiological frequencies (below 50 Hz), this feature prevents synaptic saturation by maintaining the synaptic driving force during repetitive activation of synapses. At the same time, the somatic electrical recordings reveal a powerful temporal summation of EPSP at these frequencies due to widening of the EPSP signals as they propagate in the dendrites. We also found that, at higher frequency of synaptic activation (100 and 200 Hz), both the electrical EPSC signal from the soma and the local optical EPSP signal from spines exhibit temporal summation. However, the summating signals saturate at a range of values from 15-80 pA for EPSCs and from 3-17 mv for local EPSPs. In another series of experiments, we could not detect any changes in local EPSPs size and shape after NMDA receptors were blocked using receptor antagonist AP5. Thus, we conclude that, in slices, NMDA receptors in spines were not significantly activated either by unitary or by repetitive quantal EPSPs. Finally, we obtained preliminary data suggesting that AMPA-R desensitization is, at least partially, responsible for the saturation of local EPSP summation response in spines during repetitive synaptic stimulation.

Disclosures: J. Weng: None. **C. Celis:** None. **D. Zecevic:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.04/DP02/E22

Topic: B.06. Synaptic Transmission

Support: NIH Grant DC005640
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Title: Toric spines at a site of learning

Authors: D. SANCULI[1], K. E. PANNONI[1], E. A. BUSHONG[2], M. CRUMP[1], E. G. ANTZOULATOS[1], B. J. FISCHER[3], I. S. STEIN[1], K. M. ZITO[1], D. FIORAVANTE[1], M. H. ELLISMAN[4], *W. M. DEBELLO[5], W. M. DEBELLO[1]
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Abstract: We discovered a new type of dendritic spine. It is found on space-specific neurons (SSNs) in the barn owl auditory map, a known site of experience-dependent plasticity. Partial

reconstruction of a >250,000 cubic micron volume derived from serial block face scanning electron microscopy (SBEM) revealed proliferate large, branched spines exhibiting unprecedented morphology and patterns of synaptic convergence. These spines are located on the soma and proximal dendrites of SSNs and most closely resemble thorny excrescences found in mammalian hippocampus and amygdala, but in contrast, typically exhibit a narrow tubular structure, lack bulbous heads, and have up to seven holes, hence 'toric' spines. No single feature is present in every spine (n = 78). More significantly, presynaptic terminals associated with individual toric spines display many active zones (max = 49) derived from multiple axons (max = 11) with incoming trajectories distributed widely throughout 3D space. This novel arrangement is well suited to integrate input sources. Compartmental simulations show that toric spines are electrically compact and predict that inputs sum to produce an approximately uniform membrane potential throughout the spine. At the same time, activation of responses at one spine are predicted to have only a negligible effect on neighboring spines. Together, these results suggest that toric spines may act as independent processing units. *In vitro* slice recordings using electrical stimulation of the input nucleus, or photorelease of caged glutamate, reveal the intrinsic and synaptic properties of SSNs, and provide a path towards uncovering the cellular computations performed by toric SSNs. Finally, complete reconstruction of synaptic convergence onto one toric spine revealed that it was unconnected with the majority of intertwined axons (connection fraction = 0.16), indicating a high capacity for new information storage. We propose toric spines are a cellular locus of information processing, plasticity and learning.

Disclosures: D. Sanculi: None. **K.E. Pannoni:** None. **E.A. Bushong:** None. **M. Crump:** None. **E.G. Antzoulatos:** None. **B.J. Fischer:** None. **I.S. Stein:** None. **K.M. Zito:** None. **D. Fioravante:** None. **M.H. Ellisman:** None. **W.M. DeBello:** None. **W.M. DeBello:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

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Program #/Poster #: 284.05/E23

Topic: B.06. Synaptic Transmission

Support: McKnight Foundation, NIH (1R01MH101297, 1F31NS098666 and 2T32MH067564) and NSF 1516235

Title: Investigation of optical methods for monitoring synaptic input to ca1 pyramidal neurons

Authors: *M. ADOFF, D. A. DOMBECK
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Abstract: Understanding the computations performed by CA1 pyramidal neurons would benefit from precise measurements of the excitatory synaptic inputs each cell receives across the dendritic arbor. However, few approaches exist for monitoring synaptic input (glutamate release) patterns, and the sensitivity of those that do exist has not been established for CA1 pyramidal neurons. Here we evaluated the effectiveness of the fluorescent calcium indicator GCaMP6 and glutamate indicator iGluSnFR for such recordings. Presynaptic glutamate release can result in calcium influx through NMDA receptors that might be detectable with GCaMP6 as spine isolated calcium transients, but the voltage-dependent magnesium block of NMDA receptors makes these transients also dependent on the membrane potential of the postsynaptic cell. Therefore, it is unclear if presynaptic glutamate release can be detected with GCaMP6, particularly for cells near their resting potential of ~-65 mV. iGluSnFR directly binds to glutamate, is not dependent on the membrane potential of postsynaptic cell, and therefore can directly report synaptic glutamate release, but the fluorescence change upon glutamate binding is relatively small (vs GCaMP6 calcium binding), making its detection sensitivity unclear. To test the efficacy of these indicators for reporting synaptic inputs we sparsely expressed either GCaMP6s or SF-iGluSnFR.A184S in adult mouse hippocampal slices. We then stimulated individual CA1 spines using two-photon glutamate uncaging and simultaneously imaged the spines to monitor changes in fluorescence. Slices were maintained at ~32°C and bathed in ACSF containing 3 mM MNI-caged L glutamate, 1 μM TTX and 2 μM gabazine. First, using whole-cell patch clamp recording, we established the uncaging parameters (laser intensities and illumination durations) that evoked spine potentials resembling miniature EPSPs (~0.5 mV) at resting potential. Using these uncaging parameters on single spines of GCaMP6s-labeled cells resulted in detectable calcium transients during only ~25% of stimulations. When magnesium was removed from the bath, the fraction of stimulations resulting in detectable calcium transients significantly increased (~95%), suggesting that magnesium block of NMDA receptors can significantly hinder the ability to detect synaptic input to CA1 neurons at rest using GCaMP6. Conversely, using these uncaging parameters on single spines of iGluSnFR-labeled cells resulted in detectable transients (~35-50% $\Delta F/F$) during ~90% of stimulations. These findings indicate that SF-iGluSnFR.A184S may be an effective tool for optically measuring synaptic inputs to CA1 pyramidal neurons.

Disclosures: M. Adoff: None. **D.A. Dombeck:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.06/E24

Topic: B.07. Synaptic Plasticity

Support: NIH MH115556

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Title: A tight lower bound on the storage capacity of synapses in the rat middle stratum radiatum in hippocampal area CA1

Authors: *M. SAMAVAT[1], T. M. BARTOL, Jr.[2], C. BROMER[2], K. M. HARRIS[3], T. J. SEJNOWSKI[2]
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Abstract: A detailed experimental analysis of a dense three-dimensional reconstruction of serial section electron microscopy from the middle of stratum radiatum in hippocampal area CA1 of rat has been analyzed to determine how much information can be stored at a synapse through synaptic plasticity. In a previous study (TM Bartol Jr, Elife 4 (2015)) the authors measured the coefficient of variation of spine head volumes of 10 same-dendrite same-axon (SDSA) pairs from this data set and applied a good guess of Signal-to-Noise Ratio (SNR) with a value of 1. Then, with a simulation analysis approach, it was found that 26 Gaussian distributions could span the range of spine sizes of the 10 SDSA pairs, implying that the storage capacity of the rat brain synapses for this region is 4.7 bits of information.
We have analyzed the complete data set of 287 spine head volumes using novel clustering approaches and advanced information theory and found that there are 42 distinguishable synaptic strengths equivalent to storing 5.39 bits of information at each synapse. This is a new tight lower bound on the storage capacity of synapses in stratum radiatum in rat hippocampal area CA1. Moreover, we determined the SNR of the synapse sizes to be 0.10 by analyzing the spine head volume clusters with fitted distributions and overlaps of consecutive clusters. Lastly, we have calculated the exact amount of overlap between the consecutive Gaussian distributions to be 56% by assuming 42 normal distributions spanning the range of 287 spine head volumes, which ranged in size over a factor of 163.

Disclosures: M. Samavat: None. **T.M. Bartol:** None. **C. Bromer:** None. **K.M. Harris:** None. **T.J. Sejnowski:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.07/E25

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant GM88804
AG047612
AG051513

Title: Simultaneous optical and electrophysiological analysis of presynaptic excitability and GCaMP Ca^{2+} signals: Kinetic properties and spatial distribution in glutamatergic and aminergic synaptic boutons of *Drosophila* motor terminals

Authors: *X. XING[1], C.-F. WU[2]
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Abstract: The Drosophila neuromuscular junction (NMJ) consists of tonic and phasic glutamatergic (types Ib, Is) and modulatory aminergic (type II) motor terminals. We report a first simultaneous imaging and electric recording study to directly contrast the three synapses to establish the physiological significance of their GCaMP Ca^{2+} responses. Several GCaMP variants were applied in genetic and pharmacological perturbation in low Ca^{2+} (0.1 mM), and the results reveal different combinations of K+ channel types that underlie the excitability control of type Ib, Is and II synapses. Type II synapses were most sensitive to K^+ channel perturbations, reaching extreme hyperexcitability (near saturation-level responses evoked by single stimulus), following only one insult of either Shab or eag channels, while type Is required double insults of eag with Sh, or Shab and Sh together to reach the same level of extreme hyperexcitability. In contrast, type Ib requires perturbation of triple insults, i.e. disrupting Shab and Sh, together with the application of tetraethylammonium (TEA), a broad-spectrum K^+ channel blocker. Consistent results were obtained with other mutant and drug combinations, involving TEA, 4-AP and quinidine. Simultaneous focal recording of extracellular focal excitatory junction potentials (efEJPs) showed that these striking single stimulus-evoked GCaMP signals were correlated with a remarkable high-frequency repetitive motor axon firing (> 100 Hz), representing a state of extreme hyperexcitability after deprivation of K^+ channel repolarization mechanisms. Further analysis confirmed that GCaMP responses displayed a distal-proximal gradient in type I synaptic terminals. We discovered that drug inhibition of ATP-dependent Ca^{2+} clearance or mutational enhancement of membrane excitability could obscure this gradient. However, simultaneous efEJP recording showed that the GCaMP gradient did not correlate with a clear gradient of transmitter release efficacy, a process of millisecond time course, in contrast to the slow GCaMP signals reflecting accumulation of intracellular Ca^{2+} over seconds. This simultaneous optical and

electrical measurements can provide baseline information for interpretations of GCaMP signals in the proper context of synaptic physiology.

Disclosures: C. Wu: None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.08/E26

Topic: B.07. Synaptic Plasticity

Title: Functional and morphological stability of adult human cortical Layer 2/3 Pyramidal neurons *in vitro* in organotypic slice cultures

Authors: *N. SCHWARZ[1], U. B. HEDRICH[2], B. UYSAL[3], J. BAHR[3], H. SCHWARZ[3], H. PA[3], J. B. HONEGGER[4], H. LERCHE[3], A. SKORDAS[3], T. V. WUTTKE[4], H. KOCH[3]
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Abstract: In previous studies, we showed that in contrast to artificial culturing media, hCSF significantly enhances neuron viability and maintenance of network activity. Keeping adult human cortical neurons intact in their physiologically built environment for functional and morphological analysis has been an intriguing strategy to study these neurons in vitro. Here we describe in detail the relative stability of adult human cortical neurons maintained in an organotypic slice culture for up to 21 days in vitro (DIV). To quantify the stability of function and morphology we measured electrophysiological parameters, including firing properties, action potential shape and synaptic properties as well as morphological properties of 3D reconstructed Layer 2/3 Pyramidal neurons in these slices over time. We found a surprisingly robust stability of the morphological features of the neurons including spine morphology and maintenance of firing properties. In addition, we used two-photon live cell imaging to investigate AAV-retro-h-Synapsin-eGFP transduced GFP expression to access the morphology of the neurons and directly measure the plasticity of the spines. These direct measurements of the morphology and physiology of adult human neurons over an extended period constitute our method an indispensable tool for investigating plasticity in human neurons in their physiologically built environment over a substantial amount of time.

Disclosures: N. Schwarz: None. **U.B. Hedrich:** None. **B. Uysal:** None. **J. Bahr:** None. **H. Schwarz:** None. **H. Pa:** None. **J.B. Honegger:** None. **H. Lerche:** None. **A. Skordas:** None. **T.V. Wuttke:** None. **H. Koch:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.09/E27

Topic: B.06. Synaptic Transmission

Support: NIH Grant MH099054

Title: Patterns of presynaptic connectivity and modulation in the mouse medial prefrontal cortex

Authors: *A. L. BAKER[1], A. T. GULLEDGE[2]
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Abstract: Neocortical pyramidal neurons in layer 5 of the medial prefrontal cortex (mPFC) efficiently integrate cortical and extracortical synaptic input. Little is known about the selectivity of afferent input to these neurons, or how these presynaptic inputs are influenced by modulatory transmitters. Here, we explore the connectivity and modulation of afferent input to two broad classes of layer 5 neurons: commissural / callosal (COM) neurons that provide interhemispheric connectivity, and corticofugal neurons, including corticopontine (CPn) neurons that project to the pontine nuclei. To this end, we expressed channelrhodopsin-2 (ChR2) in three distinct afferent inputs to the mPFC: callosal input from the contralateral mPFC, thalamocortical input from the medial dorsal nucleus of the thalamus, and input from local synaptic terminals of CPn neurons. We then made simultaneous paired electrophysiological recordings of light-evoked synaptic events in physiologically-identified COM and CPn neurons. Callosal afferents targeted COM and CPn neurons with equal probability, and generated excitatory postsynaptic potentials (EPSPs) of similar magnitude in both neuron types (n = 70 pairs). Thalamocortical afferents preferentially targeted, and generated larger EPSPs in, COM neurons (n = 38 pairs). Application of tetrodotoxin (TTX) and 4-aminopyridine (4-AP) to isolate monosynaptic input revealed that both callosal (n = 12 pairs) and thalamocortical (n = 8 pairs) afferents preferentially drive COM neurons relative to CPn neurons. Preliminary results suggest that local input from CPn terminals preferentially activate CPn neurons (n = 6 pairs), a result consistent with previous studies testing unitary connections among these populations. We also tested neuromodulatory control of glutamate release from these afferents onto COM and CPn neurons. We found that serotonin (5-HT, 40 µM) modestly suppressed callosal (n = 17 pairs), but spared thalamocortical (n = 10 pairs), inputs to both postsynaptic targets. Acetylcholine (ACh, 20 µM), on the other hand, potently suppressed input from both callosal (n = 10 pairs) and thalamocortical (n = 11 pairs) afferents. We are currently testing the effect of ACh and 5-HT on glutamate release from local CPn terminals. These results contribute to our understanding of the connectivity and neuromodulatory control of cortical circuits.

Disclosures: A.L. Baker: None. **A.T. Gulledge:** None.

Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.10/E28

Topic: B.06. Synaptic Transmission

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F30DA042501

Title: Disabling Gβγ-SNARE interaction disrupts GPCR-mediated presynaptic inhibition leading to physiological and behavioral phenotypes

Authors: *Z. ZURAWSKI[1,3], A. D. THOMPSON GRAY[1], L. J. BRADY[1], K. HYDE[1], B. PAGE[3], E. CHURCH[3], N. A. HARRIS[2], M. R. DOHN[1], Y. Y. YIM[1], D. P. MORTLOCK[2], D. G. WINDER[2], S. ALFORD[3], C. K. JONES[1], H. HAMM[1]
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Abstract: Disabling Gβγ-SNARE interaction disrupts GPCR-mediated presynaptic inhibition leading to physiological and behavioral phenotypes.
Zack Zurawski, Analisa D. Thompson Gray, Lillian J. Brady, Brian Page, Emily Church, Nicholas A. Harris, Michael R. Doh[n], Yun Young Yim, Karren Hyde, Douglas P. Mortlock, Danny G. Winder, Simon Alford, Carrie K. Jones, Heidi E. Hamm
$G_{i/o}$-coupled receptors modulate neurotransmission presynaptically through inhibition of exocytosis. Release of Gβγ subunits decreases the activity of voltage-gated calcium channels (VGCC), decreasing excitability. A less understood Gβγ-mediated mechanism downstream of calcium entry is the binding of Gβγ to SNARE complexes. Here, we create a transgenic mouse via CRISPR-Cas9 partially deficient in this interaction by premature truncation of the SNAP25 carboxy terminus by three residues. The SNAP25Δ3 mutation results in inhibited Gβγ-SNARE binding and diminished ability of Gβγ to compete with synaptotagmin 1 for binding sites on SNARE complexes. SNAP25Δ3 homozygote animals are viable, with a normal appearance, and have normal presynaptic inhibition by $GABA_B$ receptors that inhibit voltage gated calcium channels. Despite this, they exhibit deficits in presynaptic inhibition by receptors that work directly on the SNARE complex such as $5\text{-}HT_{1b}$ and α_{2a} receptors. Simultaneously stimulating receptors that work by both mechanisms show synergistic inhibitory effects. The SNAP25Δ3

homozygote exhibits a number of behavioral phenotypes, including elevated stress-induced hyperthermia, and defective spatial learning, as well as impaired gait and supraspinal nociception. In addition, differences in insulin sensitivity and food intake are observed. The individual $G_{i/o}$-coupled GPCRs responsible for these deficits have yet to be elucidated. These data suggest that $G_{i/o}$-coupled GPCR
inhibition of exocytosis through the Gβγ-SNARE interaction is a crucial component of numerous physiological and behavioral processes.

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Poster

284. Synaptic Connectivity and Synaptic Properties

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 284.11/E29

Topic: B.06. Synaptic Transmission

Support: NIH Grant NS031224-23

Title: Connexin36 in the mouse inferior olive is a component of the post-synaptic protein complex of glutamatergic synapses

Authors: Z. ZHU[1], J. D. LAUTZ[1], E. A. BROWN[1], S. E. P. SMITH[1,2], *J. P. WELSH[1,2]
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Abstract: Connexin36 (Cx36) is the protein that forms electrical synapses between the dendritic spines of inferior olivary (IO) neurons. Such electrical synapses are essential for robust and continuous oscillations in membrane potential that are synchronized among coupled IO neurons. NMDA receptor activation strengthens weak electrical coupling among IO neurons and there is strong co-localization of Cx36 and the GluN1 subunit of the NMDA receptor in IO dendritic spines (Turecek *et al* 2014). To further our understanding of how Cx36 and NMDA receptors interact, we investigated at the level of protein-protein association whether Cx36 interacts with proteins comprising the glutamatergic postsynaptic density (PSD). Protein lysates were prepared from the IO of adult mice dissected from the brainstem. The first experiment used western blot and demonstrated that Cx36 and GluN1 co-immunoprecipitate from IO lysates of c57BL/6J wild-type mice. The second experiment exposed IO lysates from 4 wild-type mice to a panel of 18 antibodies against glutamate synapse proteins conjugated to specific Luminex bead regions, before separation into 96 well plates and secondary incubation with a panel of 21 fluorophore-

conjugated antibodies (Lautz *et al* 2018). This Quantitative Multiplex co-Immunoprecipitation (QMI) technique measured 207 binary combinations of synaptic proteins to determine the relative frequency that Cx36 occurs in shared complexes with glutamate synapse proteins. Cx36 was found to exist in protein complexes containing the glutamate receptor subunits GluN1 and GluR2, as well as scaffolding proteins Shank1, Shank3 and Homer1, signaling proteins Homer1a and SynGap, and the structural protein neuroligin3. The experiment was repeated in 4 pairs of mice, each pair containing a wild-type mouse and a mouse heterozygous for deletion of the C-terminus of Shank3 protein [*Shank3*(+/ΔC)]. Direct pairwise comparisons by QMI revealed significant or trend-level reductions in the association of Cx36 with GluN1, GluR2, and SynGap in *Shank3*(+/ΔC) mice as compared to the wild-type, all of which were replicated and quantified to be significant 30-50% reductions by immunoprecipitation determined by flow cytometry. As initially found in goldfish (see Pereda 2014), our results support the view that neuronal electrical synapses are integrated into the cellular machinery of chemical synapses via structural interactions of Cx36 with glutamatergic PSD proteins. Our results extend the concept to mouse by indicating that Cx36 may be part of an "extended postsynaptic complex" that allows neuronal gap junctions to be scaffolded by shank3 to the glutamatergic PSD.

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Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.01/E30

Topic: B.07. Synaptic Plasticity

Support: NINDS R21 NS090397-01

Title: Calpain-2 conditional knockout mice are resistant to cell death induced by traumatic brain injury

Authors: *Y. WANG, Y. LIU, J. SUN, A. MCCLOUD, S. BIAGI, X. BI, M. BAUDRY
Western Univ. of Hlth. Sci., Pomona, CA

Abstract: Our laboratory has recently reported that two of the major isoforms of calpain found in the brain, calpain-1 and calpain-2, play opposite functions in both synaptic plasticity and neuroprotection/neurodegeneration. In particular, while calpain-1 activation is required for long-term potentiation (LTP) induction and is neuroprotective, calpain-2 activation limits the magnitude of LTP and is neurodegenerative. Homozygous disruption of the calpain-2 gene results in pre-implantation embryonic lethality. Here, we created a calpain-2 conditional knockout (CKO) mouse by crossing loxP-calpain-2 mice with Cre-CamKII promoter mice.

These mice do not express calpain-2 in excitatory neurons of the forebrain. Roles of calpain-1 and calpain-2 were then examined by comparing calpain-1 KO mice and calpain-2 CKO mice and their controls under different conditions. Cultured hippocampal neurons from calpain-1 KO mice at 21 days *in vitro* had significantly more filopodia-like immature spines, as compared to neurons from WT mice, while cultured hippocampal neurons from calpain-2 CKO mice exhibited normal spine morphology. During postnatal development, calpain-1 KO mice exhibited enhanced neuronal apoptosis throughout the cerebrum and cerebellum, while calpain-2 CKO mice showed the same levels of apoptosis rate as wild-type (WT) mice. Calpain-1 KO mice had enhanced cell death and larger lesion volume in the ipsilateral cortex and hippocampus after traumatic brain injury (TBI), as compared to WT mice. In contrast, calpain-2 CKO mice had reduced cell death and smaller lesion volume, as compared to WT mice, thereby confirming our previous result that pharmacological inhibition of calpain-2 by a selective calpain-2 inhibitor reduced TBI-induced cell death. In summary, these results indicate that calpain-1 and calpain-2 have separate functions in the brain and that selectively inhibiting calpain-2 could be protective in various brain diseases without disrupting the physiological functions of calpain-1.

Disclosures: Y. Wang: None. **Y. Liu:** None. **J. Sun:** None. **A. McCloud:** None. **S. Biagi:** None. **X. Bi:** None. **M. Baudry:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.02/E31

Topic: B.07. Synaptic Plasticity

Support: NINDS R21 NS090397-01

Title: A smarter mouse created by conditional deletion of calpain-2 gene in forebrain using the Cre/loxP system

Authors: *Y. LIU, S. BIAGI, K. BROWN, Y. WANG, J. SUN, X. HAO, X. BI, M. BAUDRY
Western Univ. of Hlth. Sci., Pomona, CA

Abstract: The hypothesis that calpain plays a significant role in synaptic plasticity and learning and memory was proposed in 1984. Since then, many studies have been directed at understanding the roles of various calpain isoforms in numerous cell functions and in the nervous system. Our laboratory has recently shown that two of the major isoforms found in the brain, calpain-1 and calpain-2, play opposite functions in both synaptic plasticity/learning and memory and neuroprotection/neurodegeneration. In particular, while calpain-1 activation is required for long-term potentiation (LTP) induction and for certain forms of learning and memory, calpain-2 activation limits the magnitude of theta burst stimulation (TBS)-induced LTP. We previously

reported that a relatively selective calpain-2 inhibitor enhanced LTP magnitude and learning & memory by prolonging ERK activation. Homozygous disruption of the Calpain-2 gene results in pre-implantation embryonic lethality between the morula and blastocyst stage (Previn Dutt, 2006). We used the Cre/loxP system to create a conditional calpain-2 knockout mouse by crossing a loxP-calpain-2 with a Cre-CamKII promoter mouse. These mice do not express calpain-2 in excitatory neurons in the forebrain. The C2KO mice displayed enhanced TBS-induced LTP in field CA1 of adult hippocampal slices, and enhanced context-fear memory in the fear conditioning paradigm. Performance in the tone test was not significantly different for that of respective control mice. The results confirm the results obtained with the selective calpain-2 inhibitor and strengthen the importance of calpain-2 function in learning and memory. This conditional calpain-2 knockout mouse represents a powerful tool for further exploring the role of calpain-2 function in brain. Our results also indicate that a selective calpain-2 inhibitor could be very beneficial in various diseases associated with learning and memory impairment.

Disclosures: Y. Liu: None. **S. Biagi:** None. **K. Brown:** None. **Y. Wang:** None. **J. Sun:** None. **X. Hao:** None. **X. Bi:** None. **M. Baudry:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.03/E32

Topic: B.07. Synaptic Plasticity

Title: Slow glutamate clearance triggers postsynaptic calcium amplification and impairs synaptic plasticity via calpain-2

Authors: *J. R. BARNES, M. P. PARSONS
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Abstract: Recent evidence suggests that poor glutamate clearance may contribute to the synaptic plasticity deficits observed in various neurodegenerative diseases. Presumably, the plasticity deficit is triggered by over-activation of extrasynaptic NMDA receptors (exNMDARs). As glutamate transporters limit exNMDAR activation by rapidly clearing glutamate from the extracellular space, an attractive and well-cited hypothesis states that glutamate transporter dysfunction underlies the long-term potentiation (LTP) and cognitive impairments in disease states. However, the precise relationship between the spatiotemporal dynamics of extracellular glutamate and synaptic plasticity has yet to be investigated. Here, we used a novel optogenetic sensor of glutamate, termed iGluSnFR, to monitor extracellular glutamate dynamics in real-time (205 Hz) in the mouse hippocampus during standard LTP-inducing protocols. We found that TBOA, a non-selective glutamate transporter blocker, slowed glutamate clearance and inhibited LTP magnitude in a concentration-dependent manner. The TBOA-induced LTP impairment was

not a result of the simultaneous activation of competing long-term depression (LTD) pathways, including presynaptic LTD, NMDAR-dependent LTD, or postsynaptic metabotropic glutamate receptor-dependent LTD. Surprisingly, impaired glutamate clearance during LTP induction caused rapid NMDAR desensitization, indicating that NMDAR over-activation cannot explain the subsequent LTP impairment. Despite NMDAR desensitization, GCaMP6f calcium imaging revealed that postsynaptic calcium transients were increased three-fold during LTP induction when glutamate uptake was compromised by TBOA. This elevated calcium response, which resulted from both L-type voltage-gated calcium channel activation and the release of internal calcium stores, was sufficient to recruit the calcium-dependent protease calpain-2 that limits LTP strength. In all, our data characterize the relationship between glutamate dynamics and LTP, and identify a novel mechanism underlying LTP impairment in cases where glutamate uptake is compromised. These results may be applicable to numerous neurodegenerative diseases associated with impaired synaptic plasticity and glutamate transporter dysfunction, including Alzheimer and Huntington disease.

Disclosures: J.R. Barnes: None. **M.P. Parsons:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.04/E33

Topic: B.07. Synaptic Plasticity

Support: Whitehall Foundation

Title: SynDIG4/Prrt1 establishes a reserve pool of extra-synaptic AMPARs required for LTP

Authors: *E. DIAZ, K. E. PLAMBECK, D. J. SPECA
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Abstract: Altering AMPA receptor (AMPAR) content at synapses is a key mechanism underlying the regulation of synaptic strength during learning and memory. Previous work demonstrated that SynDIG1 (SD1; synapse differentiation-induced gene 1) encodes a transmembrane AMPAR-associated protein that regulates excitatory synapse strength and number in vitro and in vivo (Kalashnikova et al., 2010; Chenaux et al., 2016). Activity-dependent palmitoylation underlies SD1 localization and function at synapses (Kaur et al., 2016). Previously, we demonstrated that loss of the related protein SynDIG4 (SD4; also known as Prrt1) results in reduced extra-synaptic AMPARs while long term potentiation (LTP) is abolished by single tetanus stimulation of hippocampal slices from SD4-knockout (KO) mice (Matt, Kirk, Chenaux et al. 2018). We hypothesize that SD4 regulates AMPAR trafficking through maintenance of an extra-synaptic pool of GluA1-containing AMPARs required for LTP. Here we

investigate the role of SD4 in synaptic targeting of GluA1-containing AMPARs during LTP. We find that surface GluA1-containing AMPARs are reduced in SD4-KO hippocampal neurons compared with WT cultures. Furthermore, synaptic targeting of GluA1-containing AMPARs from extra-synaptic sites is abolished during glycine-induced chemical LTP (chemLTP) in SD4-KO hippocampal neurons. Intriguingly, chemLTP stimulus of primary hippocampal neurons results in increased co-localization between SD4 and GluA1-containing AMPARs at both synapses and extra-synaptic sites, suggesting that at least some proportion of a SD4-AMPAR complex traffics to the synapse during LTP. Super-resolution microscopy is currently being employed to determine the precise subcellular localization of SD4 in relationship with GluA1-containing AMPARs in hippocampal neurons during chemLTP. SD4 is palmitoylated at two conserved cysteine residues and experiments are in progress to determine the role of activity-dependent palmitoylation in SD4-dependent chemLTP. Given that LTP requires an extra-synaptic pool of AMPARs, these data are consistent with a model whereby SD4 establishes an extra-synaptic pool of GluA1-containing AMPARs and is required to facilitate their trafficking to the synapse during LTP.

Disclosures: E. Diaz: None. **K.E. Plambeck:** None. **D.J. Speca:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.05/E34

Topic: B.07. Synaptic Plasticity

Title: Synaptic activity-dependent changes in the hippocampal palmitoyl-proteome

Authors: *N. MATIN[1], K.-M. MOON[2], L. FOSTER[2], S. X. BAMJI[3]
[2]Dept. of Biochem. & Mol. Biol., [3]Cell. and Physiological Sci., [1]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Impaired synapse function is the underlying cause of many brain disorders including Alzheimer's disease, schizophrenia, intellectual disabilities and Huntington's disease. Emerging evidence suggest that palmitoylation, the reversible addition of the fatty acid, palmitate, to substrate proteins, is disrupted in many of these neurological and psychiatric disorders. Palmitoylation is mediated by a family of 23 DHHC (Asp-His-His-Cys) enzymes and almost half of DHHC enzymes have been associated with disorders of the brain including Alzheimer's disease (DHHC12), schizophrenia (DHHC5, DHHC8 and DHHC18), intellectual disability (DHHC9, DHHC12 and DHHC15), Huntington's disease (DHHC12 and DHHC17). Presynaptic and postsynaptic membranes are enriched in palmitoylated proteins with over 41% of all synaptic proteins reported as substrates for palmitoylation. Palmitoylation of a few synaptic proteins have been to be shown to be regulated by synaptic activity suggesting that this post-

translational modification may be important for the plasticity of synaptic connections. However, a comprehensive proteomic analysis of all proteins that are differentially palmitoylated following increased synaptic activity is lacking and is essential to understand disrupted synaptic function in neurological disorders. We are currently examining the role of palmitoylation during activity-mediated synaptic plasticity. Using primary hippocampal culture and hippocampal lysates we aim to elucidate differential palmitoylation of synaptic substrates following chemical LTP and fear conditioning, respectively.

Disclosures: N. Matin: None. **K. Moon:** None. **L. Foster:** None. **S.X. Bamji:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.06/E35

Topic: B.07. Synaptic Plasticity

Support: NSERC Discovery Grant

Title: Distinct patterns of long-term potentiation within the hippocampal CA1 stratum radiatum

Authors: T. L. FONG, J. S. THACKER, Y. XU, B. LAIRD, *J. G. MIELKE
Sch. of Publ. Hlth. and Hlth. Systems, Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Long-term potentiation (LTP) is the most widely studied model of synaptic plasticity and is regarded as a critical cellular mechanism underlying learning and memory. For several decades, a large proportion of LTP experiments have taken advantage of the conserved neurocircuitry in the acutely prepared hippocampal slice; in particular, these studies have stimulated the Schaffer collaterals and measured responses in the CA1 stratum radiatum. However, large variations in the magnitude and induction patterns of LTP exist in the literature, which makes cross study comparisons challenging. One possible reason for these variations may be differences in the placement of the recording electrodes in these reports, which is notable given that increasing evidence suggests synapses within the CA1 stratum radiatum are not homogeneous. Hence, we investigated the possibility that LTP within the CA1 stratum radiatum of hippocampal slices, induced either electrically (with a 100 Hz tetanus), or chemically (using tetraethylammonium, glycine, and modified levels of Ca^{2+} and Mg^{2+}), would vary with respect to the distance between the recording position and the pyramidal somata. Using a multi-electrode array recording system, we examined LTP expression approximately 100, 200, and 300 μm away from the cell body layer in the stratum radiatum of acutely prepared rat hippocampal slices. Preliminary results show that LTP induction patterns and magnitude is different among the three recording points. In particular, tetanus induced the greatest magnitude of LTP expression at points that were 100 μm from the pyramidal cell layer. Furthermore, LTP induced by chemical

means was also substantially different across the recording points. Specifically, an immediate and dramatic increase in response amplitude was followed by an eventual decrease during washout at points 100 μm and 200 μm from the soma; in contrast, an immediate decrease was seen at points 300 μm away, and was followed by an increase during washout. Our results show that LTP is not homogeneously expressed within the CA1 stratum radiatum (regardless of the method of induction) suggesting the coexistence of multiple patterns of synaptic plasticity in the region. Furthermore, we have demonstrated the importance of precisely documenting recording position in LTP experiments involving the hippocampal slice.

Disclosures: T.L. Fong: None. **J.S. Thacker:** None. **Y. Xu:** None. **B. Laird:** None. **J.G. Mielke:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.07/E36

Topic: B.07. Synaptic Plasticity

Support: MC_U105174197
BB/N002113/1

Title: The interplay of interactions controlling postsynaptic AMPA receptor localization in synaptic transmission and plasticity

Authors: *J. F. WATSON[1], H. HO[2], A. PINGGERA[2], I. H. GREGER[2]
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Abstract: AMPA receptors (AMPARs) are localized at the postsynaptic membrane, mediating fast excitatory synaptic transmission on presynaptic glutamate release. A multitude of protein interactions have been identified, modulating receptor trafficking, gating and localization at synaptic sites, both intracellularly in the postsynaptic density, and extracellularly in the synaptic cleft. Controlling the postsynaptic AMPAR content is a critical mediator of synaptic plasticity, and a cellular mechanism of learning and memory. Recruitment and stabilization of additional AMPARs at postsynaptic sites allows synaptic strengthening, and therefore the interactions controlling receptor enrichment at synaptic sites are fundamental to our understanding of information storage in the brain.
Recent insights into synaptic function demonstrate that not only is postsynaptic recruitment of receptors important for transmission, but their precise sub-synaptic localization is essential for transmission fidelity, and control of this positioning could mediate synaptic plasticity. Both intracellular interactions with the postsynaptic density, mediated by the TARP auxiliary subunits,

and extracellular interactions of the AMPAR NTD control the synaptic localization of the receptor. Using electrophysiological and imaging techniques in wild-type and AMPAR-null neurons, we dissect the interplay between these interactions, and their roles in the positioning of AMPARs at the synapse. These interactions can act differentially to fine-tune the postsynaptic response, underlying the synapse-specific changes occurring during synaptic transmission and plasticity.

Disclosures: J.F. Watson: None. **H. Ho:** None. **A. Pinggera:** None. **I.H. Greger:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.08/E37

Topic: B.07. Synaptic Plasticity

Support: BBSRC BB/N013956/1

Title: Diverse changes in synaptic plasticity at distinct inhibitory synapses within the CA1 region of the mouse hippocampus

Authors: *M. UDAKIS, S. E. L. CHAMBERLAIN, J. R. MELLOR
Bristol Univ., Bristol, United Kingdom

Abstract: The hippocampus hosts a complex diversity of inhibitory interneurons which form an integral component of hippocampal network function. Despite some overlapping expression, Parvalbumin (PV) and Somatostatin (SST) expressing interneurons are generally considered to form synapses onto proximal and distal regions of pyramidal cells respectively [1.] They are therefore considered to perform distinct roles in network activity and alterations in synaptic inhibition at these synapses may have profound impacts on the hippocampal network. One mechanism for altering network inhibition is the capacity of inhibitory connections to undergo synaptic plasticity - increasing or decreasing the 'strength' of inhibition. However, the requirements for PV and SST synapses to undergo plasticity and the network consequence of altering the level of inhibition at these synapses remains unclear.
To investigate inhibitory plasticity, using whole-cell patch-clamp electrophysiology we recorded inhibitory synaptic transmission from CA1 pyramidal cells in acute hippocampal slices. We selectively stimulated inhibitory synapses arising from PV or SST expressing interneurons using PV-Cre or SST-Cre transgenic mice crossed with Ai32 mice expressing Cre-dependent channelrhodopsin (ChR2). Short light stimuli evoked Inhibitory Postsynaptic Currents (IPSCs) in slices from both PV-ChR2 and SST-ChR2 mice but with markedly divergent characteristics. In agreement with the proposed proximal vs distal targeting, the IPSC kinetics for PV IPSCs were faster than SST IPSCs for both rise and decay times. Furthermore, paired pulse ratios for PV

IPSCs were lower than SST IPSCs consistent with the prominent paired pulse depression observed at PV synapses. High frequency stimulation of inhibitory synapses led to long-term depression (iLTD) and long-term potentiation (iLTP) of PV IPSCs and SST IPSCs respectively. Both forms of plasticity were independent of glutamatergic activity since they were not prevented by inclusion of AMPA/kainate and NMDA receptor antagonists NBQX and D-AP5. By selectively activating distinct inhibitory synapses via optogenetics, we show that two interneuron populations exhibit opposing changes in synaptic weight in response to high frequency stimulation. This may provide a mechanism by which these two interneuron populations can regulate and update hippocampal network function in response to ongoing activity patterns.

1.Pelkey KA, Chittajallu R, Craig M, Tricoire L, Wester JC, McBain CJ (2017) Hippocampal GABAergic Inhibitory Interneurons. Physiol Rev 97:1619-1747

Disclosures: M. Udakis: None. **S.E.L. Chamberlain:** None. **J.R. Mellor:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.09/E38

Topic: B.07. Synaptic Plasticity

Support: NSFC

Title: Synaptic function of microRNA-34a

Authors: J.-Y. WANG, X. MIN, *K.-W. HE
IRCBC, Chinese Acad. of Sci., Shanghai, China

Abstract: MicroRNAs (miRNAs) are a group of short non-coding transcripts that play essential role in post-transcriptional modulation. They function by binding and further suppressing the translation or destabilizing the target mRNAs. Hundreds of miRNAs have been discovered, but their roles are scarcely known. Here we focus on understanding the neuronal function of miRNA-34a, one of the miRNA-34 family that is mostly enriched in the brain. By taking advantage of the miRNA-34a +/- mice, which has about 40% of miRNA-34a left in the hippocampus compared to their wildtype litter mates, we found miRNA-34a was a key regulator of synaptic plasticity in the schaffer collateral synapses.

Disclosures: J. Wang: None. **X. Min:** None. **K. He:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.10/E39

Topic: B.07. Synaptic Plasticity

Support: NIH R01 MH108342

Title: Endogenous neuropeptide Y release attenuates long-term potentiation in the temporoammonic pathway of hippocampus

Authors: *Q. LI, L. E. DOBRUNZ
Neurobio., Univ. of Alabama at Birimgham, Birmingham, AL

Abstract: Neuropeptide Y (NPY) is one of the most abundantly expressed neuropeptides in the central nervous system, and it has emerged as an important mediator of stress, neuroplasticity and memory processes. Multiple studies using acute or chronic administration of NPY receptor agonists and antagonists have supported a role for NPY in different functions of learning and memory. However, far less is known about how endogenous NPY release affects long-term synaptic plasticity. We have previously shown that release of endogenous NPY can modulate short-term plasticity at temporoammonic (TA) synapses onto hippocampal CA1 pyramidal cells. In particular, endogenous NPY release can be detected by observing NPY receptor dependent changes in short-term plasticity during stimulation with a physiologically-based spike train (PST). To test whether endogenous NPY release can also affect long-term potentiation (LTP), we first tested whether PST stimulation can induce LTP in the TA pathway. We find that PST stimulation induces robust potentiation of TA synapses that is maintained for at least 1 hour, indicating that it is LTP. In addition, the selective NMDA receptor antagonist AP5 prevents the induction of TA LTP by PST stimulation, indicating this type of LTP is NMDA receptor dependent. To improve the efficiency of NPY release, we used NPY Cre/ChR2 mice that express channelrhodopsin 2 in NPY interneurons; this enables us to directly activate NPY cells using photostimulation to cause NPY release. To test the effects of endogenously released NPY on PST induced LTP, we used combined electrical stimulation of the TA pathway and optical stimulation of NPY cells applied simultaneously during the PST protocol. The combined stimulation also consistently induces TA LTP lasting over 1 hour. Blocking NPY receptors with the Y1 antagonist BIBP and the Y2 antagonist BIEE before PST stimulation caused a significant increase in the magnitude of LTP. This indicates that endogenous NPY release can attenuate LTP in the TA pathway. This study is the first demonstration of the impact of endogenously released NPY on long-term plasticity in the TA pathway, and provides a possible link between NPY's effects on circuit function and its role in regulating hippocampal-dependent behavior.

Disclosures: Q. Li: None. **L.E. Dobrunz:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.11/E40

Topic: B.07. Synaptic Plasticity

Support: CIHR 114965
CIHR 126109
CIHR PDF
NSERC 402265
FRQS Research Chair 31036

Title: Cholinergic regulation of deleted-in-colorectal cancer receptor facilitates persistent firing in the entorhinal cortex

Authors: *S. D. GLASGOW[1], J. GIBON[3], P. A. SEGUELA[4], E. S. RUTHAZER[2], T. E. KENNEDY[5]
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Abstract: Changes in the structure and function of synapses underlie learning and memory. We have recently demonstrated a novel role for netrin-1, a chemotropic guidance cue, in activity-dependent synaptic plasticity through activation of the canonical netrin-1 receptor, deleted-in-colorectal cancer (DCC). These findings suggest that dynamic trafficking of DCC may contribute to on-going modification of cellular excitability and synapse function. Plasma membrane distribution of DCC is regulated by strong depolarization induced by changes in extracellular K^+ concentration. Excitatory neuromodulation, such as cholinergic receptor activation, may contribute to network connectivity via promoting dynamic changes in DCC distribution through potent depolarization of membrane potential. Here, we show that muscarinic and nicotinic cholinergic-induced membrane depolarization recruits DCC to the plasma membrane of cultured cortical neurons. Cholinergic receptor activation also increases DCC co-localization with both pre- and post-synaptic markers. In adult brain slices, we show that bath application of netrin-1 facilitates cholinergic-mediated persistent firing activity in layer V entorhinal neurons in acute adult brain slices, a form of long-lasting depolarization that has been associated with working memory processes. Together, these findings show that acetylcholine can modulate cortical synapses through the active recruitment of DCC, and this can, in turn, promote synaptic plasticity via enhancement of netrin-1-signaling.

Disclosures: S.D. Glasgow: None. **J. Gibon:** None. **P.A. Seguela:** None. **E.S. Ruthazer:** None. **T.E. Kennedy:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.12/E41

Topic: B.07. Synaptic Plasticity

Support: R01MH095905
R01GM118801

Title: LTP is modulated by interneurons containing the α5-GABAA receptor subunit

Authors: A. G. FIGUEROA[1], G. SURGES[1], *C. LOR[1], M. PERKINS[1], U. RUDOLPH[2], R. A. PEARCE[1]
[1]Anesthesiol., Univ. of Wisconsin - Madison, Madison, WI; [2]Lab. of Genet. Neuropharm., McLean Hosp. / Harvard Med. Sch., Belmont, MA

Abstract: Background: Long-Term Potentiation (LTP) of the Schaffer collateral pathway in the hippocampus is a well-established cellular model of learning and memory. Although it is based on changes in excitatory synaptic transmission, LTP is also under the control of GABAergic inhibition. To test whether α5-$GABA_A$Rs located on interneurons are instrumental in controlling LTP, we created mice that lack α5 subunits in interneurons. Here we compared LTP in "pseudo-WT" mice that are homozygous for the a5 floxed allele α5-$GABA_A$Rs (fl/fl-α5) vs. "true WT" C57BL/6J (WT) mice, and assessed the effects of the $GABA_A$R modulator etomidate (ETOM, 1μM) on LTP in WT, fl/fl-α5, and interneuron-specific α5-$GABA_A$R knockout mice.
Methods: To generate mice lacking α5-$GABA_A$R subunits in interneurons, we crossed fl/fl-α5 mice with fl/fl-α5 fl/fl-a5 mice also expressing Cre-recombinase under the control of the vesicular inhibitory amino acid transporter (VIAAT) promoter. We measured population EPSPs in coronal hippocampal brain slices by stimulating the Schaffer collateral pathway and recording from the *stratum radiatum* in the CA1 region. To induce LTP we used a theta-burst stimulus (TBS) consisting of one train of 40 stimuli, delivered as ten 100Hz bursts of 4 stimuli each repeated at 5Hz (TBS-40), or three such trains separated by 20 seconds (TBS-120). Recordings continued for 1 hour post-TBS. LTP was expressed as the % increase of the average EPSP slope during the last 10 minutes of recording. Groups were compared using Student's t-test.
Results: There were two differences between WT vs. pseudo-WT (fl/fl-α5) mice: i) LTP produced by TBS-120 under drug-free conditions was significantly greater in WT compared to fl/fl-α5 mice (60±9% vs. 43±4%, p=0.007); and ii) ETOM suppressed TBS-120 LTP in WT (65±9% vs. 40±6%, p=0.02) but not in fl/fl-α5 mice (43±4% vs. 43±5%, p=0.49). However, ETOM was able to suppress LTP in fl/fl-α5 mice using the weaker TBS-40 stimulus (38±2% vs.

17±3%, p<0.0001). We also found two differences between fl/fl-α5 and VIAAT-α5-KO mice: i) there was a trend toward lower potentiation in VIAAT-α5-KO vs. fl/fl-α5 mice (25±5% vs. 38±4%, p=0.06); and ii) VIAAT-α5-KO mice resisted LTP suppression by ETOM (25±5% vs. 14±5%, p=0.07).
Conclusions: The differences between WT and fl/fl-α5 mice indicate that the a5 floxed allele mutation is not entirely silent. Acknowledging this change in background characteristics, the lack of effect of ETOM in VIAAT-α5-KO mice, and the trend toward reduced LTP in these mice, indicate that α5-$GABA_A$Rs located on interneurons are instrumental in GABAergic control of synaptic plasticity.

Disclosures: A.G. Figueroa: None. **G. Surges:** None. **C. Lor:** None. **M. Perkins:** None. **U. Rudolph:** None. **R.A. Pearce:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.13/E42

Topic: B.07. Synaptic Plasticity

Support: MH099085
MH115188

Title: Effects of social isolation rearing and ketamine on hippocampal synaptic plasticity

Authors: *J. B. LOGUE[1], K. J. SCHOEPFER[2], Y. ZHOU[3], M. KABBAJ[4]
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Abstract: Social isolation is a long-term stressor that produces lasting effects including memory deficits, cognitive impairments, and hippocampal functional and structural alterations. Ketamine (KET) is a non-competitive N-methyl-d-aspartate receptor (NMDAR) antagonist currently of interest for its antidepressant effects at subanesthetic doses. Previous work in our lab has shown that the subject's sex and gonadal hormone status play a critical role in mediating sensitivity to the antidepressant-like effects of KET in rats, as female rats behaviorally respond to a lower dose of KET than males, an effect that requires both estradiol (E2) and progesterone (P4) on-board. However, electrophysiological mechanisms underlying female-specific dose sensitivity remain unclear. This study aims to investigate the interaction between social isolation rearing stress and low-dose KET on hippocampal synaptic plasticity in rats of both sexes. We hypothesize that: 1. The field excitatory post-synaptic potentials (fEPSPs) in dorsal hippocampus Schaffer collateral (CA3-CA1) synapses may be impaired by isolation stress in both sexes, 2. A single low dose of KET (2.5 mg/kg, i.p.) given *in-vivo* 3hr prior to slice recording may rescue stress-induced fEPSP deficits in females, but not males, 3. Female-specific KET rescue effects may be modulated by

estrous stage (Proestrus: high E2/P4, Diestrus: low E2/P4), and 4. Stress-induced fEPSP deficits in both sexes may be ameliorated with a single treatment of 5 mg/kg KET (i.p.). Postsynaptic plasticity is evaluated by measuring tetanic stimulation-induced long-term potentiation (LTP), while the responsivity of the synapse to electrical stimulation is measured with fEPSP input-output curves and presynaptic transmitter release probability is measured by paired-pulse facilitation experiments. Completion of this project will generate insights into the interactions between gonadal hormones and KET at this synapse and the potential restoration of neural plasticity.

Disclosures: J.B. Logue: None. **K.J. Schoepfer:** None. **Y. Zhou:** None. **M. Kabbaj:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.14/E43

Topic: B.07. Synaptic Plasticity

Support: CONACyT (FOINS) 474
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PAPIIT IN208616

Title: Activity in the ventral-tegmental area modulates synaptic plasticity in the insular cortex

Authors: *L. F. RODRIGUEZ-DURAN[1], M. L. ESCOBAR[2], F. BERMÚDEZ-RATTONI[3]
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Abstract: It is widely accepted that the consumption of addictive substances modifies the activity of the mesocorticolimbic dopamine (DA) system. This system originates in the ventral tegmental area (VTA) and projects to cortical areas, including the insular cortex (IC). The agranular IC in its rostral region also receives afferents from the basolateral amygdaloid nucleus (Bla). In this sense, it has been reported that Bla is involved in the search for cocaine and heroin. Previous studies show that in vivo tetanic stimulation of Bla induces long-term potentiation (LTP) in IC, and this synaptic facilitation can modulate learning. In this work, we analyze whether the LTP induced by Bla-CI could be modulated by activating the VTA-DA pathway. For this purpose, we injected stereotaxic vectors expressing channelrhodopsin-2 (ChR2) -eYFP in the VTA of transgenic TH-Cre mice. Then the animals underwent implantation of electrodes in the Bla-IC projection. The mice were subjected to 15 minutes of VTA optogenetic stimulation. Within this time period, the mice received high frequency stimulation (1s, 100 Hz, 10x trains) in order to induce LTP in the Bla-IC pathway. Our results showed that animals that underwent VTA optogenetic stimulation in the VTA expressed an increase in the magnitude of LTP

compared to the e-YFP controls. These results suggest that the Bla-IC synaptic plasticity can be modulated by VTA-dopaminergic neurons, and that the IC plays a role in the modulation of addictive memories.

Disclosures: L.F. Rodriguez-Duran: None. **M.L. Escobar:** None. **F. Bermúdez-Rattoni:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.15/E44

Topic: B.07. Synaptic Plasticity

Title: Cell surface expression of GluA1-containing AMPA receptors is enhanced by secreted amyloid precursor protein-alpha; visualized by BioPLAy

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Abstract: Cell surface expression of AMPA-sensitive glutamate receptors (AMPARs) is tightly regulated. All AMPARs permit flux of sodium and potassium ions, but receptors composed of GluA1/2 subunits possess slower ion channel kinetics, and allow greater ion flux than GluA2/3 AMPARs. While the later continuously cycle in and out of the postsynaptic membrane, GluA1-containing AMPARs are trafficked to the membrane in response to depolarization, thus underpinning synaptic plasticity. Furthermore, calcium-permeable GluA1-homomeric receptors are suggested to insert transiently into the synaptic membrane in response to stimulation. Visualizing modulations in glutamate receptor surface expression is key to understanding the mechanism/s underpinning long-term potentiation (LTP)-enhancing agents such as secreted amyloid precursor protein-alpha (sAPPα). Existing light microscope methods are limited by the requirement for a primary antibody recognizing surface-expressed epitopes and challenged by low surface expression. We have developed a technique to quantify changes in the surface expression of target proteins. BioPLAy combines membrane-impermeable biotin tags with the specificity and amplification properties of the proximity ligation assay (PLA), enabling highly sensitive, subregion-specific analysis of target proteins. As proof of concept, we present BioPLAy-mediated detection of surface levels of GluA1-containing AMPARs on dendrites of cultured primary hippocampal neurons. Cells (>DIV25) were exposed to glycine (100 μM, 20 min), to induce chemical LTP, or stimulated with sAPPα (1 nM; 2 h). BioPLAy was carried out by sequential incubation with Sulfo-NHS-SS-biotin (2.5 mg/mL; Pierce), anti-GluA1 (Abcam) and anti-biotin (Sigma) primary antibodies followed by the PLA (Duolink PLA rabbit^{plus} and mouse^{minus} probes) and signal amplification (Duolink). Using BioPLAy we found both glycine

(1.49 ± 0.16; 5-10 neurons/experiment, 3 experiments per condition; one sample t test p = 0.004) and sAPPα (1.95 ± 0.23; 10-16 neurons/experiment, 3 experiments per condition; one sample t test p = 0.0003) induced a robust increase in surface expression of GluA1. Incubation of cells without anti-GluA1 antibody, or without the biotinylation step precluded production of BioPLAy signal. Together, these data support BioPLAy as a valid tool for investigating changes in surface expression of target molecules following various stimuli, and support the hypothesis that sAPPα facilitates LTP through the increased availability of GluA1-containing AMPARs.

Disclosures: J.M. Williams: None. **M.K. Elder:** None. **W.P. Tate:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.16/E45

Topic: B.07. Synaptic Plasticity

Title: Lactate induces a Hebbian form of LTP on the recurrent collateral synapses of hippocampal area CA3

Authors: *G. HERRERA-LOPEZ, E. J. GALVAN
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Abstract: Neuronal activity within physiological range is accompanied by the production of lactate, a metabolic intermediate involved in the production of ATP. However, at the central level, lactate receptors (HCA1) were recently described, and increasing evidence supports the notion that activation of HCA1 controls neuronal excitability at various levels. Here, we explored the effects of external perfusion of lactate on the synaptic transmission converging on CA3b pyramidal cells of the hippocampus. Baseline Mossy Fiber (MF)- or Recurrent Commissural (RC)-evoked EPSC were acquired in acute slices, and lactate (1 or 2 mM) was perfused for 10 min. Lactate caused a sustained increase in the RC-EPSP that lasted up to 30 min after lactate washout (184% of basal response). Contrary to this, isolated MF EPSCs (in the presence of D-AP5 + bicuculline) did not exhibit such increase induced by lactate perfusion. The enhancement of the RC EPSC was abolished entirely when NMDARs were blocked with D-AP5. Similar results were found when CA3 pyramidal cells were intracellular loaded with BAPTA (20 mM) or were held at -100 mV during perfusion of Lactate, indicating a postsynaptic locus of RC LTP. In the presence of α-cyano-4-hydroxycinnamic acid (4-CIN; 0.5 mM;), a monocarboxylate-transporter blocker, or oxamate (10 mM) a lactate dehydrogenase inhibitor did not alter the induction of RC LTP, suggesting that lactate does not require neuronal transport and further metabolism to induce LTP. Lastly, perfusion of 3,5-DHAB (0.5 mM) an HCA1 selective agonist, mimicked the actions of lactate suggesting dependence of HCA1 activation for RC LTP. Consistently, the inclusion of pertussis toxin in the patch pipette blocked the potentiation

observed with lactate. We conclude that lactate can induce an NMDA-dependent form of LTP mediated by the activation of HCA1 receptor.

Disclosures: G. Herrera-Lopez: None. **E.J. Galvan:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.17/E46

Topic: B.07. Synaptic Plasticity

Support: Telethon GGP11043 to A.B.
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Title: Single-spine LTP modulates plasticity at neighboring GABAergic inhibitory dendritic synapses

Authors: *T. RAVASENGA, M. RUBEN, E. PETRINI, A. BARBERIS
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Abstract: A proper balance of synaptic excitation and inhibition is essential for the functioning of the neuronal networks. Traditionally, the flexibility of neuronal network was thought to mainly rely on the potentiation and depression of excitatory synapses. In contrast, inhibitory synapses were assumed to be relatively invariant. However, an increasing body of evidence has revealed several types of inhibitory plasticity, raising the important question of how GABAergic and glutamatergic plasticity are coordinated during neuronal activity. Here, we characterized a non-Hebbian form of inhibitory postsynaptic potentiation (iLTP) induced by postsynaptic depolarizations of principal cells in hippocampal cultures. Interestingly, the same protocols induced depression at glutamatergic synapses (LTD), thus indicating an anti-homeostatic relation between inhibitory and excitatory plasticity. Photolysis of caged glutamate or caged GABA revealed that the aforementioned glutamatergic LTD and GABAergic iLTP are expressed postsynaptically. Subsequently, we investigated the interplay between excitatory and inhibitory plasticity following the delivery of a hebbian-like plasticity protocol. We induced “single spine LTP” to study how plasticity induced at individual glutamatergic spines affects the strength of neighboring GABAergic synapses. In particular, we paired the postsynaptic depolarization with repetitive glutamate uncaging at individual spines while simultaneously measuring the strength of adjacent dendritic GABAergic synapses by GABA uncaging. Interestingly, we found that GABAergic synapses located within 3 microns from a stimulated spine showed depression (iLTD), while farther synapses still showed iLTP as described above. This spatial dependent reversion of inhibitory plasticity induced by heterosynaptic plasticity required the activation of the protease calpain, induced by calcium influx through L-type voltage gated calcium channels.

Our findings suggest that, following the induction of synaptic plasticity, changes of calcium concentration in dendritic micro-domains locally tuned dendritic E/I balance.

Disclosures: T. Ravasenga: None. **M. Ruben:** None. **E. Petrini:** None. **A. Barberis:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.18/E47

Topic: B.07. Synaptic Plasticity

Support: Kirschstein NRSA-Institutional Research Training Grant T-32 NIH grant

Title: Evolutionarily conserved site on Neurexin3-α modulates balance between excitation and inhibition

Authors: *S. RESTREPO[1], K. A. NELSON[2], J. AOTO[2]
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Abstract: Imperative for proper synapse formation, Neurexins are a group of evolutionarily conserved presynaptic cell-adhesion molecules whose mutations have been implicated in several neuropsychiatric disorders. Although Nrxns have been studied for decades, many of their functions have yet to be elucidated. In particular the role of **Neurexin3α**, has only been weakly decoded. Little is known regarding how the extracellular portion of **Nrxn3α** governs synaptic function. We identified a point mutation in an evolutionarily conserved region of **Nrxn3α**. The patient with this mutation suffers from severe intellectual disability and epileptic seizures. We found that this mutation, has profound effects on ligand binding and alters presynaptic morphology. Moreover, excitatory transmission is altered in the mutant. Knockdown of endogenous **Nrxn3α** and replacement with WT or mutant **Nrxn3α** brought to light the role of **Nrxn3α**'s involvement in excitatory and inhibitory transmission. These data exemplify the distinct role of **Nrxn3α** as a molecule necessary for the balance between excitation and inhibition at the synapse, and how this molecule's dysfunction can lead to unfavorable phenotypes often associated with the E/I misbalance such as epilepsy.

Disclosures: S. Restrepo: None. **K.A. Nelson:** None. **J. Aoto:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.19/E48

Topic: B.07. Synaptic Plasticity

Title: NYX-2925 facilitates auditory-evoked long-term potentiation in rats: A translational approach for measuring NMDA receptor-dependent synaptic plasticity

Authors: *J. S. BURGDORF[1,2], K. LEADERBRAND[1,2], X.-L. ZHANG[3], P. K. STANTON[3], T. M. MADSEN[2], M. A. KAHN[2], R. A. KROES[1,2], J. R. MOSKAL[1,2]
[1]Falk Ctr. for Mol. Therapeutics, McCormick Sch. of Engin., Northwestern Univ., Evanston, IL; [2]Aptinyx Inc., Evanston, IL; [3]Cell Biol. & Anat., New York Med. Col., Valhalla, NY

Abstract: Aptinyx has developed a novel class of small molecule N-methyl-D-aspartate receptor (NMDAR) modulators with broad applicability for neurologic and psychiatric disorders. A member of this platform, NYX-2925, enhances NMDAR-dependent long-term potentiation (LTP) in hippocampal slices and facilitates learning and memory in rats. NYX-2925 also facilitates synaptic plasticity as measured by enhancement of LTP in slices *ex vivo* 1-7 days post-dosing (1-10 mg/kg, PO). The present studies examine the effects of NYX-2925 (0.1, 1, 10 mg/kg, PO) on *in vivo* NMDAR-dependent auditory-evoked LTP as well as NMDAR-dependent mismatch negativity responses in the prefrontal cortex of freely behaving rats. NYX-2925 (1-10 mg/kg, PO) facilitated auditory-evoked LTP as measured by an increased N100 response to a standard tone 1 hr after auditory tetanization (6 kHz tone, 50 ms in duration, presented 10 times per second for 5 min). In addition, NYX-2925 caused an attenuation in response to the deviant tone (8 kHz). In the mismatch negativity experiment, NYX-2925 (1-10 mg/kg, PO) facilitated habituation of the N100 response to the deviant tone, whereas an NMDAR antagonist inhibited this habituation. The effects of NYX-2925 were observed 1 hr to at least 1 week following a single dose in both the *in vivo* LTP and mismatch negativity paradigms. NYX-2925 (1-10 mg/kg, PO) also increased resting qEEG power in the alpha-beta bands without affecting gamma oscillations. In contrast, NMDAR antagonists primarily facilitate gamma oscillations. These data demonstrate that NYX-2925 facilitates synaptic plasticity *in vivo*. The potential for these findings to translate to humans is currently being explored.

Disclosures: J.S. Burgdorf: A. Employment/Salary (full or part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc. **K. Leaderbrand:** A. Employment/Salary (full or part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc. **X. Zhang:** B. Contracted Research/Research Grant (principal investigator

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Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.20/E49

Topic: B.07. Synaptic Plasticity

Title: Immediate perisynaptic membrane expansion after LTP induction visualized by correlative light and electron microscopy

Authors: *Y. SUN, N. KAMASAWA, R. YASUDA
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Abstract: Dendritic spines are the major sites receiving excitatory synaptic transmission, and are widely accepted as the structural units for learning and memory. Synaptic plasticity induced by long-term potentiation (LTP) leads to both structural and functional changes in dendritic spines in an input-specific manner. More specifically, LTP is known to be associated with immediate increase of AMPA receptor-mediated current and expansion of spine volume (within ~min). In contrast to these rapid changes, the growth of the post-synaptic density (PSD), where the majority of AMPA receptors reside in, takes much longer time (~hour). It is unknown how this difference in the time scale can be reconciled.
In order to address this question, we used 2-photon microscope system to induce LTP in single dendritic spines by uncaging MNI-glutamate and to confirm input specific structural plasticity

induction. By establishing an efficient correlative light-electron microscopy workflow using serial sectioning and array tomography scanning electron microscopy, we relocated the uncaged dendritic spines and observed their sub-spine ultrastructure in the early phase of LTP (<20 minutes). As expected, we observed a dramatic increase in spine head volume following uncaging. Interestingly, the axon-spine interface expanded immediately after LTP induction, while PSD size did not increase within this period. Importantly, we identified the significant expansion of perisynaptic membrane, defined as the spine membrane without an attached PSD but having a typical synaptic cleft (<40 nm) opposing to presynaptic membrane. This perisynaptic membrane could serve as the physical location for transient accumulation of AMPA receptors to support increased synaptic transmission in early phase LTP as the first morphological response of plasticity.

Disclosures: Y. Sun: None. **N. Kamasawa:** None. **R. Yasuda:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.21/E50

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS102490

Title: Model of paradoxical LTP maintenance predicts multiple intermediate states between early and late LTP

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Abstract: The transition from early long-term potentiation (e-LTP) to late long-term potentiation (l-LTP) is a multistep process that involves both protein synthesis and degradation. The ways in which these two opposing processes interact to establish l-LTP are not well understood, however. For example, l-LTP is attenuated by inhibiting either protein synthesis or proteasome-dependent degradation prior to and during a tetanic stimulus (e.g., Huang et al., *Learn Mem* 3:74, 1996; Karpova et al., *J Neurosci* 26:4949, 2006), but paradoxically, l-LTP is not attenuated when synthesis and degradation are inhibited simultaneously (Fonseca et al,. *Neuron* 52:239, 2006). These paradoxical results suggest that counter-acting 'positive' and 'negative' proteins regulate l-LTP. To investigate the basis of this paradox, we developed a model of LTP at the Schaffer collateral to CA3 pyramidal cell synapse. The model consists of nine ordinary differential equations that describe the levels of both positive- and negative-regulator proteins (PP and NP, respectively) and the transitions among five discrete synaptic states, including a basal state

(BAS), three states corresponding to e-LTP (EP1, EP2, and ED), and a l-LTP state (LP). An LTP-inducing stimulus: **1)** initiates the transition from BAS to EP1 and from EP1 to EP2; **2)** initiates the synthesis of PP and NP; and finally, **3)** activates the ubiquitin-proteasome system (UPS), which in turn, mediates transitions of EP1 and EP2 to ED and the degradation of NP. The conversion of e-LTP to l-LTP is mediated by the PP-dependent transition from ED to LP, whereas NP mediates reversal of EP2 to BAS. We found that the inclusion of the five discrete synaptic states was necessary to simulate key empirical observations: **1)** normal L-LTP, **2)** block of L-LTP by either proteasome inhibitor or protein synthesis inhibitor alone, and **3)** preservation of L-LTP when both inhibitors are applied together. Although our model is abstract, it correctly captures the dynamics of protein synthesis- and degradation-dependent phases of LTP, and elements of the model can be correlated with specific molecular processes. Moreover, the model makes testable predictions, such as a unique synaptic state (ED) that precedes the transition from e-LTP to l-LTP, and a well-defined time window for the action of the UPS (i.e., during the transitions from EP1 and EP2 to ED).

Disclosures: P.D. Smolen: None. **D.A. Baxter:** None. **J.H. Byrne:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.22/E51

Topic: B.07. Synaptic Plasticity

Support: Wellcome Trust Grant

Title: Over-expression of GluR2 in hippocampal parvalbumin-positive interneurons impairs synaptic plasticity and memory performance

Authors: *M. J. COOPER[1], M. MONIRI[2], D. BANNERMAN[2], E. O. MANN[1]
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Abstract: Parvalbumin-expressing (PV+) inhibitory interneurons are critical for controlling spike timing and spike rates in hippocampal circuits. Excitatory synapses onto PV+ interneurons predominantly express AMPA receptors lacking the GluR2 subunit. The GluR2-lacking AMPAR are Ca^{2+}-permeable and display polyamine-dependent inward rectification. These properties enable anti-Hebbian learning at excitatory synapses onto PV+ interneurons, whereby inputs associated with membrane hyperpolarisation trigger Ca^{2+} influx and synaptic potentiation. However, the behavioural importance of anti-Hebbian plasticity in PV+ interneurons remains to be established.
In this study, we generated a virus that drives Cre-dependent expression of the Q/R-edited GluR2

AMPA receptor subunit, and injected it into the hippocampus of PV-Cre mice. We were able to selectively transfect PV+ interneurons and alter single-cell and network properties, including substantially reducing synaptically-evoked dendritic calcium signals and impairing anti-Hebbian plasticity.
Following this, we performed bilateral full hippocampal injections of the virus into a cohort and performed a battery of behavioural tests. We found that whilst locomotor activity, anxiety, and spatial reference memory were largely unaffected by the transfection, the animals showed a substantial impairment on the spatial working memory-dependant rewarded alternation T-maze task compared to a GFP virus-injected control cohort, but only with extended (30-second) delays between the sample and choice phases of trials. Additionally, whilst the animals were equally capable of learning the location of a platform during a spatial reference memory version of the Morris water maze task, the GluR2-injected group took longer to react to subsequent changes in platform location (spatial reversals). Overall, our results suggest that replacement of Ca^{2+}-permeable AMPA receptors in hippocampal PV+ interneurons with GluR2-containing AMPA receptors increases interference between competing memory traces, potentially as a consequence of impaired anti-Hebbian plasticity.

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Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.23/F1

Topic: B.07. Synaptic Plasticity

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Title: Long-term potentiation requires a rapid burst of dendritic mitochondrial fission during induction

Authors: *S. DIVAKARUNI[1,2,3], A. VAN DYKE[1], R. CHANDRA[4], T. A. LEGATES[1], M. CONTRERAS[1], P. A. DHARMASRI[1,3], H. N. HIGGS[5], M. LOBO[4,3], S. M. THOMPSON[1,3], T. A. BLANPIED[1,3]
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Abstract: Long-term potentiation (LTP) is the prevailing mechanism of synaptic strengthening by which neurons encode experience. Baseline synaptic function is bioenergetically demanding, and this demand is elevated during episodes of synaptic plasticity. Therefore, mitochondrial functions such as ATP synthesis and calcium handling are likely required for plasticity. It has recently become apparent that synaptic transmission relies on the adequate presence and function of mitochondria. However, whereas axonal mitochondria have been extensively studied, LTP induction predominantly occurs postsynaptically, where the roles of mitochondria are less well understood.

Mitochondria in dendrites at rest are stationary and rarely undergo fission or fusion. However, we found that chemical induction of LTP (cLTP) by NMDAR activation in cultured rat hippocampal neurons prompted a rapid burst of dendritic mitochondrial fission. Mitochondrial fission canonically requires actin nucleation and membrane constriction by the GTPase dynamin-related protein 1 (Drp1). Consistent with this, inhibition of actin polymerization or expression of a dominant negative (DN) mutant Drp1 each suppressed the cLTP fission burst. Furthermore, the GTPase Dynamin 2 (Dyn2) was recently implicated in fission in cell lines, and we found similarly that expressing DN Dyn2 abolished the fission burst. Drp1 function is also known to be regulated by phosphorylation, with CaMKII as a possible activator based on studies of non-neuronal cells. In line with this, we found that fission was triggered by cytosolic calcium elevation via glutamate photolysis at dendritic spines, and also that the fission burst was prevented by acutely inhibiting CaMKII activation. We then tested whether mitochondrial fission is required for LTP expression. Knocking down Drp1 or expressing DN Drp1 suppressed dendritic spine growth and synaptic AMPA receptor trafficking following LTP induction. Remarkably, postsynaptic expression of DN Drp1 prevented LTP at Schaffer collateral-CA1 synapses in acute hippocampal slices, with no effect on basal transmission or intrinsic electrophysiological properties of neurons.

Taken together, these data suggest that CaMKII activation during LTP induction rapidly increases dendritic mitochondrial fission, and that this is required for LTP expression. Impaired synaptic function is implicated in myriad neuropsychiatric diseases, many of which are also associated with mitochondrial dysfunction. Our findings raise the important question of whether neuronal mitochondrial dysfunction contributes to cognitive impairment by perturbing dendritic and/or synaptic plasticity.

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Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 285.24/F2

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01 DA017392
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Title: Endocannabinoid-mediated regulation of LTP at mossy cell to dentate granule cell synapses

Authors: *K. R. JENSEN, P. E. CASTILLO
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Abstract: Within the dentate gyrus of the hippocampus, excitatory hilar mossy cells (MCs) synapse extensively onto granule cells (GCs), the principal cell type and main output of the dentate gyrus. MCs also mediate powerful feed-forward inhibition (FFI) onto GCs through a MC-inhibitory interneuron (IN)-GC connection. Although information transfer from MCs to GCs is important for multiple forms of hippocampal-dependent learning and memory, as well as spatial navigation, we know very little about the dynamic properties of MC-GC synapses, and the feed-forward MC-IN-GC circuit. Using electrophysiology in acute rat hippocampal slices, our lab recently discovered a novel type of presynaptically-expressed, NMDA receptor-independent form of long-term potentiation (LTP) of MC-GC transmission, which involves both PKA and BDNF-mediated signaling. New results indicate that MC-GC LTP is inhibited by endocannabinoid (eCB) signaling. To mobilize eCBs from GCs in a timely manner, we delivered brief bouts of depolarizations (from -45 mV to 0 mV; for 5 seconds every 10 seconds; x12; 2 minutes total). We found that GC depolarizations delivered 1.5 minutes before and during induction of MC-GC LTP caused a significant decrease in MC-GC LTP magnitude, an effect that was abolished in the presence of the type-1 cannabinoid receptor (CB1R) inverse agonist AM251 (5 μM). To investigate the mechanism downstream from the $G_{i/o}$-coupled CB1R, we used selective pharmacology for the βγ- or α-limb. We found that inhibition of the βγ-limb with Gallein (75 μM) rescued the deficit in MC-GC LTP that resulted from GC depolarization *during* induction, while inhibiting the α-limb with NF-023 (10 μM) rescued the deficit in LTP that resulted from GC depolarization *before* induction. In contrast, multiple depolarizations delivered 1.5 and 15 min *after* LTP induction only transiently (~1.5-30 min, respectively) decreased LTP magnitude. To further examine eCB-mediated effects on MC-mediated transmission, we used optogenetics to selective activate MC axons and recruit FFI onto GCs. We found that FFI exhibits robust eCB-mediated short-term plasticity. Together, our findings highlight diverse and powerful mechanisms by which eCBs may contribute to dentate gyrus-dependent computations.

Disclosures: K.R. Jensen: None. **P.E. Castillo:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.25/F3

Topic: B.07. Synaptic Plasticity

Support: (NIDA) Grant R01 DA039533

Title: Endocannabinoid-mediated spike-timing dependent plasticity in the lateral habenula glutamatergic synapses is modulated by early life stress

Authors: *L. D. LANGLOIS[1], R. D. SHEPARD[2], M. E. AUTHEMENT[2], F. S. NUGENT[2]
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Abstract: The lateral habenula (LHb) is an epithalamic structure involved in depression and aversion by sending negative reward signals to monoaminergic systems. We have previously demonstrated a link between maternal deprivation (MD), an early life stress model, and metaplasticity of GABAergic synapses onto ventral tegmental area (VTA) dopamine neurons. Given the negative control of VTA dopamine neurons by the LHb, we extended our MD studies to the LHb and found that LHb neurons of MD rats (P21-P30) are hyperexcitable and exhibit postsynaptic glutamatergic synaptic potentiation. Up to date no study has shown that glutamatergic synapses onto LHb neurons are capable of expressing spike-timing dependent plasticity (STDP) whose modulation could underlie MD-induced changes in LHb neuronal excitability and DA signaling from the VTA. Our study here demonstrates that glutamatergic STDP can be triggered in LHb neurons in response to near-coincident pre- and post-synaptic activities. We defined the STDP window using different pre post spiking order and time intervals (ranging from -50 to +50 ms). Coincident pre and postsynaptic firing is required for glutamatergic STDP of LHb neurons as pre or postsynaptic activity alone is insufficient to induce plasticity. We classified LHb neurons based on their firing pattern. Tonic firing neurons showed presynaptic NMDAR- and Ca2+ dependent long-term potentiation (LTP) regardless of spiking order. Instead, silent and irregularly firing neurons expressed no plasticity in response to similar protocols. This suggests that LHb neurons display activity-dependent symmetrical Hebbian STDP. LTP was abolished by bath application of a CB1 receptor antagonist. Moreover, our preliminary data suggest that endocannabinoid 2-Arachidonoylglycerol (2-AG) but not anandamide may mediate this plasticity. MD impaired LTP in response to pre-post protocols and even shifted LTP toward LTD in response to post-pre protocol (-5ms interval) in tonic firing neurons suggesting an induction of metaplasticity by MD at glutamatergic synapses onto LHb neurons. The induction of STDP was unaltered for silent and irregularly firing neurons

suggesting that MD-induced metaplasticity was specific to neurons with tonic activity. We are testing the possible interaction between 2-AG and GABA-B signaling pathways as potential mediators of this form of LTP and their dysregulation during MD-induced metaplasticity.

Disclosures: L.D. Langlois: None. **R.D. Shepard:** None. **M.E. Authement:** None. **F.S. Nugent:** None.

Poster

285. LTP: Pre- and Postsynaptic Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 285.26/F4

Topic: B.07. Synaptic Plasticity

Support: USUHS Grant 308430

Title: Effects of chronic high altitude exposure on synaptic protein levels across different brain regions in a rodent model

Authors: *Z. ADAHMAN[1], R. SHARMA[1], E. MURPHY[1], N. CRAMER[1], X. XU[2], Z. GALDZICKI[2], D. L. DICKSTEIN[3], B. DARDZINSKI[5], D. P. PERL[6], D. IACONO[4]
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Abstract: Long-term operations carried out by military personnel, pilots, and astronauts are often conducted in extreme conditions such as exposure to high altitude (HA)-associated hypobaric-hypoxic environment, which have reported to result in impairments of different cognitive functions such as learning and memory. While the cerebral effects of acute HA exposure have been more extensively studied, much less is known about chronic exposure to HA and the possible biological or pathobiological mechanisms involved in the adaptive or maladaptive responses of the brain to chronic HA. In this context, we sought to investigate if synaptic protein expression levels were altered as possibly due to HA for a prolonged period of time. We chose to examine synaptic proteins in the pre- and post-synaptic compartment that have been shown to play a role in the release of neurotransmitters, formation and recycling of synaptic vesicles, neurite formation as well as anchoring of excitatory and inhibitory receptors. To address the effects of chronic HA on synaptic protein expressions, we exposed twelve C57Bl6 male mice to an altitude of 5000m (HA) above sea level (SL) for 12 weeks. We initially focused on the following proteins: synaptophysin, spinophilin, post-synaptic density protein (PSD95), and the growth associated protein 43 (GAP43). We used western blot (WB) methods to quantify the selected synaptic proteins through different regions of the brain: olfactory cortex, cerebellum and brainstem. Our preliminary findings show a significant decrease in the expression levels of

synaptophysin and spinophilin in the olfactory cortex of chronically exposed HA mice in comparison to mice kept at SL for an identical period of time. Intriguingly, we did not observe changes in the PSD95 and GAP43 levels. Moreover, we did not observe changes in any of the considered synaptic markers in the cerebellum and brainstem of mice exposed to chronic HA. These findings seem to suggest that chronic exposure to HA can regulate specific synaptic changes across different brain regions and possibly linked to specific cognitive and behavioral changes. Elucidating the molecular mechanisms by which these synaptic and other synaptic-associated changes occur in mammalian brains will have potential implications for the preservation of cognitive and behavioral skills of subjects exposed to prolonged periods of time to HA.

Disclosures: Z. Adahman: None. **R. Sharma:** None. **E. Murphy:** None. **N. Cramer:** None. **X. Xu:** None. **Z. Galdzicki:** None. **D.L. Dickstein:** None. **B. Dardzinski:** None. **D.P. Perl:** None. **D. Iacono:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.01/F5

Topic: B.07. Synaptic Plasticity

Support: NIAAA U01AA025932
NIAAA R01AA021505

Title: Reduction of alcohol-seeking behavior by optogenetic reversal of alcohol-evoked input- and cell type-specific synaptic plasticity in the dorsomedial striatum

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Abstract: Addiction is believed to be triggered by drug-evoked plasticity. The dorsomedial striatum (DMS), a brain region critically involved in drug and alcohol addiction, contains medium spiny neurons (MSNs) expressing either dopamine D1 or D2 receptors. D1-MSNs positively and D2-MSNs negatively control rewarding behaviors. The DMS receives glutamatergic inputs from the medial prefrontal cortex (mPFC). We recently found that chronic alcohol intake increased glutamatergic activity selectively at mPFC inputs onto DMS D1-MSNs. Here, we combined the dual-channel optogenetic approach and a “post-pre” spike timing-dependent protocol (STDP) to test whether the induction of input- and cell types-specific LTD at the mPFC-D1 MSN circuit could reverse the alcohol-evoked enhancement of glutamatergic activity at this circuit, thereby persistently reducing their alcohol intake. This circuit-specific LTD induction was achieved by expressing one channelrhodopsin, chronos, at the mPFC

terminals for selective presynaptic stimulation, and by expressing another channelrhodopsin, Chrimson, in the D1-MSNs for postsynaptic depolarization of this specific neuronal type. First, we used field potential recording to measure LTD from water controls, and observed that ex vivo "post-pre"-STDP induction successfully induced LTD in striatal slices, whereas mPFC stimulation alone did not cause any changes. Next, we delivered same LTD induction in slices from alcohol-drinking animals. We found that the same induction caused reliable LTD, however, the optogenetic stimulation needed to be repeated 3 times to obtain the same magnitude of LTD. Then, we examined the effect of this LTD-inducing protocol on alcohol-seeking behavior. We found that in vivo delivery of this optogenetic protocol produced significant decreases in lever presses and alcohol intake; these decreases last two days after induction. Taken together, these data suggest that optogenetically inducing D1-MSN LTD from alcohol-drinking rats reversed alcohol-evoked glutamatergic potentiation in this neuronal population, thus persistently reducing alcohol drinking in vivo. Reversal of alcohol-evoked synaptic plasticity could provide a novel circuit-based therapeutic strategy for the treatment of alcohol addiction.

Disclosures: J. Lu: None. **Y. Cheng:** None. **T. Ma:** None. **X. Wang:** None. **J. Wang:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.02/F6

Topic: B.07. Synaptic Plasticity

Support: 16H06532
16K00380
15K00413
16H06524
16K21734
MHLW H30_kagaku_ippan_003

Title: Theta phase-dependent competitive long-term potentiation in area CA1 of the hippocampal slices caused by feed-forward and feedback gabaergic control

Authors: *T. TOMINAGA, Y. TOMINAGA
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Abstract: The theta burst stimulation (TBS, a train of short 100 Hz. burst stimulations repeated in 5-7 Hz.) that mimics theta oscillation in the rodent hippocampal system is a well-used induction stimulation of the long-term potentiation (LTP) at area CA1 Schaffer (Sch)-pyramidal synapses. The TBS-induced LTP is different from the LTP induced by an also well-known "tetanic" stimulation (tetanus, 100 Hz. 1 sec stimulation). We found the significant difference of

the degree of the action of potential firing during the induction phase with voltage-sensitive dye (VSD). That is, tetanus did not cause action potentials during tetanus while a TBS exaggerated action potential. We also reported that the TBS caused exaggerated action potential firing during the sequence, even in the form of the pair of brief burst stimulations [PBS; a 100 Hz. burst stimulation consists of four stimuli with 10ms intervals (a priming burst) precedes a 170ms interburst interval to the same 100 Hz. burst stimulation (a test burst)]. A PBS applied to the Sch induced a facilitated response upon a test burst (a paired burst facilitation; PBF). The PBF accompanied the action potentiation of E-S (EPSP-spike firing) coupling without accompanying an increase of excitability of the postsynaptic cells. This is dependent on the GABA-A receptor-dependent GABAergic circuit control. In the CA1 neural circuit, the GABA-A receptor acts either as a feedforward or feedback inhibition. When we divided Schaffer collateral fibers into two groups with microsurgery and applied stimulation to these two separate input pathways, we found that feedforward inhibition is responsible for the action potential facilitation, while feedback inhibition causes suppression just after the first burst stimulation. Here, we examined the phase-dependent effect of the TBS in the different input pathways in area CA1. The TBSs on both inputs show a competitive LTP induction depending on the phase of the theta oscillation. The result shows that the input from CA3 to CA1 can carry information on the phase of the theta oscillatory activity and cause the plastic change in the synapses.

Disclosures: T. Tominaga: None. **Y. Tominaga:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.03/F7

Topic: B.07. Synaptic Plasticity

Support: CNPq 202183/2015-7
NSERC DG 2017-04730
NSERC DAS 2017-507818
CIHR NIA 288936
CIHR OG 126137

Title: Differential learning from pre- vs. postsynaptically expressed STDP

Authors: *B. E. P. MIZUSAKI[1,2], S. S. Y. LI[2], R. P. COSTA[3], P. J. SJOSTROM[2]
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Abstract: Most theoretical studies of long-term synaptic plasticity implement changes in synaptic efficacy postsynaptically, ignoring the rich presynaptic short-term dynamics, as well as

the interaction between pre- and postsynaptic expression (Costa et al, RSTB 2017 DOI: 10.1098/rstb.2016.0153). Since both forms of expression are found experimentally, this assumption has resulted in a long-standing postsynaptic bias in theoretical studies. As a consequence, the specific computational impact and functional benefits of pre- vs. postsynaptic expression remain relatively poorly studied.
To explore the functional impact of pre- and postsynaptic expression, we simulated two scenarios in which a postsynaptic neuron learns to respond to excitatory inputs via spike-timing-dependent plasticity (STDP). Each scenario quantified a particular aspect of information coding: latency to spike and correlated activity, respectively. In the first, periodic volleys of presynaptic Poisson activity were temporally ordered along the inputs. After learning, synaptic efficacy was organized according to stimulus order within the volley, with postsynaptic response latency and duration reduced (Song et al, Neuron 2000 3:919). In the second scenario, stimulation consisted of two input populations of which one had correlated activity, which lead to its selective potentiation (Song and Abbott, Neuron 2001 32:339).
Initially, we used Song and Abbott's (2000, 2001) simple additive model of STDP. As a model extension, presynaptic plasticity was implemented via alterations in release probability and short-term depression, and postsynaptic expression via quantal amplitude changes. For added biological realism, we next carried out simulations with a triplet model tuned to physiological pre- and postsynaptic expression data (Costa et al, eLife 2015, DOI:10.7554/eLife.09457), obtained from monosynaptic connections between visual cortex layer-5 pyramidal cells.
We found that presynaptic plasticity could adjust learning rates and affinity for correlated inputs, whereas postsynaptic expression was more effective for amplitude enhancement. We also found that under constant stimulation, presynaptic plasticity did not affect postsynaptic firing rates, suggesting that associative learning and frequency saturation can be uncoupled. In summary, our results highlight key differences between pre- and postsynaptic expression of STDP, demonstrating that the default postsynaptic assumption in modelling of plasticity is not neutral but may introduce a bias.

Disclosures: B.E.P. Mizusaki: None. **S.S.Y. Li:** None. **R.P. Costa:** None. **P.J. Sjostrom:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.04/F8

Topic: B.07. Synaptic Plasticity

Support: CIHR

Title: A spike timing-dependent plasticity rule for single, clustered and distributed dendritic spines

Authors: *D. E. MITCHELL, S. TAZERART, S. MIRANDA-ROTTMANN, R. ARAYA
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Abstract: Dendritic spines can undergo structural remodeling, and are the preferential site for the induction of long-term potentiation (LTP) and long-term depression (LTD). In a variant of LTP and LTD, known as spike-timing dependent plasticity (STDP), the sign and magnitude of the change in synaptic strength depends on the timing between the spikes of two connected neurons. Although STDP has been extensively studied in cortical pyramidal neurons, the precise structural organization of excitatory inputs that supports STDP, as well as the structural, molecular and functional properties of dendritic spines during STDP remain unknown. Here we developed a spine STDP protocol, in which two-photon glutamate uncaging over single or multiple spines from the basal dendrites of layer 5 pyramidal neurons, which mimics presynaptic release of glutamate (pre), was paired with somatically generated postsynaptic spikes (post). We found that the induction of STDP in single spines follows a classical Hebbian STDP rule, where pre-post pairings at timings that trigger LTP (t-LTP) produce shrinkage of the activated spine neck and a concomitant increase in its synaptic strength; and post-pre pairings that trigger LTD (t-LTD) decrease synaptic strength without affecting the activated spine shape. Furthermore, we tested whether the *single spine*-Hebbian STDP rule could be affected by the activation of neighboring (clustered) or distant (distributed) spines. Our results show that the induction of t-LTP in two clustered spines (< 30 μm apart) enhances LTP via a mechanism that requires actin polymerization-dependent neck shrinkage, which permits AMPA receptor transport to the spine head and insertion into the postsynaptic density (PSD). Moreover, the induction of t-LTD is disrupted when two clustered spines (< 30 μm apart) are activated, but can be recovered if the activated spines are separated by > 30 μm. These results indicate that the induction of STDP in single, or distributed spines (separated by > 30 μm), follow a Hebbian STDP rule. Interestingly, synaptic cooperativity, induced by the co-activation of clustered spines and the local spatio-temporal summation of clustered synaptic inputs, provides local dendritic depolarization that is sufficient to disrupt t-LTD, leading to STDP only encompassing LTP.

Disclosures: D.E. Mitchell: None. **S. Tazerart:** None. **S. Miranda-Rottmann:** None. **R. Araya:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.05/F9

Topic: B.06. Synaptic Transmission

Support: 8051 WELLCOME TRUST 101029/Z/13/Z

Title: Acetylcholine controls input selectivity in CA1 of the hippocampus by pathway specific muscarinic regulation of feedforward excitatory-inhibitory ratio

Authors: *J. PALACIOS, J. R. MELLOR
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Abstract: Acetylcholine fundamentally reconfigures cortical circuits to switch their function. In the hippocampus acetylcholine is thought to prioritise input to CA3 and CA1 circuits from sensory modalities containing new information about the environment and away from internally held representations. This reconfiguration enables acetylcholine to signal that previously held representations require updating with new information (Dannenberg et al., 2017). However, the mechanism by which acetylcholine enables this critical switch in function is unclear. In the CA1 region, internally held representations are proposed to enter via the Schaffer collateral (SC) pathway from CA3 whereas new information enters via the temporoammonic (TA) pathway direct from the entorhinal cortex. Therefore, it is predicted that acetylcholine will reduce SC input whilst enhancing TA input to CA1. Previous studies have reported that acetylcholine reduces excitatory synaptic transmission in both SC and TA pathways apparently contradicting this prediction. However, these studies did not measure the effects of acetylcholine on feedforward inhibition which have a major role in determining the CA1 response to SC or TA input. Therefore, our goal was to test the core hypothesis that acetylcholine prioritises TA input over SC input. We used electrical stimulation to obtain monosynaptic excitatory or disynaptic inhibitory postsynaptic currents (mEPSC or dIPSC respectively) from SC and TA pathways on the same CA1 pyramidal neuron. The acetylcholine receptor agonist carbachol (CCh) or optogenetically evoked release of acetylcholine reduced both mEPSC and dIPSC synaptic responses for the SC input which resulted in no change to excitatory-inhibitory balance and indeed a decrease in postsynaptic spiking. In contrast, TA mEPSC and dIPSC were also reduced by cholinergic receptor activation, but a boost in facilitation of excitatory and the lack of it in the inhibitory drive resulted in an increase of excitatory-inhibitory balance, which produced an increment in postsynaptic spiking. Our data suggest that distinct interneuron populations engaged by SC or TA pathways participate in input selective modulation. Pharmacological interventions revealed that presynaptic muscarinic M3 receptors mediated cholinergic induced facilitation of excitatory-inhibitory balance on TA pathway, in contrast the SC pathway where muscarinic M4 receptors mediate presynaptic inhibition. We conclude that differential expression of presynaptic muscarinic receptors on SC and TA inputs to CA1 enable acetylcholine to reconfigure the network to favour new information over internally held representations.

Disclosures: J. Palacios: None. **J.R. Mellor:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.06/F10

Topic: B.07. Synaptic Plasticity

Support: Wellcome Trust WT100000
BBSRC Grant BB/N019512/1
Leverhulme RPG-2016-446

Title: A dendritic model of CA1 place-field formation and remapping through excitatory and inhibitory synaptic plasticity

Authors: P. A. BOZELOS[1,2], E. J. AGNES[1], *T. VOGELS[1], P. POIRAZI[2]
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Abstract: Spatial navigation learning and memory have been in the spotlight of neuroscience research for decades, producing a compelling amount of evidence on the critical role of hippocampus, and particularly of the CA1 subregion, in the construction of flexible cognitive maps. Indeed, place field formation and spatial remapping are now well-characterized computational functions at the neural population level. However, our understanding at the single-cell level lags behind. What are the contributions of dendritic non-linearities and / or synaptic plasticity mechanisms in place-field formation? How is remapping actualized at the individual neuron level? What are the effects on learning flexibility and memory capacity of the network? Here we explore these questions by investigating the spatial encoding properties of a plasticity-enabled network model consisting of multi-compartmental neurons. We simulate an environment exploration task by anchoring the spike-timing tuning of excitatory and inhibitory network afferents to a series of consecutive locations across a virtual environment. We allow the neurons to organise their dendritic inputs according to excitatory and inhibitory plasticity rules that interact locally at the level of dendrites. We show how the afferent connectivity patterns that allow the emergence of place representations can arise naturally via branch-specific allocation of the spatially-tuned excitatory drives and selective inhibitory gating. When the network model experiences a novel environment (i.e., a shuffled set of correlated inputs), synaptic allocation patterns restructure to accommodate the matching afferents along same dendrites. Remapping thus follows from a complex interaction between new and previously learned receptive fields. We show that encoding capacity is dramatically increased through the introduction of dendrites that allow for the branch-wise registration of more than one place-field per neuron, corresponding to distinct virtual environments, and allowing for the possibility of context dependent switching.
To our best knowledge, this is the first modelling study to show how place-fields can be learned

via the implementation of codependent synaptic plasticity rules to explain how spatial remapping can occur.

Disclosures: P.A. Bozelos: None. **E.J. Agnes:** None. **T. Vogels:** None. **P. Poirazi:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.07/F11

Topic: B.06. Synaptic Transmission

Support: Intel ISRA on neuromorphic computing

Title: Spike-timing computation with complex vectors: Emergence of theta oscillations, place-fields and phase-precssion in a model of hippocampus

Authors: *E. P. FRADY[1], P. KANERVA[1], F. T. SOMMER[2]
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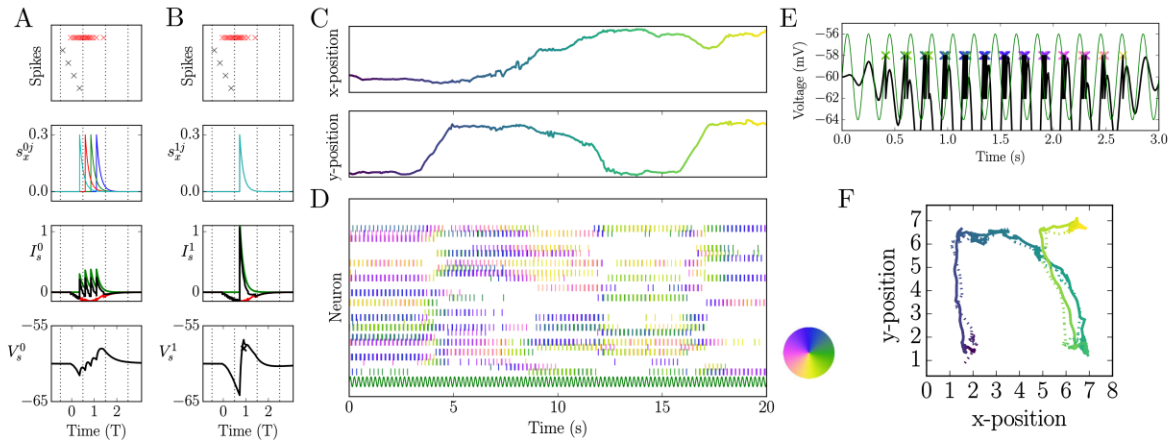
Abstract: A major challenge in Neuroscience is to develop models that bridge both the computational and mechanistic levels. We have made recent advances understanding the structured representations in connectionists models known as Vector Symbolic Architectures (VSA). Here, we demonstrate the utility of VSA models in a neuroscience theory framework by developing algorithms for navigation at the computational level that can also explain hippocampal data at the mechanistic level. Specifically, we focus on a VSA model based on high-dimensional vectors of complex numbers, Fourier Holographic Reduced Representations (FHRR). We have developed a novel model of synaptic integration to implement FHRR with spiking neurons that express periodic population firing, where the timing of a spike relative to an internal oscillation represents the phase of a complex number. This makes FHRR useful for understanding the theta-rhythm and phase coding in hippocampus. We propose synaptic circuitry and dynamics that transforms a presynaptic spike into an excitation/inhibition-balanced postsynaptic current oscillation. The timing of presynaptic spike and synaptic delay determines the phase of the postsynaptic current oscillation. The oscillatory currents from many synapses will sum in the neuron, effecitively implementing a dot product between complex vectors. The effect of spikes depends now on their relative timing and stored synaptic patterns - it can be small in the decoherent case (A), or large in the coherent case (B). In essence on the computational level, we develop a model that forms a neural code of location in a 2-D environment (C). We demonstrate how the computations in the model can be implemented in spiking neurons to produce neural response activity similar to CA1 principal neurons, exhibiting place fields and phase-precession (D,E). This activity can be decoded by a readout population (F), and used as part of a navigation algorithm, such as for path-integration.



Disclosures: E.P. Frady: None. **P. Kanerva:** None. **F.T. Sommer:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.08/F12

Topic: B.06. Synaptic Transmission

Support: KAKENHI, no. 17H06036
RIKEN Junior Research Associate Program

Title: Analysis of complex temporal information streams by dendritic neuron model

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Abstract: Maximization of mutual information is widely thought to play a crucial role in sensory and motor information processing by cortical neurons. Hebbian synaptic plasticity may also be regarded as a biological machinery to realize this information theoretical principle. However, if the brain models the external world or monitors its internal processes, it should extract characteristic features from externally or internally driven information streams. This operation requires a certain level of abstraction, and optimal information transmissions do not seem to characterize the principles governing these processes. Here, we propose the conditional entropy minimization as an alternative principle of neural information processing. We derive a learning rule from this principle for a two-compartment neuron model and demonstrate its excellent performance in learning various signal processing tasks. For instance, simple networks of such neurons can perform unsupervised learning and denoising of orientation-tuning maps in the visual processing, chunking of visual and other information streams, detection of population

spike sequences repeated in noisy background, and the blind source separation of mixture signals from significantly correlated auditory sources. In particular, our network model can separate the sounds of music instruments playing the same music piece, which was not possible for the standard ICA-based method. Thus, our model will provide new insights into the principles of neural processing of temporal information.

Disclosures: T. Asabuki: None. **T. Fukai:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.09/F13

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS093866

Title: Imaging STDP: Potentiation and depression with timed dual-site stimulation in hippocampal CA3 region

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Abstract: Spike-timing dependent plasticity (STDP) enables neural circuits to store information based on the time interval between the activation of synaptic inputs. STDP incorporates a basic Hebbian principle of synaptic plasticity and gives a neural circuit unique storage capabilities. Prior experimental studies of STDP varied the timing between a synaptic input and a postsynaptic spike induced by direct current injection, rather than by varying the timing between the stimulation of two synaptic inputs. Furthermore, prior studies employed recordings from single cells without evaluating the spatial distribution of STDP through the circuitry. The present study used voltage sensitive dye imaging to study STDP in the CA3 region of horizontal hippocampal slices from 4 to 7-week old rats. Electrical stimulation was applied to two sites in the stratum radiatum; stimulating each site alone elicited robust optical responses over broad overlapping areas. Stimulating two sites repeatedly at different times separated by 10 msec induced STDP. Simultaneous stimulation of the two sites did not induce changes in responses. Following dual-site stimulation at 10 msec intervals responses to stimulation of each site were potentiated at some locations and depressed at other locations. In general, with timed induction the potentiation and depression varied in magnitude as well as in location relative to the sites of stimulation. Depression and potentiation occurred in the same slice at different locations. Comparing sites with the greatest potentiation indicated greater potentiation of responses to the site stimulated first compared to the site stimulated 10 msec later. When the sites showing the greatest depression were compared, the amount of depression was similar for responses to the

site stimulated first or second. STDP was not effective in the storage of spatial response patterns elicited by stimulation of one or both sites. These results demonstrate STDP plasticity can be induced by activation of synaptic inputs. Furthermore, both depression and potentiation can be elicited in the same slice to both the site stimulated first and the site stimulated second. Thus, STDP has complex manifestations in the processing of information by the hippocampal CA3 region.

Disclosures: M.B. Jackson: None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.10/F14

Topic: B.07. Synaptic Plasticity

Support: PJ ERC 692692

Title: An increase of the readily releasable pool accounts for post-tetanic potentiation at the hippocampal mossy fiber bouton-CA3 pyramidal neuron synapse

Authors: D. VANDAEL, *P. JONAS
Inst. of Sci. and Technol. (IST) Austria, Klosterneuburg, Austria

Abstract: The hippocampal mossy fiber synapse is a key synapse in the tri-synaptic circuit of the hippocampus, characterized by a particularly large post-tetanic- potentiation (PTP) (Salin et al., 1996, PNAS 93:13304). Interestingly, PTP turns mossy fiber boutons (MFBs) from conditional-detonators into full detonators (Vyleta et al., 2016, Elife e17977). MFBs show a large readily releasable pool, but initial release probability is low because of loose coupling of presynaptic calcium channels to the calcium sensors of exocytosis (Hallermann et al., 2003, PNAS 100:8975; Vyleta and Jonas, 2014, Science 343:665). A recent study showed that chemically induced LTP at this synapse leads to tightening of the coupling, thereby increasing release probability (Midorikawa and Sakaba, 2017, Neuron 96:1033). It is thus tempting to hypothesize that MFBs rely on a similar mechanism to achieve PTP. To test this hypothesis, we examined PTP at the unitary level by paired recordings between MFBs and synaptically connected CA3 pyramidal neurons. MFBs were non-invasively stimulated in the cell-attached configuration, and EPSCs were recorded in the CA3 pyramidal neuron. High-frequency stimulation (100 spikes at 100 Hz) evoked highly robust PTP (162.9 ± 26.4 pA before and 441.8 ± 68.9 pA after PTP, 14 pairs; p=0.0002). Bursts of 18 spikes at 100 Hz were sufficient for induction (171.4 ± 39.8 pA before and 425.4 ± 124.5 pA after PTP, n=7). After induction, PTP decayed with a time constant of 91 ± 24.9 s. Unexpectedly, paired pulse ratio (a robust indicator of release probability) was unchanged after PTP (1.8 ± 0.3 before and 1.5 ± 0.16 after PTP;

p=0.28), indicating that PTP may be independent of changes in release probability. To quantitatively analyze vesicle pool dynamics during PTP, we plotted cumulative release against number of stimuli during 50-Hz trains. Fitting the linear portion of the relation revealed that PTP doubled pool size (908 ± 243 pA before versus 2103 ± 450 pA after PTP, 7 pairs; p=0.01), but left release probability unaffected (0.25 ± 0.05 before and 0.22 ± 0.02 after PTP; p=0.3). The effects of PTP on evoked release were accompanied by a 1.5-fold increase in spontaneous EPSC frequency (10.4 ± 1.3 Hz before versus 15.5 ± 2.4 Hz after PTP; p=0.047). This effect decayed with a time constant similar to that of PTP and therefore might temporarily increase the excitability of CA3 pyramidal cells. In conclusion, PTP mechanistically differs from LTP at MFB-CA3 pyramidal cell synapses. Our results suggest that multiple orthogonal forms of presynaptic plasticity coexist at hippocampal mossy fiber synapses, enriching the information processing capacity of this important connection.

Disclosures: D. Vandael: None. **P. Jonas:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.11/F15

Topic: B.07. Synaptic Plasticity

Title: The modulation of back-propagating action potential by LTP induction on dendrite in rat hippocampal dentate-granule cells

Authors: *S. SUGIMOTO[1], J. KASAI[1], M. KONDO[2], K. KATO[3], T. AIHARA[1]
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Abstract: The hippocampus is an area related to the integration and storage of several sensory information. In recent studies, dentate granule cells of rat hippocampus individually receive place information and the other sensory information (e.g. odor) from entorhinal cortex on dendrites, medial dendrite (MD, at the middle molecular layer) and lateral dendrite (DD, at the outer molecular layer), separately. On the other hand, spike timing dependent plasticity (STDP) were reported in hippocampal pyramidal neurons and granule cells. The associative mechanism is based on the timing of pre-synaptic spikes (associated EPSPs) and post-synaptic spikes (associated back-propagating action potential, bAP) and it determines the sign and magnitude of long-term potentiation (LTP) or depression (LTD). However, the information integration by a cooperative association as STDP in two parts of dendrite, MD and DD, is still unclear. Our previous studies reported that the transmission distance and the magnitude of bAP, which is one of inducing factors for STDP, were modified by induction of LTP along dendrites in hippocampal CA1 pyramidal neurons. It suggested that cooperatively integration of the context

information from CA3 and the other information through a direct pass from EC were facilitated in CA1 pyramidal neurons. However, the influence of synaptic plasticity along dendrites on the bAP modification in the hippocampal dentate gyrus was not investigated. Therefore, the change of integration ways between two input information on MD and DD, during associative consolidation, is not still unclear. In this study, in order to investigated the information integration in dendrites of dentate granule cells, we analyzed the distance and magnitude of the bAP before and after LTP induction by high-frequency electrical-stimuli in the granule cells of the hippocampal dentate gyrus, using optical imaging method with voltage sensitive dye. As the result, the bAP transmission distances were extended from MD to DD and the magnitude of bAP was increased at DD. The result suggests that the cooperative integration of place information to MD and the other sensory information to DD in dentate granule cell was influenced by the bAP modulation based on the plasticity induced on dendrites.

Disclosures: S. Sugimoto: None. **J. Kasai:** None. **M. Kondo:** None. **K. Kato:** None. **T. Aihara:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.12/F16

Topic: B.07. Synaptic Plasticity

Title: *In vivo*-like irregular activity reveals dominance of firing rate over spike-timing in synaptic plasticity

Authors: *M. GRAUPNER[1], Y. DEMBITSKAYA[2], S. VALTCHEVA[3], S. OSTOJIC[4], L. VENANCE[2]
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Abstract: Synaptic plasticity, the change in efficacy of connections between neurons, is thought to underlie learning and memory. Plasticity can be elicited by pre- and postsynaptic activity patterns, where the outcome is determined by the firing rate and spike-timing correlations. Plasticity is typically induced experimentally with regular activity patterns consisting of evenly-spaced firing patterns and fixed relative spike-timings. However, such regularity strongly differs from *in vivo* activity. Therefore, it remains unclear how irregular, *in vivo*-like patterns shape synaptic plasticity. To address this question, we combined mathematical modelling and experiments inducing synaptic plasticity at corticostriatal synapses. As a first step toward natural firing patterns, we studied plasticity induced by spike-pairs with fixed time lag between pre- and postsynaptic spikes (Δt) but irregular occurrence. Theoretical prediction suggested that under

irregular spike-pair stimulation, the firing rate has greater impact on the outcome of plasticity compared to spike-timing correlations, in particular at intermediate to large firing rates. We experimentally verified these predictions and observed that irregular spike-pair stimulation diminished long-term depression (LTD) and widened the Δt range of long-term potentiation (LTP) compared to regular patterns at low firing rate (~1 spk/sec). Furthermore, increasing in the firing rate completely abolished LTD and led exclusively to LTP in the whole range of Δt's (>3 spk/sec). Here, we demonstrate the prevalent importance of firing rate over spike-timing correlations for the emergence of synaptic plasticity under *in vivo*-like irregular stimulation. These results highlight the importance to consider the dependence of plasticity on natural firing statistics and call into question the dominant role of spike timing for plasticity in natural conditions. Instead, our findings suggest that spike correlations shape plasticity at low firing rates, while the influence of firing rate dominates at intermediate and large firing rates.

Disclosures: M. Graupner: None. **Y. Dembitskaya:** None. **S. Valtcheva:** None. **S. Ostojic:** None. **L. Venance:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.13/F17

Topic: B.06. Synaptic Transmission

Support: Université Sorbonne Paris Cité Doctoral Fellowship
Fondation Pour la Recherche Médicale

Title: Dissecting synaptic dynamics underlying the neuronal code with *in vivo* dynamic clamp manipulation of visually-evoked excitation and inhibition in mouse primary visual cortex

Authors: M. GAJOWA, *L. J. GRAHAM
Neurophotonics Lab., CNRS UMR8250, Univ. Paris Descartes, Paris, France

Abstract: A first step towards understanding the mechanistic basis for the neuronal code is describing the coupling between synaptic integration and spiking. Towards this end we have developed a protocol to study functional I/O using blind whole-cell patch clamp recordings in mouse V1 in vivo, comprising successive applications of current clamp recording mode to establish a neuron's functional responses, voltage clamp recording mode to estimate the somatic signature of the underlying synaptic inputs, and dynamic clamp (DC) recording mode for the re-injection of the estimated synaptic inputs and variations of same. This protocol provides a description of how specific patterns of excitatory and inhibitory synaptic input influence the spiking response during visual processing. Our results confirm the feasibility of the closed loop protocol, in particular with respect to recording quality and stability required for the quantitative

measurements. We show how changes in spike number and timing in response to DC injections of variations of the estimated excitatory and inhibitory synaptic conductance waveforms, in particular in comparison to the originally measured visual responses, allow describing integrative properties of V1 neurons depending on their electrophysiological type (RS vs. FS), and illuminate constraints on the functional neuronal code. In particular, when comparing visually-evoked and DC-evoked spiking responses, the averaging over trials inherent in the estimation of evoked synaptic conductances, which necessarily minors the impact of uncorrelated fluctuations between single trials, implicates consideration of the constraints of rate based versus spike-timing based codes.

Disclosures: M. Gajowa: None. **L.J. Graham:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.14/F18

Topic: B.06. Synaptic Transmission

Support: Wellcome Trust
ERC
Marie-Skłodowska Curie Fellowship

Title: Fast 3D two-photon Ca2+ imaging in mouse V1 reveals patterns of layer II/III and V pyramidal cell dendrite activity *in vivo*

Authors: *T. J. YOUNTS[1], S. SADEH[2], C. BARAGLI[2], A. R. SILVER[2]
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Abstract: How sensory information is represented in dendrites in vivo is poorly understood because it is difficult to measure activity within morphologically complex structures. We used a custom built 3D two-photon acousto-optic lens microscope to measure dendritic activity in layer II/II and V pyramidal cells in mouse primary visual cortex in vivo. Pyramidal cells were sparsely co-labelled with the genetically-encoded Ca2+ indicator GCamp6f (to measure activity) and the red fluorophore TdTomato (to detect and correct for brain motion). Patterns of activity were characterized across behavioral states (anaesthesia, awake and stationary, running). Layer II cells exhibited mainly relatively small local multi-branch Ca2+ events that were sometimes coupled to somatic events. Somatic Ca2+ events were rarely associated with global dendritic events. Activity was little affected by anaesthesia and locomotion. In layer V cell apical dendritic tufts, Ca2+ events were either small and localized to a few branches or large and global. Compared to rest, anaesthesia suppressed while locomotion enhanced activity. In vitro slice experiments suggest the patterns of dendritic activity observed in vivo involve synaptically-driven local

events for both cell types, whereas global events in layer V cells involve synaptic and back-propagating action potential coupling. These data indicate that layer II/III and V pyramidal cell dendrites exhibit unique spatial and functional patterns of activity, implying different integration strategies during sensory processing. These results are also consistent with the idea that layer II/III cells are largely driven by bottom-up feedforward inputs, while top-down inputs conveying information about animal state effectively activates layer V cells.

Disclosures: T.J. Younts: None. **S. Sadeh:** None. **C. Baragli:** None. **A.R. Silver:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.15/F19

Topic: B.07. Synaptic Plasticity

Support: Howard Hughes Faculty Scholarship
Klingenstein Fellowship
NIH DC012557

Title: Heterosynaptic plasticity normalizes cortical excitatory-inhibitory balance

Authors: *R. E. FIELD[1], J. D'AMOUR[2], R. TREMBLAY[3], F. ZENKE[4], J. GJORGJIEVA[5], T. VOGELS[4], B. RUDY[6], R. C. FROEMKE[7]
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Abstract: The fine tuning of inhibition to excitation is critical for spike generation, synaptic plasticity, and seizure generation (Isaacson & Scanziani, 2011). During development, cortical excitatory-inhibitory (E:I) balance is refined in an experience-dependent manner (Dornn et al., 2010). Chronic E:I imbalances have been implicated in various neurological and psychiatric conditions, including epilepsy and autism (Rubenstein & Merzenich, 2003; Yizhar et al., 2011). Here we examine how spike-timing-dependent plasticity (STDP) calibrates E:I balance across multiple inputs to layer V pyramidal neurons in developing mouse auditory cortex and human temporal lobe tissue from epilepsy patients. Using an 8-channel array, we monitored multiple inputs before inducing synaptic modifications at one set of inputs by repetitively pairing single E/IPSPs with postsynaptic spikes. Pre-before-post pairing elicited excitatory and inhibitory long-term potentiation (LTP) at paired inputs, while post-before-pre pairing elicited excitatory long-term depression (LTD) and inhibitory LTP (D'amour and Froemke, 2015). Spike pairing also

induced heterosynaptic modifications that increased overall E:I balance. Approximately 10 minutes after pre-before-post pairing, the original best excitatory input and the original best inhibitory input underwent LTD, and the overall E:I correlation across all channels increased. Heterosynaptic modifications were abolished by inhibiting calcium release from internal Ca^{2+} stores, providing a mechanism for regulating heterosynaptic plasticity. 2-photon Ca^{2+} imaging in slices revealed that spike pairing activated internal stores in the dendrites. In addition, heterosynaptic plasticity was activity-dependent, such that removing the original best excitatory and inhibitory inputs from the stimulus set for ten minutes after pairing blocked LTD at the original best inputs and induced LTD at the next best excitatory and inhibitory inputs. These experiments helped to constrain computational studies examining the requirements for activity across channels for heterosynaptic plasticity and the functions of heterosynaptic changes for overall regulation of E:I balance. Our results show that heterosynaptic plasticity rapidly normalizes excitation and inhibition in neurotypical and epileptic circuits, suggesting that larger-scale manipulation of heterosynaptic inputs might allow for rescue of E:I balance within epileptic circuits and offer a promising approach to treating temporal lobe epilepsy.

Disclosures: R.E. Field: None. **J. D'Amour:** None. **R. Tremblay:** None. **F. Zenke:** None. **J. Gjorgjieva:** None. **T. Vogels:** None. **B. Rudy:** None. **R.C. Froemke:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.16/F20

Topic: B.07. Synaptic Plasticity

Support: János Bolyai Research Scholarship of the Hungarian Academy of Sciences
NAP1: KTIA_NAP_13”B”
ERC: 682426 — VISONby3DSTIM

Title: Sharp wave-ripple associated dendritic signal integration in awake mice

Authors: *B. CHIOVINI[1,2], D. PÁLFI[2,1], G. JUHÁSZ[1,2], L. JUDÁK[1], Z. MEZRICZKY[2], G. KATONA[1,2], B. RÓZSA[1,2]
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Abstract: Hippocampal sharp wave-ripple (SPW-R) complexes have crucial role in memory formation and consolidation. SPW-R activities appear during slow wave sleep and consummatory behaviour. These hippocampal patterns are responsible for encoding, storage and retrieval of memory. Several facts suggest that SPW-R-associated cell assemblies can activate dendritic hot-spots. Because of technical and methodical problems the relationship between

SPWs, field ripple oscillations and dendritic hot-spots have not yet been studied in awake animals. Beside the field potential recordings we were able to measure simultaneously the activity pattern of neuronal populations and their dendritic signal integration mechanisms in large volume. We developed new surgical methods in order to apply two-dimensional (2D) and three-dimensional (3D) two-photon random-access point scanning imaging techniques combined with ipsilateral multi-channel electrophysiology. We show complex Ca^{2+} events at different subcellular regions of hippocampal neurons *in vivo*. Moreover, we found the existence of dendritic Ca^{2+} spikes in awake animals. We were able to record hippocampal activity patterns during physiological rhythms among neurons or along their dendrites in high volumes and in real time, in order to better understand the mechanisms of hippocampal coincidence detection and neuronal functions during input-output formation and conversion *in vivo* in deep brain areas.

Disclosures: B. Chiovini: None. **D. Pálfi:** None. **G. Juhász:** None. **L. Judák:** None. **Z. Mezriczky:** None. **G. Katona:** None. **B. Rózsa:** None.

Poster

286. Network Interactions and Synaptic Integration I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 286.17/F21

Topic: B.06. Synaptic Transmission

Title: Enhanced dendritic compartmentalization in human cortical neurons

Authors: *L. BEAULIEU-LAROCHE[1], E. TOLOZA[1], M. LAFOURCADE[2], M.-S. VAN DER GOES[1], D. BARNAGIAN[1], E. N. ESKANDAR[4], M. FROSCH[5], S. S. CASH[6], M. T. HARNETT[3]
[1]Brain and Cognitive Sci., [2]Neurosci., [3]MIT, Cambridge, MA; [4]Massachusetts Gen. Hosp., Boston, MA; [5]C.S. Kubik Lab. for Neuropathology, Massachusetts Gen. Hosp., Boston, MA; [6]Dept Neurol, Mass Genl Hosp, Boston, MA

Abstract: The human cortex exhibits exceptional computational power compared to other species, but the underlying biological mechanisms are unknown. Here, we perform direct patch clamp recordings from human cortical dendrites and report enhanced electrical compartmentalization in layer 5 pyramidal neurons. Distance-dependent voltage attenuation is similar between human and rat dendrites, demonstrating that the longer physical length of human neurons translates into a longer electrotonic length. Compared to rat dendrites, input into human distal apical dendrites is much less effective at driving somatic action potentials, even in the presence of dendritic spikes. Human somas also exhibit less bursting in response to somatic current injection due to decreased recruitment of dendritic electrogenesis. We conclude that greater functional compartmentalization of single neurons increases the number of electrical

processing compartments that can perform independent operations, which may contribute to the computational power of human cortex.

Disclosures: L. Beaulieu-Laroche: None. **E. Toloza:** None. **M. Lafourcade:** None. **M. Van Der Goes:** None. **D. Barnagian:** None. **E.N. Eskandar:** None. **M. Frosch:** None. **S.S. Cash:** None. **M.T. Harnett:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.01/F22

Topic: B.07. Synaptic Plasticity

Support: ERC SalienSy 335333
Swiss National Funds Grant 31003A

Title: Experience-dependent synaptic plasticity in the lateral habenula

Authors: *M. TRUSEL, S. LECCA, M. MAMELI
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Abstract: In everyday life, proper behavioral responses when foreseeing an unpleasant event are necessary for survival. Seminal work performed in awake monkeys indicated that neurons in the lateral portion of the epithalamic nucleus habenula (LHb) are excited upon a negative event. Furthermore, after conditioning an animal to recognize a neutral stimulus anticipating the occurrence of a punishment, LHb neurons show excitation when the conditioned stimulus is presented (Matsumoto and Hikosaka, 2007). However, whether synaptic adaptations occur within the LHb during learning, allowing anticipating an aversive stimulus, remains unknown. We hypothesized that, during the formation of an association between an external stimulus and the successive administration of a punishment, plasticity at excitatory synapses occurs in the LHb. To investigate this issue, we interrogated synaptic transmission onto LHb neurons in acute brain slices from animals at different stages of learning using an active avoidance paradigm (30 trials/day, 5 days). The animals learned to avoid a footshock preannounced by a tone already from the second and third sessions (“learners”). Control mice instead received the footshocks and the CS randomly, not contingently. 24h after training session 2 we measured spontaneous excitatory postsynaptic currents (sEPSC) in acute brain slices containing the LHb. The frequency of sEPSCs, but not amplitude, was significantly increased in the LHb of learners, compared to control mice. Recording trains of EPSCs revealed similar paired-pulse ratios between learners and controls. We then measured AMPA and NMDA currents elicited by electrical stimulation within the LHb, observing a significant increase in AMPA/NMDA ratio in learners compared to controls. Furthermore, this AMPA/NMDA increase was similarly observed when evoking

EPSCs using uncaged glutamate in the proximity of dendrites. These data suggest that learning to predict an aversive stimulus engages post-synaptic strengthening at excitatory synapses in the LHb.

Disclosures: M. Trusel: None. **S. Lecca:** None. **M. Mameli:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.02/F23

Topic: B.07. Synaptic Plasticity

Support: ERC
SNF

Title: Resolving plasticity at accumbal to lateral hypothalamus synapse in feeding behaviour

Authors: *S. THOENI, E. O'CONNOR, C. LÜSCHER
Dept. of Basic Neurosciences, Univ. of Geneva, Geneva, Switzerland

Abstract: Inhibition of nucleus accumbens (NAc) dopamine D1 receptor-expressing medium spiny neurons (D1R-MSNs) projecting to the lateral hypothalamus (LH) enables feeding in mice. Here, using whole-cell patch clamp recordings, we investigated the plasticity of this NAc-to-LH synapse in the context of feeding behavior. Surprisingly, a high frequency stimulation protocol previously shown to potentiate NAc-pallidum or NAc-midbrain synapses, was without effect on NAc-LH synapses in slices from control mice. Chemical long-term potentiation (LTP), normally elicited by PKA activation, also had no effect on the NAc-LH inhibitory postsynaptic currents. This was true regardless of the postsynaptic identity of LH neurons receiving NAc inhibition. Conversely, a depression of the NAc-LH synapse was observed following activation of GABA-B or CB1-receptors, but not after low frequency stimulation protocol shown to be efficient at the NAc-pallidum synapse. Consistent with these observations, tracing experiments revealed that NAc-D1-MSNs projecting to LH are largely non-overlapping to those that project to the midbrain and pallidum. Finally, mice were exposed to a regime of food restriction and exercise to trigger hyperphagia and excess weight gain upon resuming *ad libitum* food access. At the timepoint of hyperphagia, PKA activation now led to potentiation of the NAc-to-LH synapse in *ex vivo* brain slices, most likely reflecting a decrease in release probability at these terminals. Taken together, our findings point to a model in which experience-dependent plasticity at the NAc-LH synapse may support rebound food intake in periods following weight loss. This model may reflect elements of weight gain associated with human yoyo dieting.

Disclosures: S. Thoeni: None. **E. O'Connor:** None. **C. Lüscher:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.03/F24

Topic: B.07. Synaptic Plasticity

Title: Exogenous coenzyme Q treatment affects age-related alterations of the motor cortex in aged mice

Authors: *R. INOUE, M. TAKAHASHI, M. MIURA
Tokyo Metro Inst. Gerontology, Tokyo, Japan

Abstract: Motor deficits occur during not only disease like Parkinson's disease but also normal aging. Takahashi et al (2016) found behavioral and histological alterations that were associated with age-related decline of brain mitochondrial function. Mitochondrial function is assessed by measuring mitochondrial oxygen consumption rate (OCR). They suggested that OCR, coenzyme Q (CoQ) content, vesicular glutamate transporter 1 (VGluT1) level in the motor cortex, and motor function were reduced in aged mice compared to young mice. CoQ, which is present in mitochondria, is a coenzyme and an electron transporter in the respiratory chain. They also showed that chronic administration of CoQ to aged mice restored OCR, CoQ content, VGluT 1 level, and motor function. In this study, we examined whether normal aging affects electrophysiological activities in the motor cortex of mice, and whether exogenous CoQ treatment affects the physiological alteration in the aged mice. Brain slices were obtained from aged mice after chronic CoQ treatment. Identification of the motor cortex was done using a brain atlas. In some experiments, Nissl staining was performed to confirm the characteristic layer structure of the motor cortex. Field excitatory postsynaptic potentials (fEPSPs) of motor cortex in brain slices of young or aged male mice were recorded by a multi-electrode array or a glass recording pipette. Electrophysiological measurements revealed that aging significantly affected fEPSPs of aged mice compared to young mice. Considering that motor function declined even in normal aging, the changes observed in the motor cortex might relate to the motor decline. Although more detailed studies are needed to clarify the relation between central nervous system and age-related motor decline, these results may serve as the basis for developing therapy of age-related motor impairment.

Disclosures: R. Inoue: None. **M. Takahashi:** None. **M. Miura:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.04/F25

Topic: B.07. Synaptic Plasticity

Support: National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Division of Intramural Clinical and Biological Research

Title: Monitoring Rem2 interaction with the CamKIIα holoenzyme by simultaneous homo- and hetero-FRET measurements

Authors: *D. J. LIPUT[1], T. NGUYEN[2], H. L. PUHL, III[4], S. VOGEL[3]
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Abstract: Rem2, a member of the RGK family of small GTPases, is enriched in the nervous system and implicated in molecular mechanisms of neuroplasticity. RGK proteins are known for interacting with high-voltage-activated calcium channels, resulting in robust channel inhibition. In addition, Rem2 can interact with other cellular molecules, including CaMKIIα. To investigate the interactions between Rem2 and CaMKIIα, we employed a fluorescence polarization technique that can simultaneously monitor Homo- and Hetero-FRET, to study Rem2-CamKIIα binding and subsequent conformational changes in CaMKIIα catalytic domain pairing. HEK cells were transfected with plasmids encoding CaMKIIα tagged with mVenus on the N-terminal catalytic domain (V-CaMKIIα), Rem2 tagged with mCherry on the N-terminus (mCh-Rem2), or untagged Rem2. Approximately 24 h after transfections, cells were harvested and homogenates from each transfection were prepared to measure V-CaMKIIα time-resolved anisotropy (Homo-FRET) and lifetime (Hetero-FRET). V-CaMKIIα homogenates were incubated with Rem2 homogenates and saturating concentrations of calcium calmodulin (CaM) to activate the holoenzyme. Under these conditions, Rem2 increased steady state anisotropy (SSA) compared to V-CaMKIIα alone (0.052 ±0.001, 16.5% decrease in homo-FRET), suggesting that Rem2 disrupts V-CaMKIIα catalytic domain pairing. An increase in SSA also suggests that Rem2 is binding to the catalytic domain T-site as a similar increase in SSA was observed with the NR2B C-terminus (0.090 ± 0.002, 28.7% decrease in homo-FRET), a well characterized T-site ligand. Further corroborating a direct interaction between Rem2 and V-CaMKIIα, incubation with mCh-Rem2 not only increased SSA (0.086 ± 0.02, 26.7% decrease in homo-FRET), but also decreased the lifetime of V-CaMKIIα (0.18 ± 0.01 ns, 6% hetero-FRET), demonstrating a close proximity interaction between Rem2 and the V-CaMKIIα catalytic domain. To further characterize this interaction, we are currently analyzing a library of Rem2 mutants and peptide fragments to define the precise CaMKIIα binding domain. The CaMKIIα catalytic domain T-site is critical for

CaMKIIα functions in neural plasticity. For example, activated CaMKIIα binds to NR2B via the T-site, which is required for CaMKIIα translocation to post synaptic sites and long-term potentiation (LTP). Furthermore, the T-site appears to be required for CaMKIIα scaffolding functions thus promoting the recruitment of additional proteins to post synaptic sites following LTP induction. Therefore, Rem2 may be involved in molecular mechanisms of neuroplasticity by interacting with the CaMKIIα catalytic domain T-site.

Disclosures: D.J. Liput: None. **T. Nguyen:** None. **H.L. Puhl:** None. **S. Vogel:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.05/F26

Topic: B.07. Synaptic Plasticity

Support: NSF Grant IOS-1051734
NIH Grant F31 NS074473
NIH Grant R01NS092716

Title: Interaction between NMDA receptor- and endocannabinoid-mediated modulation of nociceptive synapses

Authors: *B. D. BURRELL[1,2], S. YUAN[1]
[1]Basic Biomed Sci., Univ. of South Dakota, Vermillion, SD; [2]Ctr. for Brain and Behavior Res., Vermillion, SD

Abstract: Nociceptors, sensory neurons that detect damage or potential damage to the body, are the first stage of communicating noxious stimuli from the periphery to central nervous system (CNS). In this study, long-term potentiation (LTP) in the CNS of the medicinal leech, *Hirudo verbana*, was examined, taking advantage of the ability to intracellularly record from nociceptive synapses in this model organism. High frequency stimulation (HFS) of nociceptors did produce a persistent increase in synaptic transmission and this LTP was both NMDA receptor-mediated and synapse-specific. Surprisingly, inhibition of NMDA receptors during HFS "uncovered" a persistent form of synaptic depression. This long-term depression (LTD) was mediated by the endocannabinoid transmitter 2-arachidonoyl glycerol (2-AG) acting on a TRPV (transient receptor potential vanilloid) -like channels. Previous studies have demonstrated that low frequency stimulation could produce LTD in these nociceptive synapses that was 2-AG- and TRPV-mediated (*J Neurophysiol* 104: 2766-2777; *J Neurosci.* 33:4349-4358). However, it was surprising to find this same form of LTD in the context of HFS plus NMDA receptor blockade. These observations suggest that a synapse-specific, NMDA receptor-mediated form of LTP in nociceptors is an evolutionarily-conserved process that is observed across vertebrate and

invertebrate phyla. Furthermore, there may be an interaction between NMDA receptor-mediated and endocannabinoid-mediated forms of synaptic plasticity in nociceptive synapses. Specifically, the NMDA receptor mediated processes may “suppress” endocannabinoid signaling. Such findings could be significant for understanding cellular mechanisms behind nociceptive sensitization and perhaps even contribute to chronic pain.

Disclosures: B.D. Burrell: None. **S. Yuan:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.06/G1

Topic: B.07. Synaptic Plasticity

Support: NIH Grant 1R21NS081786-01A1

Title: Mitochondria dependent metabolic programming drive hebbian long term potentiation

Authors: *H. ROLYAN
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Abstract: Long-term potentiation (LTP) and depression (LTD) are the mechanisms that neurons use to modulate their inherent synaptic plasticity and support storage and recovery of memories in the brain. The ability to potentiate a synapse over long term declines significantly in neurodegenerative disorders. In addition to deficiencies in synaptic plasticity, degenerating neurons display acute and chronic mitochondrial dysfunction, suggesting that dysregulated mitochondria play a role in synaptic dysfunction, in addition to their role in apoptosis. Our previous work has shown that the anti-apoptotic protein Bcl-xL not only prevents somatic cell death, but also potentiates long-term synaptic responses. Here, we show that Bcl-XL is responsible for dramatic changes in ATP levels in hippocampal neurons during LTP. Using fluorescence imaging of a FRET based ATP reporter (ATeam) in living hippocampal neurons, we find that LTP induction causes a sharp decrease in ATP levels followed by a persistent long term increase in ATP production. This suggests that after intense synaptic stimulation, neurons may become metabolically more efficient. The long-term increase in ATP levels of LTP-stimulated synapses is blocked by inhibition of Bcl-xL and by inhibition of ATP synthase with oligomycin. Bcl-xL inhibition also prevents the long-term increase in surface glutamate receptor insertion. In hippocampal slice recordings, inhibition of Bcl-xL greatly impairs early stage LTP and prevents late stage LTP. Our findings suggest that long term changes in mitochondrial efficiency brought by activity-dependent translocation of Bcl-xL to mitochondria are required for LTP and shed light on the role of mitochondrial metabolic programming and dynamics in acute induction and long-term maintenance of learning and memory processing. If such mitochondria-

dependent metabolic changes fail to occur, synaptic dysfunction and neurodegeneration may ensue.

Disclosures: H. Rolyan: None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.07/G2

Topic: B.07. Synaptic Plasticity

Support: Japan Society for the Promotion of Science KAKENHI Grant 16K08070
Japan Society for the Promotion of Science KAKENHI Grant 17J06198

Title: Spontaneously hypertensive rat exhibits increased synaptic plasticity

Authors: *S. TANIGUCHI[1], M. OGURA[1], K. TANABE[1], D. YAMANAKA[1], K. ITO[2]
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Abstract: Spontaneously Hypertensive Rat (SHR) is established from Wistar-Kyoto rat (WKY) at Kyoto University and it shows hypertension from 7 weeks old. As recent studies demonstrated that SHR exhibits impulsivity, inattention and hyperactivity, this rat is used as an animal model for attention deficit hyperactivity disorder (ADHD). However, the ability of learning and memory and synaptic plasticity of SHR are poorly understood, while ADHD patients show low cognitive performance. In this study, we recorded field EPSPs (fEPSPs) from Schaffer collateral - CA1 pyramidal cell synapses to elucidate how synaptic plasticity in the hippocampus of SHR differs from that in WKY by evaluating the long-term potentiation (LTP) which is a well-established form of synaptic plasticity. We used the 9-15-month-old male SHR and age-matched WKY. First, we checked the amount of food ingested and body weight to know the characteristics of feeding because ADHD patients sometimes have problems with eating. The body weight of SHR was significantly lighter than that of WKY although the food consumption of SHR was significantly more than that of WKY. Next, we made horizontal hippocampal slices (0.35 mm thickness) for fEPSP recordings, and induced LTP with high-frequency stimulation (100 Hz). The slope of fEPSPs of SHR was comparable with that of WKY. On the contrary, LTP in SHR was significantly larger than that in WKY (SHR:159±7%, WKY:141±3%). Moreover, Morris water maze test, which is commonly used for assessment for spatial learning and memory, revealed that the dwell time in the targeted area of SHR was significantly longer than that of WKY in the probe trial. These results indicate that SHR has increased synaptic plasticity and cognitive function, and that SHR is not always suitable for ADHD model. Although the underlying mechanism of increased synaptic plasticity of SHR is yet to be investigated, the use of SHR as ADHD model requires considerable attention.

Disclosures: S. Taniguchi: None. **M. Ogura:** None. **K. Tanabe:** None. **D. Yamanaka:** None. **K. Ito:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.08/G3

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R03 NS057215
NSF Grant IOS-1121054

Title: Presynaptic DCAF12 is part of a negative feedback loop regulating TGF-beta signaling at the *Drosophila* neuromuscular junction

Authors: *M. TORVUND, L. A. PATRON, K. E. ZINSMAIER
Univ. of Arizona, Tucson, AZ

Abstract: Synaptic growth at the *Drosophila* neuromuscular junction is regulated by a canonical retrograde Transforming Growth Factor-β (TGF-β)/Bone Morphogenetic Protein (BMP) signaling pathway. The ligand Glass bottom boat (Gbb) is secreted from the muscle and activates the presynaptic receptors Wishful thinking (Wit), Thickveins or Saxophone, which phosphorylate the transcription factor Mothers against decapentaplegic (Mad). Phosphorylated Mad (pMad) translocates to the nucleus and regulates transcription, promoting synaptic growth. In addition, non-canonical presynaptic Gbb secretion likely mediates synaptic transmission and plasticity but the precise mechanism remains unclear.
Previously, we showed that *Drosophila* DCAF12 is required for multiple independent synaptic functions at the *Drosophila* larval NMJ, including the upregulation of evoked neurotransmitter release, the downregulation of glutamate receptor subunits, and expression of synaptic homeostasis. Here, we show that presynaptic DCAF12 is a negative regulator of normal TGF-β signaling at larval NMJs. Deletion of DCAF12 increase synaptic levels of pMad, which can be rescued by pre- but not postsynaptic DCAF12 expression.
In addition, presynaptic expression of DCAF12 expression is tightly regulated by TGF-β signaling. RNAi-mediated knock-down (KD) of the TGF-β ligand Maverick (Mav) in glia cells and its putative receptor Punt in muscles strongly reduced DCAF12 levels in motor neurons but not muscles. Similarly, KD of postsynaptic Gbb in the muscle and presynaptic Wit and Mad in the motor neuron strongly reduced DCAF12 levels in motor neurons but not the muscle. Hence, this indicates that DCAF12 expression in motor neurons is upregulated by retrograde TGF-β signaling at the *Drosophila* NMJ. When considered in conjunction with the elevated pMad levels of DCAF12 deletions, we suggest that DCAF12 is part of a negative feedback loop regulating

TGF-β signaling at the synapse. Ongoing experiments aim to identify the mechanisms underlying presynaptic DCAF12's control of synaptic pMAD levels.

Disclosures: L.A. Patron: None. **K.E. Zinsmaier:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.09/G4

Topic: B.06. Synaptic Transmission

Support: NRSA T32 GM007270
NIH R01 NS085214

Title: Electrical synapses as modulators of behavior

Authors: *L. VOELKER[1,2], I. RABINOWITCH[1], J. BAI[1,2]
[1]Fred Hutch Cancer Res. Ctr., Seattle, WA; [2]Univ. of Washington, Seattle, WA

Abstract: An animal must constantly adjust its behavior in order to respond to changing environments and fluctuations in internal states. Animals achieve this by altering neural activity levels through changes known as neural plasticity. While much research has focused on understanding changes that occur at chemical synapses, it is becoming clear that electrical synapses also have important roles to play. Electrical synapses are specialized sites of cytoplasmic communication between neurons and are known to coordinate local electrical activity and to pass the small molecules associated with neural plasticity. In *C. elegans,* electrical synapses are known to coordinate inputs from multiple different sensory modalities to influence behavior. I have shown that an electrical synapse between the primary quinine sensory neuron ASH and its neighbor ASK is required for modulation of the response to quinine. The innexin INX-18 is necessary within ASK, while INX-19 is necessary in both ASK and ASH. INX-18 and INX-19 colocalize at points of contact between the ASK and ASH neurons. Quinine sensitivity is also modulated by mutations in the cGMP generating guanylyl cyclase GCY-27, which is expressed in ASK but not ASH. This suggests that the ASK/ASH electrical synapse may be modulating behavior via the passage of cGMP.

Disclosures: L. Voelker: None. **I. Rabinowitch:** None. **J. Bai:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.10/G5

Topic: B.06. Synaptic Transmission

Support: NIH Grant MH060605
NSF Grant 1608077

Title: Distinct mechanisms underlie electrical coupling resonance and membrane potential resonance

Authors: *X. LI[1,2], H. G. ROTSTEIN[1,2], F. NADIM[1,2]
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Abstract: Neurons and synapses can exhibit frequency selectivity that influences the dynamics of oscillatory circuits. Many neurons exhibit membrane potential resonance, a maximal subthreshold voltage amplitude response to oscillatory current input at a non-zero (resonant) input frequency. The influence of resonance on network oscillations has been hypothesized to play a role in the generation of brain rhythms.
In electrically coupled networks, an oscillatory current input to one neuron produces voltage oscillations in both pre- and post-junctional neurons. In recent studies, both the post-junctional neuronal response and the coupling coefficient (the ratio of post- and pre-junctional neuronal responses) have been shown to exhibit preferred frequency responses. However, the resonance properties of electrical coupling have been demonstrated in current clamp, but not in voltage clamp experiments. It is therefore unclear whether coupling resonance reflects the properties of the gap junctions, or it emerges from the interaction between the coupling current and membrane properties of the post-junctional neuron. In any case, the relationship between the resonance frequencies of the coupled neurons and that of the electrical coupling remains to be determined. We examined these questions by recording pairs of electrically coupled neurons that show resonance in the oscillatory pyloric network of the crab *C. borealis*. To examine whether the gap junction conductance itself shows resonance, we performed dual voltage clamp recordings and quantified the frequency preference of the coupled neurons, the gap junction conductance, and the post-junctional neuronal response. We found that all three components exhibit frequency selectivity, but with distinct preferred frequencies. Furthermore, the resonance properties of the electrical coupling were subject to neuromodulation. Our modeling results suggest that, resonance in the neurons alone is sufficient to produce resonance in the electrical coupling, but only at the same preferred frequency as the coupled neurons. A distinct resonance frequency therefore emerges from the gap junction conductance itself.

To study the functional effect of the resonance of the gap junction conductance, we examine its role in synchronizing neuronal activities and influencing network frequency in electrically coupled model neurons, and how neuromodulation affects these effects. Together, our findings demonstrate the mechanisms underlying electrical coupling resonance and highlight the interaction between preferred frequency responses at different levels of organization in shaping the network dynamics.

Disclosures: X. Li: None. **H.G. Rotstein:** None. **F. Nadim:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.11/G6

Topic: B.06. Synaptic Transmission

Support: Whitehall Foundation
NSF IOS-1557474

Title: Long-term potentiation of electrical synapses in the thalamic reticular nucleus

Authors: B. A. FRICKER, E. L. HECKMAN, P. CUNNINGHAM, *J. S. HAAS
Dept. of Biol. Sci., Lehigh Univ., Bethlehem, PA

Abstract: Synaptic plasticity is a fundamental process that is thought to underlie human learning and brain development. Activity-based bidirectional learning rules have been well characterized for neurotransmitter-based synapses. However, a bidirectional relationship between physiological activity and synaptic strength has not yet been established for mammalian electrical synapses. In the thalamic reticular nucleus (TRN), gap junctions comprising cx36 form electrical synapses that are the dominant source of communication between neurons. Like all thalamic cells, TRN neurons exhibit two primary modes of activity: bursting, which features a low-threshold calcium spike crowned with regular sodium spikes; and tonic spiking, where the only spikes are regular sodium-based. Our previous work has demonstrated that paired bursting in coupled TRN neurons induces LTD of electrical synapses between them (Haas et al., 2011) that arises from calcium-based mechanisms (Sevetson et al., 2017). Here we show, in whole-cell patch recordings of pairs in rodent brain slices of both genders age p11-p14, that low-frequency tonic spiking in one cell of a coupled pair, in the presence of T-type calcium channel antagonists, leads to LTP of the synapse. We further show that LTP does not result from paired tonic spiking, and depends on calcium dynamics within neurons. Our results lead us to propose a calcium-based bidirectional rule for activity-dependent plasticity of electrical synapses, where small influx of calcium in tonic spiking leads to LTP while larger influx during bursting leads to LTD.

We expect that similar bidirectional plasticity rules are a widely defined principle of electrical synapses in all brain regions.

Disclosures: B.A. Fricker: None. **E.L. Heckman:** None. **P. Cunningham:** None. **J.S. Haas:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.12/G7

Topic: B.07. Synaptic Plasticity

Support: NIH Grant DC012063
NIH Grant DC016314

Title: Na^+-dependent regulation of vesicular glutamate transport at an auditory synapse

Authors: *H. HUANG, D. LI, Y. ZHU
Dept. of Cell and Mol. Biol., Tulane Univ., New Orleans, LA

Abstract: Auditory information is encoded by action potentials phase-locked to sound frequencies at high rates. Accordingly, synaptic vesicles need to be recycled and refilled rapidly to support the high-frequency signaling. Accumulating studies have uncovered the mechanisms of vesicle fusion and recycling; however, the control of the contents of synaptic vesicles has received considerably less attention. We have recently found that a Na^+/H^+ exchanger expressed on synaptic vesicles promoted vesicle filling with glutamate. Using the calyx of Held, a giant glutamatergic synapse in the auditory brainstem that permits direct pre- and postsynaptic recordings and manipulation of the cytosolic environments, we showed that presynaptic cytosolic Na^+ facilitated glutamate loading into synaptic vesicles and increased excitatory postsynaptic currents. During high-frequency signaling, when large amounts of glutamate were released, Na^+ accumulated in terminals. The elevated Na^+ facilitated vesicular glutamate uptake and enhanced the postsynaptic excitatory currents, while did not affect the readily releasable pool or release probability. Moreover, high concentration of Na^+ was required to maintain reliable high-frequency transmission from presynaptic calyces of Held to postsynaptic MNTB neurons. Therefore, we established a new role of intracellular Na^+ as a feedback signal to modulate glutamate loading according to the level of vesicle release.

Disclosures: H. Huang: None. **D. Li:** None. **Y. Zhu:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.13/G8

Topic: B.07. Synaptic Plasticity

Support: PAPIIT IN-215816
CONACYT 389142

Title: BDNF induces *in vivo* long-term synaptic plasticity at hippocampal mossy fiber pathway in a transcription and translation-independent manner

Authors: *A. MARTÍNEZ, M. L. ESCOBAR
Univ. Nacional Autónoma De México, Ciudad DE Mexico, Mexico

Abstract: Brain-derived neurotrophic factor (BDNF) is an essential protein synthesis product that has emerged as one of the most potent molecular modulators of synaptic plasticity in the hippocampus. Our previous studies have demonstrated that acute intrahippocampal administration of BDNF induces a lasting potentiation of synaptic efficacy at the MF projection accompanied by a structural reorganization at the CA3 area within the stratum oriens region. In the present study we investigate whether the inhibition of translation and protein transcription interferes with the persistence of the MF functional and structural synaptic plasticity elicited by BDNF in adult rats *in vivo*. Our results show that the inhibition of either transcription or protein synthesis does not affect the expression of the functional and structural synaptic plasticity induced by the administration of BDNF. These findings suggest that BDNF is an essential plasticity related product, that is necessary and sufficient to induce and maintain functional and structural synaptic plasticity at MF-CA3 pathway.

Disclosures: A. Martínez: None. **M.L. Escobar:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.14/G9

Topic: B.07. Synaptic Plasticity

Support: MH070727 (to L.M.M.)

MH066198 (to E.T.K.)

Title: The role of synaptic BDNF-TrkB signaling in ketamine-mediated antidepressant effects

Authors: *P.-Y. LIN[1], E. T. KAVALALI[2], L. M. MONTEGGIA[2]
[1]Neurosci., UTSouthwestern Med. Ctr., Dallas, TX; [2]UT Southwestern Med. Ctr., Dallas, TX

Abstract: Brain-derived neurotrophic factor (BDNF) and its high affinity receptor, tropomyosin receptor kinase B (TrkB), regulate synaptic plasticity in the hippocampus. However, the precise site of BDNF release and location of TrkB receptors in ketamine-mediated synaptic plasticity are still unclear. To directly examine the role for BDNF-TrkB signaling in hippocampal subregions that mediates antidepressants response of ketamine, we used a viral mediated approach to genetically delete the genes in specific subregions of the hippocampus of adult mice. The mice were allowed to recover for 3 weeks following the stereotaxic surgeries before all electrophysiological and behavioral testing, a time point sufficient to induce gene recombination. The mice with deletion of BDNF or TrkB in specific hippocampal subregions were given an acute low dose of ketamine and then tested two hours later in either the novelty suppressed feeding or forced swim test. In separate experiments, we examined synaptic BDNF-TrkB signaling in ketamine mediated synaptic potentiation that correlates with antidepressant efficacy. In preliminary findings, we find that the regional specific deletion of BDNF impacts ketamine mediated antidepressant responses and synaptic plasticity. Further experiments are underway to determine how TrkB initiates its downstream signaling to engage in ketamine-mediated synaptic potentiation and antidepressant-like effects.

Disclosures: P. Lin: None. **E.T. Kavalali:** None. **L.M. Monteggia:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.15/G10

Topic: B.06. Synaptic Transmission

Title: Serotonergic modulation on the inhibitory synaptic transmission in the lateral amygdala

Authors: *R. YAMAMOTO, T. SUGAI, N. KATO
Dept. of Physiol., Kanazawa Med. Univ., Ishikawa, Japan

Abstract: Accumulating evidence has shown that serotonergic innervations unto the amygdaloid complex modulate the affective states and behaviors. It has been reported that serotonin suppresses the inhibitory transmission in the lateral amygdala. However the fine mechanisms of the modulation is still unclear. In this paper, we examined the fine effects of serotonin (5-HT) on inhibitory synaptic inputs to principal neurons in the rat lateral amygdala (LA) by whole-cell

recording. The $GABA_A$ component of inhibitory post synaptic currents (IPSCs) was isolated by the blockade of AMPA, NMDA and $GABA_B$receptors. Bath-application of 5-HT suppressed the amplitude of $GABA_A$ currents and increased the paired-pulse ratio. α-m-5-HT, a broad agonist for 5-HT receptors (including $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$ & $5\text{-}HT_2$ receptors) also suppressed the amplitude of $GABA_A$ current. The $GABA_A$ current induced by the direct application of GABA under the blockade of AMPA, NMDA and $GABA_B$ receptors were not altered by 5-HT. The $GABA_B$ component of IPSCs was induced by repetitive LA stimulation or puff-application of baclofen/GABA to the soma under blockade of AMPA, NMDA and $GABA_A$ receptors. The synaptically induced $GABA_B$ current was reduced by 5-HT. By contrast the $GABA_B$ currents elicited by a focal application of Baclofen or GABA were enhanced by 5-HT, indicating that the suppression of $GABA_B$ component are relatively preserved by the post-synaptic enhancement than the $GABA_A$ component. These results suggest that serotonin generally suppresses inhibitory transmission in LA, whereas under the situation that the GABA neurons exhibit high activities, the long-lasting $GABA_B$ dependent suppression would be relatively preserved and this will maintain the dynamism of inhibitory tone in the LA.

Disclosures: R. Yamamoto: None. **T. Sugai:** None. **N. Kato:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.16/G11

Topic: B.06. Synaptic Transmission

Support: R01MH104641

Title: Oxytocin enhances excitatory and inhibitory synaptic transmission in a layer specific manner in the rat medial prefrontal cortex

Authors: *S. M. SINGHAL, S. W. HARDEN, C. J. FRAZIER
Dept. of Pharmacodynamics, Col. of Pharm., Univ. Of Florida, Gainesville, FL

Abstract: Activation of oxytocin receptors (OTRs) in the rodent medial prefrontal cortex (mPFC) has previously been demonstrated to modulate maternal behavior, socio-sexual behavior, and stress/anxiety related behaviors, however relatively little is known about the cellular and synaptic mechanisms underlying such effects. Here we use in vitro electrophysiology to reveal novel effects of OTR activation in the rat mPFC that vary with respect to cortical layer. We report that the specific OTR agonist TGOT can directly depolarize a subset of OTR expressing layer 5 pyramidal neurons via a mechanism that appears to involve inhibition of barium sensitive G-protein coupled potassium permeant leak channels. We also report that OTR activation increases the frequency and amplitude of spontaneous excitatory

postsynaptic currents (sEPSCs) in the same layer 5 pyramidal cells, likely due to direct activation of local recurrent excitatory connections. By contrast, in layer 2 pyramidal neurons, activation of OTRs increases the frequency and amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) without affecting sEPSCs. Consistent with that observation, we find that a subset of layer 2 GABA interneurons (INs) are depolarized by TGOT, yet these interneurons display significant heterogeneity in their firing pattern in response to direct current injection. Overall, these studies are among the first to demonstrate layer specific effects of OTR activation in mammalian cortex, and should ultimately contribute to our developing understanding of how oxytocin modulates activity of cortical efferent projections to influence behavior.

Disclosures: S.M. Singhal: None. **S.W. Harden:** None. **C.J. Frazier:** None.

Poster

287. Synaptic Plasticity

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 287.17/G12

Topic: B.08. Intrinsic Membrane Properties

Support: NIMH (R01 MH099054)

Title: Effects of temperature during brain slice preparation on the physiology of cortical neurons

Authors: *J. C. MERCADO DEL VALLE[1], A. T. GULLEDGE[2]
[1]Dartmouth Col., Hanover, NH; [2]Mol. and Systems Biol., Geisel Sch. of Med., Hanover, NH

Abstract: Preparation of acute brain slices for *ex vivo* electrophysiology typically involves cooling the brain in "ice-cold" (< 4 °C) artificial cerebral spinal fluid (aCSF), which is thought to slow cellular metabolism and minimize excitotoxicity following ischemic insult during brain dissection. Yet previous studies have reported that preparation of hippocampal brain slices in ice-cold temperature results in a dramatic reduction of dendritic spines in CA1 neurons, with spine regrowth and proliferation occurring during post-slice re-warming of the tissue (Kirov et al., *Neuroscience* 127:69-80, 2004). A subsequent study (Bourne et al., *Neuropharmacology* 52:55-59, 2007) found that preparation at warmer temperatures (~25 °C) prevented the loss and proliferation of dendritic spines. We tested the impact of temperature during tissue preparation on the physiology and morphology of retrogradely-labeled corticopontine (CPn) neurons in layer 5 of the medial prefrontal cortex (PFC). Eighteen Adult mice were injected with fluorescent retrobeads (Lumafluor) in the pons to retrogradely label CPn neurons; acute brain slices were then prepared several days later using either ice-cold (< 4°C; n = 5 female and 4 male mice) or room temperature (25 °C; n = 5 female and 4 male mice) aCSF. After cutting, slices were incubated in 35 °C aCSF for an hour before electrophysiological recordings were made (also at 35 °C) from labeled CPn neurons. Qualitatively, we could not distinguish any obvious

differences in the health or number of targetable neurons (labeled or unlabeled) in slices prepared in iced or room-temperature aCSF. Further, we found no significant differences in resting membrane potentials ($p = 0.23$), input resistances ($p = 0.35$), or HCN-channel-mediated responses ($p = 0.60$) in the two experimental conditions ($n = 30$ for each). Action potential kinetics were also similar in most respects, including spike threshold ($p = 0.76$), amplitude ($p = 0.25$), and rise-time ($p = 0.09$). However, action potential half-widths were slightly longer (at 568 ± 13 vs 510 ± 15 μs; $p = 0.005$) in CPn neurons in slices prepared at room temperature. No sex-dependent differences were observed in either condition. These results confirm that healthy slices can be obtained in the absence of significant brain cooling (see Huang & Uuisaari, *Frontiers in Cellular Neuroscience* 7:48, 2013). We are currently testing the impact of temperature during slicing on spine morphology.

Disclosures: J.C. Mercado Del Valle: None. **A.T. Gulledge:** None.

Poster

288. Synaptic Protein Dynamics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 288.01/H1

Topic: B.07. Synaptic Plasticity

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Title: Identification of long-lived synaptic proteins by proteomic analysis of synaptosome protein turnover

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Abstract: Memory formation is believed to result from changes in synapse strength and structure. While memories may persist for the lifetime of an organism, the proteins and lipids that make up synapses undergo constant turnover with lifetimes from minutes to days. The molecular basis for memory maintenance may rely on a subset of long-lived proteins (LLPs). While it is known that LLPs exist, whether such proteins are present at synapses is unknown. We

performed an unbiased screen using metabolic pulse-chase labeling *in vivo* in mice and *in vitro* in cultured neurons combined with quantitative proteomics. We identified synaptic LLPs with half-lives of several months or longer. Proteins in synaptic fractions generally exhibited longer lifetimes than proteins in cytosolic fractions. Protein turnover was sensitive to pharmacological manipulations of activity in neuronal cultures or in mice exposed to an enriched environment. We show that synapses contain LLPs that may underlie stable long lasting changes in synaptic structure and function.

Disclosures: S. Heo: None. **G.H. Diering:** None. **C. Na:** None. **R.S. Nirujogi:** None. **J. Bachman:** None. **A. Pandey:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 288.02/H2

Topic: B.07. Synaptic Plasticity

Support: NIH Grant P50MH100024
NIH Grant RO1NS036715

Title: Cortex-wide synaptic AMPA receptor plasticity during motor learning

Authors: *R. H. ROTH[1,2], R. H. CUDMORE[1,2], H. L. TAN[1,2], Y. ZHANG[3,4], R. L. HUGANIR[1,2]
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Abstract: Modulation of synaptic strength through trafficking of AMPA receptors (AMPARs) is a fundamental mechanism underlying synaptic plasticity and has been shown to be an important process in learning and memory. However, the in vivo dynamics of AMPAR trafficking into and out of dendritic spines, and how this correlates with learning, have not been defined. Here, we train mice on a forelimb reaching task and use in vivo two-photon microscopy to visualize AMPARs in the mouse cortex over the course of learning. We use in utero electroporation to express the AMPAR subunit GluA1 tagged with Super Ecliptic pHluorin (SEP, a pH-sensitive GFP) in layer 5 neurons of the motor cortex and visualize their apical dendrites after each training session. We found that, following daily motor training, individual spines of layer 5 neurons show vastly different modulation of their AMPAR content. On average, motor learning leads to an increase in surface GluA1 levels at dendritic spines in the motor cortex compared to untrained control mice. This synaptic potentiation is driven by a subset of spines that are spatially clustered. Additionally, we also observed increases of spine GluA1 levels in the

somatosensory and visual cortex of mice learning the motor task. Synaptic potentiation in the visual cortex is dependent on visual input during motor training and follows a different time course than in the motor cortex. These results indicate that motor learning induces synaptic potentiation by increasing the net trafficking of AMPARs into spines not only in the motor cortex but also in sensory brain regions previously not thought to be involved in this behavioral task.

Disclosures: R.H. Roth: None. **R.H. Cudmore:** None. **H.L. Tan:** None. **Y. Zhang:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 288.03/H3

Topic: B.07. Synaptic Plasticity

Support: P50MH100024

Title: Imaging endogenous AMPA receptor dynamics *in vitro* and *in vivo*

Authors: *A. R. GRAVES[1,2], R. H. ROTH[1,2], D. J. TWARD[3,2,4], M. I. MILLER[3,2,4], J. T. VOGELSTEIN[3,2], R. L. HUGANIR[1,2]
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Abstract: The synapse is the fundamental unit of the nervous system, enabling communication between brain cells and providing a substrate for experience-dependent plasticity to drive adaptive behaviors. As AMPA receptors (AMPARs) mediate a majority of fast synaptic transmission throughout the brain, dynamic regulation of AMPARs is though to underlie higher brain functions such as learning and memory. Indeed, roles for AMPARs in long-term potentiation and depression have been elucidated in vitro, and activity-dependent changes in AMPAR expression and function have been reported following learning in vivo. Despite the clear significance of synaptic transmission, a large-scale analysis of how AMPARs across the brain are distributed and change during learning has not been performed. To address this question, we have developed several knockin mouse lines with Super Ecliptic pHluorin-tagged AMPAR subunits (GluA1-4), enabling two-photon imaging of the distribution and dynamics of endogenous AMPARs in behaving mice. By developing methods to image millions of synapses over many weeks, we are able to track changes in synaptic strength with molecular resolution during learning, providing an unprecedented view of how AMPARs dynamics may shape learning and memory.

Disclosures: A.R. Graves: None. **R.H. Roth:** None. **D.J. Tward:** None. **M.I. Miller:** None. **J.T. Vogelstein:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

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Program #/Poster #: 288.04/H4

Topic: B.07. Synaptic Plasticity

Support: NIH Grant RO1NS036715

Title: ICA69-mediated AMPA receptor trafficking regulates activity-dependent synaptic strengthening and learning and memory

Authors: *S.-L. CHIU[1,2], R. L. HUGANIR[1,2]
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Abstract: Long-term potentiation (LTP) has been considered to be one of the major cellular mechanisms for learning and memory. Activity-dependent increase in the surface delivery of AMPA receptors (AMPARs) is important for enhanced synaptic efficacy during LTP. Two major intracellular trafficking pathways regulate surface delivery of AMPARs and synaptic transmission: 1) the de novo secretory pathway in which newly synthesized AMPARs are delivered onto the membrane; and 2) the recycling pathway in which endocytosed AMPARs can return to the membrane. This study aims to study the contribution of AMPAR secretory trafficking in synaptic plasticity and animal behavior through studying a Golgi-localized protein, ICA69. ICA69 is part of the AMPAR protein complex through its interaction with PICK1, which binds to GluA2 or 3 subunits of AMPARs directly. We found that ICA69 determines the subcellular localization of PICK1 in hippocampal neurons, which in turn may regulate AMPAR distribution and function. To test whether ICA69 regulates basal synaptic AMPAR localization and composition, we isolated postsynaptic density (PSD) protein fractions from hippocampi of *Ica1* knockout mice and their wild-type littermates. GluA1, 2 and 3 protein levels in the PSD fractions are comparable between genotypes suggesting that ICA69 does not regulate AMPAR trafficking at basal states. To test whether ICA69 regulates activity-dependent AMPAR trafficking, we examined variety forms of plasticity at the hippocampal Schaffer collateral to CA1 Synapses. We found that *Ica1* knockout mice showed normal NMDAR- or mGluR-dependent LTD. However, *Ica1* knockout mice exhibited impaired NMDAR-dependent LTP and behavioral deficit in inhibitory avoidance learning. In summary, our results show a specific role of ICA69-mediated secretory trafficking of AMPARs in LTP, but not LTD, and associative learning and memory.

Disclosures: S. Chiu: None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

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Program #/Poster #: 288.05/H5

Topic: B.07. Synaptic Plasticity

Support: NIH Grant P50AG005146
NIH Grant RO1NS036715

Title: Phosphorylation of GluA2 tyrosine 876 is necessary for homeostatic plasticity

Authors: *A. J. YONG[1,2], A. M. BYGRAVE[1,2], H. L. TAN[1,2], R. L. HUGANIR[1,2]
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Abstract: Homeostatic plasticity is a mechanism whereby neurons alter their synaptic strength to maintain firing rates in response to changes in network activity. At excitatory synapses, the dynamic control of AMPA receptor (AMPAR) expression at the postsynaptic surface is crucial for homeostatic scaling. Surface AMPARs increase with scaling up and decrease with scaling down, and the regulation and trafficking of the AMPAR subunit GluA2 is essential for this process. While tyrosine phosphorylation on the C-terminal domain of GluA2 is known to change bi-directionally during homeostatic scaling, the exact tyrosine residue and whether these changes are necessary for AMPAR trafficking during homeostatic scaling is unknown. Here, we show that phosphorylation of GluA2 at the tyrosine residue 876 (Y876) is necessary for homeostatic scaling-up, both in vivo and in vitro. We found that bi-directional changes in phosphorylation of GluA2 Y876 occurs during the homeostatic scaling process. To test the necessity of GluA2 Y876 phosphorylation, we generated phospho-deficient Y876F knockin mice, which have normal synaptic composition and function. Strikingly, cultured neurons derived from these mice show deficient scaling-up induced by TTX and Y876F knockin mice lack scaling-up in the visual cortex after visual deprivation in vivo. Thus, our study suggests that AMPAR trafficking during homeostatic scaling up can be gated by a single phosphorylation site on the GluA2 subunit.

Disclosures: A.J. Yong: None. **A.M. Bygrave:** None. **H.L. Tan:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01NS036715
NIH Grant P50MH100024

Title: Distance-dependent AMPA receptor dynamics following visual deprivation *in vivo*

Authors: *H. L. TAN[1,2], R. H. ROTH[1,2], A. R. GRAVES[1,2], R. H. CUDMORE[1,2], R. L. HUGANIR[1,2]
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Abstract: Modulation of surface AMPA receptor (AMPAR) expression is a key process implicated in synaptic plasticity and has been shown to play critical roles in higher brain function such as learning and memory. The trafficking of AMPARs into and out of synapses is highly dynamic and regulated by subunit-specific AMPAR binding proteins as well as by various post-translational modifications. In the past, many studies have revealed the molecular mechanisms underlying AMPAR trafficking in vitro. However, an in vivo approach examining intact brains of living animals is necessary to fully understand the role of AMPAR trafficking in synaptic plasticity and brain function. Here, we employed in utero electroporation in conjunction with in vivo two-photon imaging to visualize Super Ecliptic pHluorin (SEP, a pH-sensitive form of GFP)-tagged GluA1 in synapses of layer 2/3 neurons in the visual cortex of living mice. We observed that individual spine GluA1 expression and size were very dynamic over days even under basal states in adult primary visual cortex (V1) neurons and that the changes were negatively correlated with their initial GluA1 levels. Moreover, synaptic GluA1 expression in layer 2/3 V1 neurons was significantly increased at day 7 after visual deprivation. These changes were distance-dependent: deep spines increased faster and more than superficial spines. Further, the deprivation-induced increase of synaptic GluA1 was specific to layer 2/3 neurons, as layer 5 neurons did not show increases in synaptic GluA1 after deprivation. Collectively, our study demonstrates that synaptic AMPAR expression in adult mice is very dynamic under basal conditions and is highly regulated after visual deprivation.

Disclosures: H.L. Tan: None. **R.H. Roth:** None. **A.R. Graves:** None. **R.H. Cudmore:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

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Program #/Poster #: 288.07/H7

Topic: B.07. Synaptic Plasticity

Support: NIH Grant RO1NS036715

Title: Mitochondrial ROS regulate structural and functional synaptic plasticity

Authors: *H. FANG[1,2], B. LIU[1,2], P.-H. WU[3,4], D. WIRTZ[3,4], R. L. HUGANIR[1,2]
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Abstract: In the past two decades more and more evidence has emerged showing that mitochondria are involved in neuronal physiology and neurodegenerative diseases. Besides being the powerhouse of the cell, mitochondria are also involved in many other cellular processes, such as apoptosis, protein degradation, calcium homeostasis, and reactive oxygen species (ROS) generation. Mitochondrial ROS represent the majority of cellular ROS and are generated during oxidative phosphorylation. During neuronal activity, mitochondrial ROS have been observed but their functional significance remain unclear. Here, we assessed the role of mitochondrial ROS in long-term potentiation (LTP). We observed mitochondrial flashes (mitoflashes) in neurons, as a cellular marker of mitochondrial ROS generation, and found that mitoflash frequency transiently increased during chemical LTP (cLTP). We also found that in neurons with knockdown of mitochondrial superoxide dismutase (SOD2) leading to increased ROS level, LTP was enhanced, with larger dendritic spines and synaptic AMPA receptors (AMPARs) increase. Phosphorylation of AMPA receptors plays a critical role in their proper synaptic trafficking during synaptic plasticity. We found that ROS scavenger treatment decreased GluA1 phosphorylation at Serine 831 and 845 sites, which was mediated by decreased activity of calcium/calmodulin-dependent protein kinase type II (CaMKII) and protein kinase A (PKA). These results demonstrate that mitochondrial ROS regulate structural and functional synaptic plasticity in neurons potentially through the regulation of CaMKII and PKA activity.

Disclosures: H. Fang: None. **B. Liu:** None. **P. Wu:** None. **D. Wirtz:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

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Program #/Poster #: 288.08/H8

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01MH112151
NIH Grant R01NS036715
NIH Grant P50MH100024

Title: Distinct translocation patterns and biochemical characteristics of SynGAP isoform and gene mutations in diseases during synaptic plasticity

Authors: *Y. ARAKI[1,2], T. R. GAMACHE[1,2], R. L. HUGANIR[1,2]
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Abstract: SynGAP is a Ras GTPase-activating protein (GAP), and is one of the most abundantly expressed proteins in excitatory synapses, along with PSD-95. We previously discovered that SynGAP is rapidly dispersed from the postsynaptic density (PSD) upon LTP, leading to activation of Ras signaling, and resulting in downstream processes such as AMPA receptor insertion and spine enlargement. SynGAP and PSD-95 form highly concentrated liquid-like droplets by liquid-liquid phase separation when combined in vitro. Recent genetic studies have identified a myriad of missense and nonsense mutations of SynGAP linked to human neurocognitive disorders, including intellectual disability (ID), autism spectrum disorder (ASD), and Schizophrenia (SCZ). We have characterized some of these mutations and found that the mutations found in each disease group differentially affect biochemical property and synaptic plasticity. SynGAP has 4 different C-terminal isoforms resulting from alternative splicing: alpha1, alpha2, beta, and gamma. We discovered that SynGAP translocation and function are differentially regulated in an isoform-specific manner during synaptic plasticity. Additionally, the different SynGAP isoforms exhibit distinct biochemical characteristics, including those related to their interaction and phase transition behavior with PSD-95. Coordinated function of each specific SynGAP isoform over the course of development may support proper formation of synapses.

Disclosures: Y. Araki: None. **T.R. Gamache:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

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Program #/Poster #: 288.09/H9

Topic: B.07. Synaptic Plasticity

Support: RO1MH11516

Title: Platform for longitudinal *in vivo* two-photon imaging with sub-micron precision

Authors: *I. HONG[1,2], R. H. ROTH[1,2], J. B. ISSA[3], R. L. HUGANIR[1,2]
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Abstract: Two-photon in vivo brain imaging has revealed the internal structure and dynamics of neurons in their native environment. Tracking the structural dynamics and activity of neurons and their subcellular compartments quantitatively over days and weeks is crucial for the study of higher order brain function such as synaptic plasticity and learning and memory. However, accurate repeated imaging in vivo has proven difficult, due to non-isotropic resolution, scar tissue growth, inflammation and other obstacles that hinder the reliable longitudinal microscopic tracking of a given field of view. The axially-elongated point spread function of two-photon imaging casts a ‘smear’ depending on the imaging direction and prevents accurate quantitative comparison of images acquired from different axial directions. To resolve this technical challenge, we have developed multi-axis rotational head-fixation stage hardware and 3D-registration software to allow accurate longitudinal imaging of a given focal plane with submicron precision over days and weeks. Our head fixation stage incorporates two goniometers through which the roll and pitch of the specimen can be adjusted to match original imaging conditions. The design is highly modular, allowing anesthetized imaging on a heated pad or awake imaging with a circular treadmill. The accompanying software suite, StackGPS, uses 3D registration to guide rapid position and angle adjustment in 3D. Usage examples demonstrate that our protocol ensures sub-micron, <1° longitudinal tracking of a given field of view, which allows the observation of neurons, dendrites and spines across multiple days. The StackGPS software suite also allows post-hoc 3D registration of in vivo volume images, which can vastly accelerate subsequent analysis for spine dynamics and calcium imaging. Collectively, this platform expands the temporal window and accuracy of chronic brain imaging to allow the tracking of subcellular phenomena in normal brain function as well as dysfunction.

Disclosures: I. Hong: None. **R.H. Roth:** None. **J.B. Issa:** None. **R.L. Huganir:** None.

Poster

288. Synaptic Protein Dynamics

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Topic: B.07. Synaptic Plasticity

Support: Brain Initiative Grant R01 MH111516 (to R.L.H. and J.Z.)
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NIH Grant R01 DK073368 (to J.Z.)
NIH Grant R01 GM111665 (to J.Z.)

Title: A suite of single-fluorophore biosensors for sensitive and multiplexed detection of signaling activities

Authors: *S. MEHTA[1], R. H. ROTH[2,3], B. LIU[2,3], R. L. HUGANIR[2,3], J. ZHANG[1,4]
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Abstract: Intracellular signaling pathways in the brain play a central role in regulating neuronal activity and synaptic plasticity. Unraveling the dynamic molecular interplay behind these complex physiological processes requires the ability to both detect changes in biochemical states in response to physiological signals and track multiple signaling activities simultaneously. Fluorescent protein-based biosensors have enabled the real-time monitoring of dynamic signaling processes within the native context of living cells, yet most commonly used biosensors exhibit poor sensitivity (e.g., dynamic range) and are limited to imaging single signaling activities at a time. Here, we address this challenge by developing a new class of excitation ratiometric kinase activity biosensors that offer the highest reported dynamic range and enable the detection of small changes in signaling activity that could not be reliably detected previously, as well as a suite of single-fluorophore biosensors that enable the simultaneous tracking of as many as six distinct signaling activities in single living cells. These new tools will allow the imaging of complex multiple signaling pathways occurring during synaptic transmission and plasticity in neurons in vitro and in vivo.

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Poster

288. Synaptic Protein Dynamics

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant P50MH100024

Title: Novel transgenic mouse line for visualizing endogenous AMPA receptor trafficking *in vitro* and *in vivo*

Authors: *Q. ZHU[1,2], A. M. BYGRAVE[1,3], H. L. TAN[1,2], R. H. ROTH[1,2], A. R. GRAVES[1,2], R. C. JOHNSON[1,2], R. L. HUGANIR[1,2]
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Abstract: Regulation of AMPA receptor (AMPAR) trafficking is a fundamental mechanism underlying synaptic plasticity and has been shown to be a crucial process for learning and memory. AMPAR trafficking is a highly dynamic process involving exocytosis, endocytosis, and lateral diffusion along the plasma membrane. So far, many studies have investigated these processes through overexpression of exogenous fluorescently tagged AMPARs in vitro and in vivo. However, the dynamics and regulation of AMPAR trafficking are still a mystery, partly due to the lack of tools to visualize endogenous AMPARs in vivo. Here, we report the generation of a knockin mouse line in which Super Ecliptic pHluorin (SEP, a pH-sensitive GFP) is tagged to the extracellular domain of the endogenous AMPAR subunit GluA1. This mouse line enables dynamic imaging of endogenous surface GluA1 trafficking in vitro and in vivo. We have characterized these SEP-GluA1 mice using immunohistochemistry, biochemistry, electrophysiology, two-photon imaging, and behavioral examinations, and found that these knockin mice showed regular synaptic targeting of GluA1, normal basal transmission and synaptic plasticity, as well as intact behaviors known to require GluA1. Thus, this SEP-GluA1 knockin mouse line serves as a reliable tool to visualize synaptic plasticity with molecular resolution in behaving animals.

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Poster

288. Synaptic Protein Dynamics

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Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

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Title: Depalmitoylation of GluA1 by CPT1C enhances AMPAR trafficking

Authors: *E. GRATACÒS-BATLLE[1,2], N. SÁNCHEZ-FERNÁNDEZ[1], M. OLIVELLA[3], F. MIGUEZ-CABELLO[1], X. GASULL[1,2,4], D. SOTO[1,2,4]
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Abstract: In the central nervous system, the trafficking of AMPARs is finely regulated by a large number of intracellular proteins binding to AMPAR subunits. Amongst these interacting proteins it has been recently described that carnitine palmitoyltransferase 1C (CPT1C) binding to GluA1 subunit of AMPARs enhances surface expression of these glutamate receptors in such a way that synaptic AMPAR content in CPT1C deficient animals is diminished. A possible role of CPT1C – together with other proteins as FRRS1L – in priming AMPARs at endoplasmic reticulum has been proposed. This priming would prepare AMPARs to bind to *bona fide* auxiliary subunits (as TARPs and Cornichons) for their delivery to the plasma membrane. Despite a positive role of CPT1C on AMPAR surface expression, the molecular mechanisms of such modulation remain obscure. In this work, we explore a putative depalmitoylating role of CPT1C on GluA1 based on evidences obtained in an *in silico* analysis. We identified a group of three aminoacids in CPT1C (Ser 252, His 470 and Asp 474), which are homologous to a catalytic triad with palmitoyl thioesterase (PTE) activity in palmitoyl thioesterase APT1. The impairment of the CPT1C putative PTE activity with Palmostatin B – a well described inhibitor of the depalmitoylating enzyme APT1 – precludes AMPAR trafficking modulation effect of CPT1C. Indeed, the mutation of these putative catalytic residues in CPT1C avoids the CPT1C-dependent trafficking modulation of AMPARs in both cell lines and hippocampal neurons. Moreover, we found that merely the histidine residue (His 470) of CPT1C is crucial for the increase in GluA1 surface expression. Finally, we show that CPT1C effect appears to be specific for CPT1C isoform (not shared by CPT1A) and it occurs exclusively at the endoplasmic reticulum level. In

summary, this work reveals the mechanism by which CPT1C modulates AMPAR trafficking and it adds a pinch of additional information to the complex mechanisms that are involved in traffic regulation of AMPARs.

Disclosures: E. Gratacòs-Batlle: None. **N. Sánchez-Fernández:** None. **M. Olivella:** None. **F. Miguez-Cabello:** None. **X. Gasull:** None. **D. Soto:** None.

Poster

288. Synaptic Protein Dynamics

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Topic: B.07. Synaptic Plasticity

Support: BBSRC grant BB/P000479/1
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ANR-10INBS-04-0

Title: Neuronal receptors display cytoskeleton-independent directed motion on the plasma membrane

Authors: *L. C. ANDREAE[1], R. D. TAYLOR[1], M. HEINE[2], N. J. EMPTAGE[3]
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Abstract: Neurons need to ensure proteins can be rapidly localized to specific membrane destinations in response to stimuli. The current models for transmembrane protein movement describe either active intracellular trafficking by molecular motor driven vesicles along the cell cytoskeleton, or passive lateral diffusion within the plasma membrane. We developed a pH-sensitive quantum dot probe which exhibits virtually undetectable fluorescence when localized to intracellular transport vesicles but allows single particle tracking on the surface of membranes. Using this probe in dissociated rat hippocampal neurons, we tracked the surface movement and behavior in dendrites of the transmembrane tyrosine kinase receptor, EphB2, a well-known neuronal protein with important roles in synapse formation and plasticity. We applied a ‘time resolved’ sliding window method (based on mean squared displacement, custom written in MATLAB) to analyse the membrane surface trajectories and identified two patterns of movement among the diffusing population of EphB2Rs: diffusive and super-diffusive, as well as, surprisingly, a subpopulation of neuronal EphB2 receptors that exhibit directed motion within the plasma membrane itself. Disruption of the actin cytoskeleton with latrunculin A caused greater movement in the super-diffusive group with no effect on the more freely diffusing receptors, consistent with the concept of an actin ‘fence’ forming part of the membrane skeleton. However, neither actin disruption, nor depolymerization or stabilization of the microtubule

network (with different doses of nocadazole), altered the directed motion, indicating that this was occurring independently of the cytoskeletal network. Instead, directed motion was modulated by the cholesterol composition of the cell membrane. Comparison of trajectories with a postsynaptic marker indicated that while EphB2Rs show diffusive behaviour at synapses, directed motion occurs only outside synapses. Furthermore, increasing neural activity by electrical field stimulation resulted in receptors spending longer periods of time in directed motion mode. We propose that this directed motion mode could provide an alternative energy efficient method of protein delivery to specialized locations within the plasma membrane.

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Poster

288. Synaptic Protein Dynamics

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Program #/Poster #: 288.14/H14

Topic: I.06. Computation, Modeling, and Simulation

Support: AFOSR MURI FA9550-18-1-0051

Title: Spatial and geometrical aspects of cAMP dynamics in dendritic spines

Authors: *D. OHADI[1], D. L. SCHMITT[1], T. M. BARTOL[2], T. J. SEJNOWSKI[2,1], J. ZHANG[1], P. RANGAMANI[1]
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Abstract: Dendritic spines are the primary excitatory synaptic sites that have been associated with morphological changes observed during long-term potentiation. Despite the central role of some molecular events such as cAMP-PKA signaling pathway in the regulation of the spine formation and its morphological modifications and ultimately, learning and memory, little is known about the geometrical and spatial parameters affecting the cAMP-PKA dynamics in dendritic spines. There is a strong evidence that for cyclic adenosine monophosphate (cAMP) to activate its main effector, protein kinase A (PKA)- an enzyme that can phosphorylate multiple targets in the cell- a distinctive subcellular concentration of cAMP is required. Compartmentalization of different signaling components of cAMP-PKA pathway in subcellular domains may be responsible for activating PKA with significantly different cAMP concentration than in the bulk cytosol. cAMP signaling domains may form as a result of A-kinase anchoring proteins (AKAPs) providing a distinctive subcellular response by anchoring to e.g. PKA to bring it together with key modulators of the signaling system such as adenylate cyclase (AC) or phosphodiesterases (PDEs). In this study, through a reaction-diffusion framework, we developed a computational spatiotemporal model to shed light on the contributions of various compartmentalization mechanisms that control the cAMP local concentrations in dendritic

spines. Using this model, we investigate how geometrical aspects such as shape and size of the spine, or diffusional barriers such as spine apparatus and spine neck can affect the cAMP dynamics. We also study the role of functional barriers such as phosphodiesterases in creating cAMP compartmentalization. Our computational model has important implications for the understanding of cAMP regulations in dendritic spines.

Disclosures: D. Ohadi: None. **D.L. Schmitt:** None. **T.M. Bartol:** None. **T.J. Sejnowski:** None. **J. Zhang:** None. **P. Rangamani:** None.

Poster

288. Synaptic Protein Dynamics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 288.15/H15

Topic: B.06. Synaptic Transmission

Support: CSU/CVMBS Startup
R01 NS035812

Title: Heteromeric JIP proteins regulate synaptic transport of AMPARs

Authors: *F. J. HOERNDLI[1], P. J. BROCKIE[3], J. E. MELLEM, JR[3], R. WANG[4], D. MADSEN[3], B. E. PULFORD[2], A. V. MARICQ[3], R. DOSER[2]
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Abstract: Regulated long distance transport of AMPA-type ionotropic glutamate receptors (AMPARs) is emerging as an important cellular mechanism used to modulate synaptic strength. However, the precise mechanisms for loading and unloading AMPAR cargo from molecular motors at synapses *in vivo*, in intact neuronal circuits, are largely unknown. Using *in vivo* confocal imaging of long distance synaptic AMPAR transport in *C. elegans*, we have previously described a new role for CaMKII in activity-dependent loading of AMPAR vesicles onto Kinesin-1 motors. Here, we show that the scaffold proteins UNC-16/JIP3a and JIP-1/JIP1 are required for the motor-mediated delivery and removal of synaptic AMPARs (GLR-1/2) in *C. elegans*.
Mutations in the scaffold proteins UNC-16 and JIP-1 severely disrupted AMPAR transport, synaptic AMPARs levels as well as glutamate-gated currents. The mammalian homolog of UNC-16 (JIP3a) rescued the defective AMPAR transport in transgenic *C. elegans* mutants, suggesting that the signaling pathways are conserved.
Using *in vivo* simultaneous dual wavelength spinning disk microscopy, we show that UNC-16 and JIP-1 co-transport with GLR-1 and Kinesin-1 motors. Co-transport analyses in loss of

function mutants of JIPs and CaMKII, indicate that JIPs depend on each other and CaMKII function to form a transport complex. To test the hypothesis that JIPs are required for constitutive regulation of AMPAR transport to synapses we will use heatshock-induced gene expression of UNC-16 or JIP-1. To test the hypothesis that these JIPs are essential scaffolds for activity-dependent loading of AMPAR onto Kinesin-1, we will use *in vivo* chromophore-assisted-light-inactivation (CALI) of JIPs and CaMKII at the neuronal soma or at synapses. Together our results and experimental design identify an essential new role for UNC-16/JIP3a and JIP-1/JIP1 in the regulation of long-distance synaptic transport of AMPARs. Since these scaffolds were originally identified as MAPK and JNK signaling scaffolding proteins, our results suggest that both MAPK and JNK, binding to these scaffolds might play important roles in synaptic AMPAR transport dynamics.

Disclosures: F.J. Hoerndli: None. **P.J. Brockie:** None. **J.E. Mellem:** None. **R. Wang:** None. **D. Madsen:** None. **B.E. Pulford:** None. **A.V. Maricq:** None. **R. Doser:** None.

Poster

288. Synaptic Protein Dynamics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 288.16/H16

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Role of sorting nexin-1 in metabotropic glutamate receptor (mGluR's) trafficking

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Abstract: Group I metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors, function as modulators of neuronal physiology and they have also been implicated in various neuropsychiatric disorders. These Group I mGluRs are present at the perisynaptic region of postsynapse and are positively coupled with G-protein. Our work is directed towards understanding the regulation of Group I mGluRs in the central nervous system. The accurate physiological response depends on their specific localization in the neuronal membrane at a specific time. Trafficking is the process which regulates the spatiotemporal localization of these receptors at the synapse, hence playing a crucial role in regulating their function. Trafficking also regulates the activity like desensitization, resensitization, and downregulation of various GPCRs. Despite this obvious significance, we know very little about the cellular machineries that control the trafficking of group I mGluRs in the central nervous system. Sorting nexin 1 (SNX1) has been shown to regulate the endosomal sorting of few cell surface receptors either to lysosomes where they are downregulated or back to the cell surface. It's been reported that mGluR1 gets endocytosed upon ligand stimulation and it follows slow recycling route via recycling endosome. In the current study, we illustrate how sorting nexin 1 (Snx1) regulates the trafficking of Group I

mGluRs in primary hippocampal neurons using “molecular replacement” approach. We have shown that the knockdown of endogenous SNX1 resolutely affects the receptor trafficking. Our data suggest that both, N-terminal and C-terminal region of SNX1 play critical role in the normal trafficking of the receptor. Thus, these studies reveal a mechanistic role of SNX1 in the trafficking of group I mGluRs.
Our study also reveals the role of Snx1 in mGluR mediated AMPAR trafficking, the cellular correlate for the mGluR-dependent synaptic plasticity.

Disclosures: R. Gulia: None. **S. Bhattacharyya:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.01/H17

Topic: B.10. Epilepsy

Support: European Union's Seventh Framework Programme (FP7) under grant agreement 602102 (EPITARGET)

Title: Evaluation of the antiepileptogenic efficacy of promising multitargeted drug combinations

Authors: *L. WELZEL[1,2], F. TWELE[1], P. KLEIN[3], W. LÖSCHER[1,2]
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Abstract: Symptomatic epilepsies, including temporal lobe epilepsy (TLE), often result from acute brain injuries, such as status epilepticus (SE), traumatic brain injury, ischemic stroke, tumors or infections. Epilepsy prevention in patients at risk remains a major unmet clinical need. The time interval between the initiating brain insult and the onset of spontaneous recurrent seizures (SRS) is defined as the latent period, which would be an ideal time window for treatment preventing or modifying the epileptogenic process. The development of multitargeted antiepileptogenic drug combinations (“network pharmacology”), using clinically approved drugs for rapid translation into clinical trials, is an approach that targets the multiple mechanisms involved in epileptogenesis. We selected drugs with promising mechanisms or already known disease-modifying effects (*Klein and Tyrlikova (2017), Epilepsy Behav.,72: 188-194*) to be combined as the following rationally chosen drug combinations: A) levetiracetam + atorvastatin + ceftriaxone, B) levetiracetam + gabapentin + deferoxamine + fingolimod, C) levetiracetam + alpha-tocopherol. Using an algorithm based on the drug development phases in humans (*Klee et al. (2015), Epilepsy Res., 118: 34-48*), the drug combinations were tested for tolerability in naïve male NMRI mice and in post-SE mice before being tested for antiepileptogenic efficacy in the

intrahippocampal kainate mouse model. We induced a status epilepticus (SE) in groups of male NMRI-mice (age 8 weeks), which were treated with the drug combination 3 times daily over 5 days. Continuous (24/7) EEG- and video monitoring was performed over 7 subsequent days at 4 and 12 weeks post-SE. Blinded analysis of electrographic and electroclinical seizures and blinded histological analysis of neurodegeneration occurring in the hippocampus were performed. Contrary to expected, treatment with the drug combination levetiracetam + atorvastatin + ceftriaxone did not lead to a reduction in frequency or severity of electroclinical seizures 4 or 12 weeks post-SE. Analysis of the drug combinations B) levetiracetam + gabapentin + topiramate, C) levetiracetam + gabapentin + deferoxamine + fingolimod, and D) levetiracetam + alpha-tocopherol is currently being finished. Due to the still incomplete understanding of epileptogenesis, the challenge of finding novel treatment for epilepsy prevention remains problematic. Supported by the European Union's Seventh Framework Programme (FP7) under grant agreement 602102 (EPITARGET).

Disclosures: L. Welzel: None. **F. Twele:** None. **P. Klein:** None. **W. Löscher:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.02/H18

Topic: B.10. Epilepsy

Title: Inhibition of cholesterol 24-hydroxylase improves the survival of a mouse model of epileptic phenotype and modulates extracellular levels of glutamate

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Abstract: Cholesterol 24-hydroxylase (CH24H also known as CYP46A1) is an enzyme responsible for the conversion of brain cholesterol into 24*S*-hydroxycholesterol (24HC). Early experimental evidence supporting the therapeutic potential of CH24H inhibition was observed in the extended life expectancy of amyloid precursor protein (APP) and presenilin 1 (PS1) Tg mice cross-bred with homozygous or heterozygous CH24H knockout mice. The model carryies transgenes implicated in familial Alzheimer's disease, whereas also known for an epileptic character and an altered glutamate regulation. In this study, TAK-935, a potent and selective CH24H inhibitor was tested in the APP/PS1-Tg model. APP/PS1-Tg mice orally treated with TAK-935 showed a dose-dependent reduction in the brain level of 24HC. The dose of TAK-935 10 mg/kg was found to reduce the brain level of 24HC by approximately 50% compared with the vehicle-treated control mice, recapitulating the heterozygous CH24H deficiency. Seven-week old female APP/PS1-Tg mice were orally treated with vehicle or TAK-935 10 mg/kg once daily for

8 weeks (n=30). During the survival observation, the hazard ratio for sudden death was 5.849 in the vehicle-treated arm compared with TAK-935. A significant improvement in mortality was observed in the TAK-935 group ($p<0.01$ vs control). Based on an assumption that high seizure susceptibility is the underlying cause of mortality in these mice, 100 mM potassium chloride (KCl) was continuously injected through a microdialysis probe in the hippocampus to unmask their epileptic phenotype. KCl-challenged APP/PS1-Tg mice were found to be more susceptible than their wild-type (WT) control not only to seizure but also to extracellular glutamate elevation (fold increase from baseline: WT, 4.0; Tg, 22.8, n=4-5, $p<0.05$). Two-week treatment of TAK-935 (10 mg/kg orally every day) significantly suppressed the KCl-induced glutamate elevation in APP/PS1-Tg mice (fold increase from baseline: vehicle, 28.9; TAK-935, 1.6, n=12, $p<0.01$). This result indicates that TAK-935 normalized the high susceptibility of APP/PS-Tg mice to extracellular glutamate elevation, leading to a hypothesis that CH24H inhibition is a potential new pharmacological mechanism to modulate seizure susceptibility in the epileptic brain consistent with our previous studies in kindling development model. The consistency in the survival advantage of genetic and chemical ablation of CH24H in APP/PS1-Tg mice highlights the relevance of CH24H inhibition as a new therapeutic strategy.

Disclosures: T. Nishi: A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **S. Watanabe:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **S. Hasegawa:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **S. Fujimoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **E. Sunahara:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **M. Ohori:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **T. Koike:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **M. Miyamoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical. **S. Kondo:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.03/I1

Topic: B.10. Epilepsy

Title: Cholesterol 24-hydroxylase inhibition is a novel pharmacological mechanism that exerts neuroprotective effects against glutamate excitotoxicity in rats

Authors: S. HASEGAWA, T. NISHI, S. WATANABE, S. FUJIMOTO, *S. KONDO
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Abstract: Glutamate toxicity plays a central role in a variety of neurological disorders and is thus studied as a promising treatment target. We previously reported that pharmacological

inhibition of cholesterol 24-hydroxylase (CH24H also known as CYP46A1) has a potential to delay the acquisition of kindling seizure, which led us to an assumption that CH24H inhibition can be protective against glutamate toxicity. A small-molecule CH24H inhibitor TAK-935 was tested in the rat kainic acid (KA) hippocampal injury, a representative model of excitotoxicity. The Y maze test was conducted 4 days after KA injection, and dose-dependent effects were observed at doses of TAK-935 10 and 30 mg/kg (orally every day). The spontaneous alteration rates of the saline-treated control, KA-induced vehicle control, and TAK-935 10 and 30 mg/kg were 78.6, 60.9, 71.6, and 74.4%, respectively ($p<0.025$ vs vehicle). Brain samples were obtained 5 days after KA injection and underwent Fluoro Jade-C (FJC) staining, which showed that TAK-935 dose-dependently reduced FJC-positive areas in CA3 by 80% and 85% from that in the vehicle control group, respectively, at 10 and 30 mg/kg ($p<0.025$ vs vehicle). In addition to the neuroprotective effects, tumor necrosis factor alpha and glial fibrillary acidic protein expression levels were reduced in the treatment arm, suggesting a modulation of inflammatory glial reactions. It was also shown that 24S-hydroxycholesterol (24HC), the enzymatic product of CH24H, potentiated cell death induced by glutamate in primary neuron culture. Importantly, its neurotoxic potential was highly dependent on the N-methyl-D-aspartate (NMDA)-type glutamate receptor, but not on the KA or AMPA-type. It was thus presumed that CH24H inhibition exerted neuroprotective effects by reducing 24HC, which has neurotoxic potential mediated by NMDA receptors. TAK-935 was further tested for potential effects on locomotor activity, which is typically increased by NMDA receptor blockade. Under the treatment condition where brain 24HC decreased approximately by 90%, TAK-935 did not affect locomotor activity in mice. Taken together, we infer that CH24H inhibition is a novel neuroprotective mechanism against the KA-induced excitotoxicity. Although its pharmacological mechanisms remain to be fully investigated, CH24H inhibition may reduce glutamate toxicity differently from the conventional NMDA receptor blockade.

Disclosures: S. Hasegawa: A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **T. Nishi:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **S. Watanabe:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **S. Fujimoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **S. Kondo:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.04/I2

Topic: B.10. Epilepsy

Title: Suppression of seizure-induced increased expression of JAK/STAT signaling in kindling model of epileptogenesis using isoxylitones [E/Z]

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Abstract: Purpose: Epilepsy is a serious neurological disorder marked by recurring seizures. To date a broad category of AEDs are available, but unfortunately over one-third of the epileptic patients do not respond to these drugs. Thus finding new therapeutics to overcome the untreatable epilepsy and side effects of the current drug therapies is needed. The activation of the Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) signaling pathway has also been reported to link with epilepsy. This can be use as a target molecular pathway to interrupt the process of epileptogenesis. In the present study, we targeted the JAK/STAT pathway using isoxylitones [E/Z] in order to inhibit the development of epilepsy following a brain insult in an animal model. The outcome of these studies could lead to new therapies that can be used to prevent or inhibit development of acquired epilepsy following brain injury.
Methods: Pentylenetetrazole (PTZ)-induced kindling in mice was used as a model of epileptogenesis. Seizure-related behaviors were monitored for 30-45 minutes following PTZ administration. JAK/STAT were analyzed in brain samples of mice using RT-PCR and immunohistochemistry.
Results: The results revealed that isoxylitones [E/Z], a sodium channel blocker halt the development of epileptogenesis in PTZ-kindled mice. Isoxylitones effectively reduces the expression of JAK-1, JAK-3, and STAT-5a in hippocampus and cortex.
Conclusion: The present data suggests that isoxylitones act at the underlying molecular mechanism to control the seizure pattern, such as the downregulation of JAK/STAT most in hippocampus followed by cortex. These findings uncover a potential effect of the JAK/STAT pathway in epileptogenesis and may provide a new therapeutic target that can be harnessed for the prevention of epilepsy development and/or progression. At this stage we propose to examine isoxylitones to determine 1) its potency to inhibit JAK/STAT pathway and cellular toxicity in primary hippocampal neurons, 2) ability to block acute seizure- induced JAK/STAT pathway activation in brain and off-target effects on other kinases. The expected outcome is identification of lead JAK/STAT inhibitors that can be advanced towards clinical testing for epilepsy disease modification.

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Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.05/I3

Topic: B.10. Epilepsy

Title: Targeting exaggerated TGF-β signaling pathway to inhibit pentylenetetrazole-induced epileptogenesis in mice

Authors: *M. SHAHID[1], U. NISAR[1], F. SHAHEEN[1], .. ATTA UR RAHMAN[1,2], M. CHOUDHARY[1,2], M. ASKANI[1], S. U. SIMJEE[1,2]
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Abstract: Epilepsy is illustrated by persistent predisposition of the brain to generate seizures and considered as one of the most common, chronic, neurological disorder affecting around 1% of the individuals worldwide. A growing body of advanced researches now points a link between inflammation and various epilepsy syndromes, reflecting both an inflammatory state inside the epileptic brain along with increased permeability of the blood–brain barrier, heading towards enhanced neuronal excitability. The probable contribution of TGF-β in epileptogenesis is reinforced by animal studies viewing TGF-β up-regulation as measure of inflammatory reaction in the brains of kindled animals that are exposed to status epilepticus. While focusing on the other side of TGF-β signaling pathway to explore better treatment targets for epilepsy, Tumor necrosis factor-α receptor-associated factor-6 (TRAF6), transforming growth factor beta-activated kinase 1 (TAK1), which are the crucial elements of TGF-β associated inflammation, are still ambiguous in epilepsy.
The main focus of this study was to investigate the potental relatioship between the TGF-β associated genes and epilepsy which will aid in confirming that up regulation of TGF-β genes can be an underlying cause of epilepsy.
To confirm these evidences, expression levels of TRAF6 and TAK1 genes along with inflammatory cytokine interleukin-1β (IL-1 β) were analyze in pentylenetetrazole-induced epileptogenesis model in mice. A novel anticonvulsant Isoxylitones and its derivatives were used to treat epileptic seizures along with standard antiepileptic drugs Diazepam and Valproic acid. It was observed that gene expression of TRAF6 was increased in pentylenetetrazole-induced status epilepticus group followed by increase expression of TAK1 which is phosphorylated by TRAF6. However expressions of these genes were significantly reduced in Isoxylitones and standard antiepileptic drugs treatment groups. Inflammatory cytokine IL-1b expression was also decreased in treated groups. In conclusion, up regulation of TGF-β genes can be an underlying

cause of epileptogenesis and inhibiting it's upregulated expression can aid in reducing seizure duration and associated neuronal death in epilepsy.

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Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.06/I4

Topic: B.10. Epilepsy

Support: DARPA ElectRx

Title: Myelinated axons are clustered in the rat cVN and localized stimulation reduces the off-target activation of Aα motor axons in the recurrent laryngeal nerve

Authors: *A. WELLS[1], M. GONZÁLEZ GONZÁLEZ[1], S. A. HAYS[1], M. P. KILGARD[2], R. L. RENNAKER[1], M. I. ROMERO-ORTEGA[1]
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Abstract: Cervical vagus nerve stimulation (cVNS) is an effective clinical alternative for intractable epilepsy and drug-resistant depression, with potential use in heart failure, anxiety disorders, post-stroke motor recovery and tinnitus. However, the stimulation of the entire nerve can cause undesirable side effects such as voice alteration, cough, and dysphagia by the off-target stimulation of axons that innervate the recurrent laryngeal nerve (RLN). Voice alteration is the most common of these side effects, and is caused by activation of the large myelinated Aα branchiomotor efferents, which have a low stimulation threshold due to their size. We hypothesize that specific localization of these fibers combined with localized stimulation could be used to minimize the side effects caused by RLN activation. Using toluidine-blue label of ultrathin left VN sections and histomorphometric analysis, we identify a bimodal distribution in the fiber diameter histogram of the adult rat, corresponding to populations of large myelinated A fibers (peak diameter 7-8 μm) and medium to small myelinated Aδ/B fibers (peak diameter 2-3 μm). Image analysis of the left cVN using DBSCAN in R allowed the identification of clusters of large A and small/medium Aδ/B myelinated axons approximately 2 cm from the subclavian branching point of the RLN. Furthermore, a k- means algorithm was employed to divide each nerve into different regions. The cluster centroids were used to generate Voronoi diagrams, which were fitted to the dimensions of the nerve and used to create local density maps. Results show a statistical significance between the density of the densest region and the least dense region for both large A fibers and smaller Aδ/B fibers. In order to evaluate if the bundled large A axons can be avoided using localized stimulation, we fabricated a custom multi-contact cuff

electrode to selectively stimulate the nerve. Using this method, we selectively minimize the activation of the Aα fibers in the RLN while effectively evoking Aδ/fiber activation in the proximal cVN. Together, the results show that the main fascicle of the rat cVN has significant clustering of both large and small myelinated fibers, and that localized stimulation using multi-contact cuff electrodes can be used to selectively target the Aδ-fibers while avoiding some of the off-target activation of Aα motor axons in passage to the larynx. Avoiding the activation of Aα RLN fibers can prevent deleterious side effects otherwise caused by the concomitant RLN activation that occurs when the cVN is stimulated indiscriminately. This work supports the use of multi-contact cuff electrodes in cVNS applications.

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Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.07/I5

Topic: B.10. Epilepsy

Support: NIH Grant U01 NS102131 to KWG & JHM

Title: Enaminone modulators of extrasynaptic alpha$_4$beta$_3$delta GABA$_A$receptors reverse electrographic seizures and prevent neuronal cell death after acute organophosphate poisoning

Authors: T. JOHNSTONE[1], H. S. MCCARREN[2], J. SPAMPANATO[3], F. E. DUDEK[4], J. H. MCDONOUGH[2], D. HOGENKAMP[1], *K. W. GEE[1]
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Abstract: The current specifications for a standard medical countermeasure to organophosphate (OP) chemical nerve agent exposure is the development of a pharmaceutical agent that can augment or replace clinically-used anticonvulsant benzodiazepines (BZs) to effectively control OP-induced epileptogenesis. BZs do not fully control nerve agent induced seizures because they only engage synaptic gamma-aminobutyric acid A receptors (GABA$_A$Rs) that rapidly internalize under status epilepticus (SE) conditions. Extrasynaptic GABA$_A$Rs such as those containing alpha$_4$beta$_3$delta subunits are a putative pharmacological target to comprehensively manage nerve agent seizures since they do not internalize during SE and are continuously accessible for activation. Neurosteroids related to allopregnanolone have been tested as a possible replacement for BZs because they target both synaptic and extrasynaptic GABA$_A$Rs. Delayed treatment duration/efficacy and neuroprotection represent significant advantages of neurosteroids over BZs, but neurosteroid use is limited by poor physicochemical properties arising from the intrinsic

requirement of the androstane or pregnane steroid core structure for efficacy, rendering drug formulation problematic. We tested a non-steroidal enaminone $GABA_AR$ modulator that interacts with synaptic and extrasynaptic $GABA_A$ receptors on a binding site distinct from neurosteroids or BZs for efficacy to control electrographic seizures induced by diisopropyl fluorophosphate and soman intoxication. We found that the enaminone 2-261 has an extended duration of seizure termination (>10 hrs) in the DFP intoxication model in the presence or absence of midazolam. 2-261 moderately potentiates midazolam in GD-induced seizure model, but has limited efficacy alone due to slow onset of action. 2-261 significantly reduces neuronal cell death in brain areas associated with either diisopropyl fluorophosphate or soman induced SE. Thus, 2-261, may represent a more drug-like chemical template directed towards enhancing extrasynaptic $alpha_4beta_3$delta $GABA_AR$ activity for OP intoxication because it and related compounds may have a wider latitude for synthetic optimization than a neurosteroid-based template.

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Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.08/I6

Topic: B.10. Epilepsy

Title: Retinoic acid decreases the epileptic activity through the interaction of Sox-1 with β-catenin in the cerebellum of kindling rats

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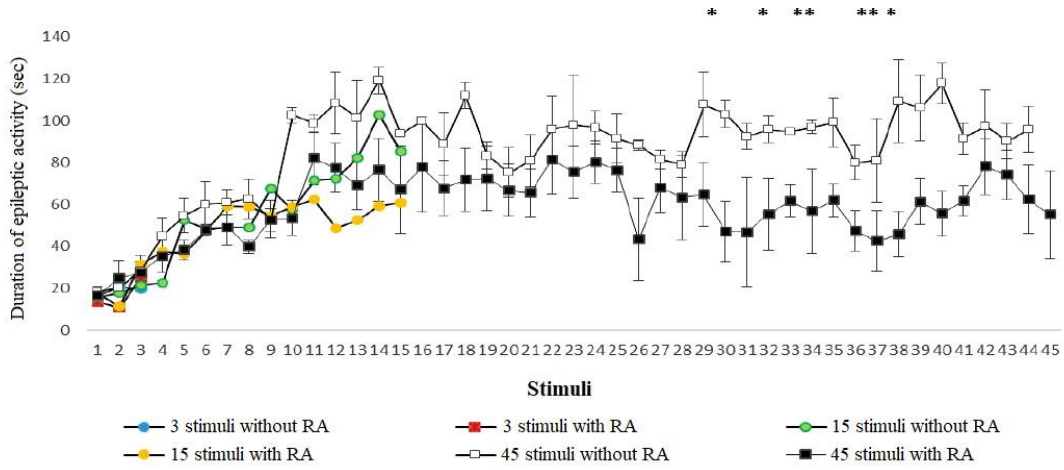
Abstract: The role of cerebellum in the physiopathology of epilepsy remains subject of study. Bergmann glia (BG) in the cerebellar cortex regulates the homeostasis of Purkinje cells, whose axons targets the dentate and interpositus nuclei, which form the main cerebellar output to other structures in the central nervous system involved in Epilepsy. Sox-1 is a transcription factor expressed in BG and its binding to β-Catenin (βC) further inhibits the canonical Wnt pathway. In the cerebellum of rat with the kindling model, it is known that there is a decreased expression of Sox-1 with generalized seizures, furthermore it has been reported, higher activity of the βC signaling with the recurrence of seizures associated with apoptosis, one of the mechanisms proposed is the interaction o Sox-1 with βC. It is known that retinoic acid (RA) has an

antiepileptic effect through its metabolite alls-trans-retinoic acid (ATRA), in addition it has been seen that the ATRA causes an increase in the expression of Sox-1. Here we present the effect of RA in the duration of the epileptic activity (EA) and its relationship with the Sox-1 expression and the signaling of βC in the cerebellum of kindling rats. We used Wistar rats separated into groups with and without administration of RA, that received 3, 15 and 45 stimuli, recording and analyzing the EA. The cerebellum was processed for immunohistochemistry assay for Sox-1 and βC. We found that the administration of RA decreases the duration of the EA in the group of generalized seizures. For βC we found an increase of the immunopositivity in the groups of 45 stimuli with and without administration of RA. For Sox-1 we found a progressively increase of the immunopositivity, in the groups with RA administration. We conclude that the administration of RA produces a decrease in the duration of the EA associated with the regulation in the expression of Sox-1 and the signaling of βC, in the cerebellum. In this way we suggest this mechanism as a one of the possible explanations of the antiepileptic effect of RA.



Disclosures: A. Rosiles: None. **C. Rubio-Osornio:** None. **C. Trejo-Solís:** None. **V. Custodio:** None. **C. Mendoza:** None. **L. Hernández-López:** None. **E. Gonzalez-Ruiz:** None. **J.C. Martínez-Lazcano:** None. **E. Gonzalez:** None. **C. Paz:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.09/I7

Topic: B.10. Epilepsy

Support: NIH Grant 5R37NS077908-07

Title: Delayed post-traumatic neuronal death in the developing hippocampus

Authors: *T. BALENA[1], N. RAHMATI[3], K. P. LILLIS[4], K. J. STALEY[2]
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Abstract: New fluorophores and microscopy techniques have made possible more detailed explorations of the process of neuronal death. In the present study we evaluated the death of neurons in a chronically epileptic *in vitro* preparation in which multiphoton microscopy could be performed over a period of several days. Organotypic hippocampal slice cultures were made from P6 wild-type C57BL/6J mice, and two-photon imaging was performed using transgenic fluorophores as well as the ratiometric Na^+ dye SBFI-AM. We report the following sequence of events in delayed neuronal death following the substantial trauma involved in brain slice preparation. The first detectable event was loss of participation in network activity and mild, sustained elevation of cytoplasmic Ca^{2+}. The second stage was marked by activation of caspases evidenced by FLICA staining. During the second stage, fluorescence of transgenic fluorophores was lost. pH and ionic sensitivity did not influence fluorophore quenching. In the third stage, neurons admitted AM dyes including SBFI-AM and Fura-AM. The fourth stage was marked by steady increases in cytoplasmic Na^+ concentrations from 10 mM to concentrations approaching that of the extracellular solution. Cytoplasmic Ca^{2+} remained elevated during this interval. During this fourth stage, cytoplasmic membrane damage could be demonstrated by Annexin V staining, retraction of dendrites and axons was completed, and condensation of nuclear chromatin visualized by NucBlue became progressively evident. Throughout the fourth stage, TMRM staining, pharmacological antagonists, and ion-sensitive fluorophores confirmed ongoing glycolysis and mitochondrial respiration and ATP production, sodium transport via Na^+/K^+ ATPases, and secondary transport including cation-Cl^- cotransport and Na^+/Ca^{2+} exchange. The transition to the fifth and final stage was marked by progressively more intense propidium iodide staining. Key final events included microglial engulfment (as indicated by isolectin staining), sharp rises in Na^+ and Ca^{2+} concentrations, and terminal cell shrinkage. A number of pharmacological interventions ameliorated ionic disequilibria but did not prevent or retard eventual cell death. These studies provide a framework with which to understand the stages of delayed neuronal death in relation to the clinical evolution of brain injury, as well as the effects of neuroprotective and disease-modifying treatments.

Disclosures: T. Balena: None. **N. Rahmati:** None. **K.P. Lillis:** None. **K.J. Staley:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

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Program #/Poster #: 289.10/I8

Topic: B.10. Epilepsy

Support: NIH/NINDS (Y1-O6-9613-01)
USAMRICD (A120-B.P2009-2)

Title: Evaluation of repurposed antiepileptic drugs to treat spontaneous recurrent seizures in instrumented male C57Bl/6 mice following a sublethal soman exposure

Authors: *D. L. NGUYEN, M. R. EISEN, C. E. ARDINGER, E. N. DUNN, K. M. HAINES, A. N. SANTORO, P. M. BODNER, P. B. DUBEE, H. S. MCCARREN, P. M. MCNUTT
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Abstract: Exposure to nerve agent (NA) can result in rapid onset of generalized status epilepticus (SE), which if uncontrolled can cause permanent brain damage and death. Many efforts have focused on ways to stop the initial seizure, but few have addressed the long-term symptoms and complications of exposure. Following SE, individuals may develop spontaneous recurrent seizures (SRS) or epilepsy that often leads to severe neurological deficits and lower quality of life. Though dozens of FDA-approved antiepileptic drugs (AEDs) are on the market, it is unknown which, if any, would be effective against NA-induced SRS. We designed this experiment to test five AEDs (levetiracetam, phenobarbital, valproate, carbamazepine, and clonazepam) on SRS onset and characteristics in telemetry-instrumented mice following a sublethal, supraconvulsant soman (GD) challenge. Starting 24 hours after SE, mice were repeatedly dosed with an AED or vehicle for 14 days, followed by a 14-day washout period. Dosing regimens were based on published pharmacokinetic data. Levetiracetam and valproate had no apparent effect on SRS number, duration, or onset of SRS. Although phenobarbital-treated mice exhibited a delay in SRS onset compared to vehicle, mice developed phenobarbital resistance prior to the end of the treatment period. Data are still being acquired on the effects of carbamazepine and clonazepam on SRS activity. Continued analysis will focus on the effects of these AEDs on SRS activity and low frequency epileptiform events.

Disclosures: D.L. Nguyen: None. **M.R. Eisen:** None. **C.E. Ardinger:** None. **E.N. Dunn:** None. **K.M. Haines:** None. **A.N. Santoro:** None. **P.M. Bodner:** None. **P.B. Dubee:** None. **H.S. McCarren:** None. **P.M. McNutt:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

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Program #/Poster #: 289.11/I9

Topic: B.10. Epilepsy

Support: NIH/NINDS grant #R01-NS 079214
Dravet Syndrome Fellowship award to AG
UCSF Catalyst award to SCB

Title: Development of serotonin modulators for Dravet syndrome through phenotypic drug screening in zebrafish

Authors: *A. GRIFFIN[1], J.-M. GRANDJEAN[2], P. JAISHANKAR[3], A. R. RENSLO[3], S. H. OLSON[2], S. C. BARABAN[1]
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Abstract: Dravet syndrome (DS) is a catastrophic childhood epilepsy often caused by genetic mutations in the voltage-gated sodium channel gene *SCN1A*. The currently available antiepileptic drugs fail to provide adequate seizure control for these patients. Recently, preclinical and clinical evidence suggests that compounds which activate serotonin receptors can have therapeutic benefits for DS patients. This study aimed to uncover the precise antiepileptic mechanism of action of these compounds using a zebrafish phenotypic drug screening approach. Zebrafish with a mutation in the *SCN1A* homologue, *scn1lab*, have spontaneous seizure activity in the brain and convulsive behavioral movements. Importantly, *scn1lab* mutant zebrafish also show pharmacoresistance to many antiepileptic drugs (AEDs), emulating the persistent drug resistant seizures observed in human patients. Given the zebrafish *scn1lab* mutant replicates the genetic, behavioral and pharmacological phenotype of DS patients they offer a valuable model for phenotypic drug-screening for antiepileptic compounds. Using the *scn1lab* mutant zebrafish in a two-stage drug screening platform (consisting of behavior screening and electrophysiology confirmation), approximately 3000 compounds spanning several drug classes underwent blind testing to identify potential antiepileptic properties. Only three compounds were identified as potential anti-epileptics (trazodone, clemizole and lorcaserin) and all are modulators of HTR2 receptors. Structure-activity relationship (SAR) studies were performed by synthesizing a library of clemizole analogs (n = 28) and screening them for antiepileptic activity in the *scn1lab* zebrafish. Three “clemalogs” were identified as capable of suppressing the convulsive seizure behaviors. In vitro radioligand binding assays confirmed binding affinities to human HTR2B receptors for all three compounds. Using a more traditional target-based approach, commercially available compounds were also screened based on their potency and agonism of HTR2 receptors. Despite similar in vitro binding profiles many of these compounds failed to elicit anti-seizure activity. We conclude that in vivo phenotypic drug screening can successfully identify a class of compounds with a common mechanism which are clinical relevant for patients. Additionally, for AED discovery, phenotypic drug screening using appropriate disease models can overcome many of the difficulties observed when translating results from other traditional drug discovery methods.

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Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.12/I10

Topic: B.10. Epilepsy

Support: NIH Grant U01-NS083460

Title: Role of protein kinase c phosphorylation in neurosteroid modulation of extrasynaptic gaba-a receptors in the hippocampus

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Abstract: Endogenous neurosteroids such as allopregnanolone (AP) are powerful modulators of GABA-A receptors. Phosphorylation status of GABA-A receptors play a critical role in receptor surface expression, channel conductance, and sensitivity to neurosteroids. Therefore, alterations in the phosphorylation status of these receptors can dramatically affect neurosteroid actions. Here, we sought to determine the role of phosphorylation of extrasynaptic GABA-A receptors in neurosteroid potentiation of tonic currents in the δ-subunit-rich dentate gyrus granule cells (DGGCs). Adult male mice were used for electrophysiology studies. GABAergic tonic currents were recorded from DGGCs using whole-cell patch clamp. To explore the effects of phosphorylation on neurosteroid potentiation of tonic currents, a protein kinase C (PKC) inhibitor GF109203X was applied to the bath solution for 15 or 30 minutes before the perfusion of GABA and the application was continued during GABA and neurosteroid co-perfusion. In hippocampus slices, synthetic neurosteroid GX potentiated and directly activated tonic currents in DGGCs in a concentration-dependent fashion. However, these responses were significantly diminished in DGGCs from δ-subunit knockout (δKO) mice, confirming the selectivity of GX for extrasynaptic δGABA-A receptors. Pretreatment of PKC inhibitor significantly attenuated GABA-evoked tonic currents. Moreover, the GX potentiation of tonic currents was completely prevented by PKC inhibition. The endogenous neurosteroid AP also potentiated tonic currents in a PKC-sensitive fashion, signifying an important role of receptor phosphorylation by PKC in neurosteroid modulation of tonic inhibition. These results demonstrate a critical role of PKC-mediated phosphorylation of neurosteroid-sensitive, extrasynaptic δGABA-A receptors in the dentate gyrus that regulate hippocampal network inhibition and seizure susceptibility.

Disclosures: S. Chuang: None. **S. Reddy:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.13/I11

Topic: B.10. Epilepsy

Support: INPRFM NC123240.1

Title: Effects of ruta chalepensis L. (rutaceae) over EEG activity and PTZ induced seizures in mice

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Abstract: Ruta chalpensis, known as “ruda”, is one of the oldest natural drugs and is often used to treat a wide variety of conditions such as vertigo, stomachaches, intestinal parasites, intoxications, headaches, anxiety, ocular problems and epilepsy. Preliminary data of their effects was described in the acute model of seizures induced by PTZ, using a polar extract and evaluating the motor behavior in mice. Nevertheless, the effects using median polarity substances and the associated electroencephalographic activity (EEG) have not been described. In the present study, under such conditions, different doses were evaluated (100, 300, and 1000 mg/kg, i.p.) using behavioral and EEG recordings for 30 min and during tonic-clonic seizures induced with PTZ (85 mg/kg, i.p.) in 36 SW mice (27-36 g; n=6 per experimental condition). The vehicle, 100 mg/kg, diazepam (1mg/kg, i.p.) and naïve mice groups didn’t present significant changes neither in the ambulatory activity nor EEG. On the other hand, a decrement in such activity was observed in mice that received 300mg/kg and 100 mg/kg, suggesting a hypnotic effect at the time of the first application and in the case of higher doses a “burst-suppression” alteration in the EEG pattern was observed. With respect to convulsive seizures, diazepam, 300 mg/kg and 1000 mg/kg of R. chalepensis protected against generalized tonic-clonic seizures mediated by the depressor effect over brain electrical activity. In conclusion, the EEG can be used to detect sedating or alerting effects of different doses of plant extracts and its effects on PTZ induced seizures in mice. On the other hand, these data reinforced the anticonvulsive properties of this medicinal species, although in higher doses the extract could produce neurotoxic effects, indicating that is important to be careful about its uses.

Disclosures: D. Martinez-Vargas: None. **M. Gonzalez-Trujano:** None. **M. Hernández-Arámbulo:** None. **E. Urbina-Trejo:** None. **F. Santos-Valencia:** None. **B. Villasana-Salazar:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

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Program #/Poster #: 289.14/I12

Topic: B.10. Epilepsy

Support: DFG Grant LO 274/15-1
PhD Scholarship by the Konrad-Adenauer-Stiftung

Title: NKCC1 is not obligatory for epileptogenesis and the manifestation of seizures in the intrahippocampal kainate mouse model

Authors: *P. HAMPEL[1,2], K. RÖMERMANN[1], A. VOGEL[1], W. THEILMANN[1], B. GAILUS[1], M. JOHNE[1,2], K. TÖLLNER[1], K. KAILA[3,4], W. LÖSCHER[1,2]
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Abstract: Epileptogenesis is a process of pathological changes in the brain that take place after epilepsy-initiating insults and result in acquired epilepsy. In humans, e.g., craniocerebral injury, infections, or *status epilepticus* (SE), can lead to the development of acquired epilepsy with spontaneous recurring seizures (SRS). Epileptogenesis has often been shown to be associated with upregulation of Cl^- uptake by Na^+-K^+-$2Cl^-$ cotransporter isoform 1 (NKCC1) in neurons. This in turn, is expected to lead to a change from inhibitory to excitatory GABA actions. NKCC1 upregulation has been described in post-SE rodent models in subsequent days after SE. However, it is yet unknown whether this process is protective or proepileptogenic. This study aimed at determining whether the disruption of NKCC1 expression prevents the development of SRS in the intrahippocampal kainate mouse model of epilepsy or leads to disease modification, e.g., in the progression of SRS, neuronal loss or granule cell dispersion.
Kainate was injected into the CA1 region of the right hippocampus in 10-15 weeks old male and female $NKCC1^{-/-}$- and $NKCC1^{+/+}$-mice of the strain B6-*Slc12a2*$^{sy\text{-}ns}$/J to induce SE. A bipolar electrode was implanted at the injection site. EEG- and video-monitoring was performed following kainate injections and both one month and three months after SE for seven days each. Results up to this point can be summarized as follows: 21/21 $NKCC1^{-/-}$-mice developed polyspikes, which are characteristic for the SE, or showed behavioral seizures during SE following kainate injection. Similarly, polyspikes were observed in 8/10 $NKCC1^{+/+}$-mice. One month post SE, 6/6 $NKCC1^{-/-}$-mice showed clinical seizures (range: 3-8 seizures/week). These

included focal and generalized seizures ranging from type III-V on the Racine scale. Neuronal loss and granule cell dispersion are currently assessed.
This study demonstrates that NKCC1 does not play an obligatory role in epileptogenesis and manifestation of SRS in the intrahippocampal kainate mouse model.

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Poster

289. Anticonvulsant and Antiepileptic Therapies

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Program #/Poster #: 289.15/I13

Topic: B.10. Epilepsy

Support: Pfizer Inc.

Title: Pronounced antiepileptic activity of the subtype-selective $GABA_A$ positive allosteric modulator PF-06372865 in the GAERS model

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Abstract: Absence epilepsy is a form of epileptic syndrome where patients show generalized non-convulsive seizures characterized by a brief unresponsiveness to environmental stimuli and cessation of activity. In human, typical absence seizures are associated with bilateral, synchronous and regular spike-and-wave discharges (SWD). Genetic absence epilepsy rat from Strasbourg (GAERS) is a selectively inbred strain of Wistar rats displaying spontaneous SWD. For the last twenty years, the GAERS has become a reference model for absence epilepsy, since these rats were shown to present behavioral, electrophysiological and pharmacological features of absence seizures. The pharmacology of the GAERS model is like the human one. For instance, valproate, ethosuximide and levetiracetam show an anti-epileptic effect. In the present work, we tested the dose-dependent effect of a newly developed subtype-selective $GABA_A$ positive allosteric modulator, PF-06372865. PF-06372865 induced a dose-dependent reduction of the number of SWD in the GAERS model. At the low dose (0.3 mg/kg), no significant effect as compared to vehicle and baseline was observed. At the dose of 1 mg/kg no significant effect was detected immediately after administration (10-30 min post-administration). A partial effect started to appear 30-50 min after administration of this low dose: at this time-point, the number of SWD was reduced by 59% of baseline value. It was significantly different from baseline and from the vehicle. The number of SWD continued to reduce 50 min after administration of the

low dose, to reach almost complete reduction at time-point 70-90 min. At the two higher doses (3 and 10 mg/kg), the inhibition was significant already at the first post-treatment time-point (10-30 min) as compared to the baseline and the vehicle. The reduction was complete and persistent from 30 to 90 min after administration. No significant difference was found as compared to the reference compound valproate, except for the 3 mg/kg dose at the first time-point (10-30 min post-administration). In comparison, the reference compound diazepam showed a complete reduction of SWD during the 10-30 min time-period. This effect is gradually disappearing but remained significant for the rest of the recording period (between 30 and 90 min post-treatment). PF-06372865 dose-dependently reduced the occurrence of SWD in the GAERS model with a significant effect at 1, 3 and 10 mg/kg. In comparison to the reference compound diazepam, PF-06372865 has a slower peak time effect but a longer efficacy. The subtype-selective $GABA_A$ positive allosteric modulator PF-06372865 shows an anti-epileptic potential to treat absence epilepsy.

Disclosures: C. Roucard: A. Employment/Salary (full or part-time):; SynapCell SAS. **R. Gurrell:** A. Employment/Salary (full or part-time):; Pfizer Inc. **D. Buhl:** A. Employment/Salary (full or part-time):; Pfizer Inc. **A. Evrard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Ruggiero:** A. Employment/Salary (full or part-time):; SynapCell SAS. **V. Duveau:** A. Employment/Salary (full or part-time):; SynapCell SAS.

Poster

289. Anticonvulsant and Antiepileptic Therapies

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Program #/Poster #: 289.16/I14

Topic: B.10. Epilepsy

Support: NIH Grant NS29709
CPRIT
HHMI

Title: Tau loss modifies network excitability in brain tumor related epilepsy

Authors: *A. HATCHER[1], K. YU[2], I. AIBA[2], B. DENEEN[3], J. L. NOEBELS[2]
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Abstract: Hyper-excitability of neuronal networks underlies the pathophysiology of epilepsy, and is known to be a component of other neurological disorders including cancers of the brain. Previous work has shown that genetic removal of neuronal microtubule organizer and stabilizer tau can significantly reduce epileptiform activity and lethality across a number of models of hyper-excitability, including Alzheimer's Disease models, the Kcna1 early lethal mouse model of epilepsy, and the Scn1a mouse model of Dravet syndrome. We recently confirmed a

progressive seizure phenotype in a novel transgenic mouse model of brain tumor related epilepsy. The effect of tau loss on hyper-excitability and lethality in this glioblastoma model was unknown. To answer this question, we generated glial derived brain tumors on a tau knockout background using a CRISPR in utero electroporation strategy. Using chronic video electroencephalography (EEG), we recorded cortical inter-ictal spike and seizure activity in these tumor mice at various timepoints in disease progression, monitored survival, and assessed tumor burden via immunohistochemically methods. tau KO tumor mice exhibited reduced inter-ictal spike activity and slightly longer survival times compared to tau WT tumor-bearing littermates. These data suggest that tau loss may provide a modest protective effect in this model of cortical hyper-excitability.

Disclosures: A. Hatcher: None. **K. Yu:** None. **I. Aiba:** None. **B. Deneen:** None. **J.L. Noebels:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.17/I15

Topic: B.10. Epilepsy

Title: Adenosine A1 receptor antagonism reduces the effect of gamma-decanolactone on acute and chronic seizures in mice

Authors: *P. PEREIRA[1], G. REGNER[1], L. L. SILVA[1], L. TOUGUINHA[2], M. SALVADOR[2], P. PFLÜGER[1]
[1]Federal Univ. of Rio Grande Do Sul, Porto Alegre, Brazil; [2]Univ. de Caxias do Sul, Caxias, Brazil

Abstract: Gamma-decanolactone (GD) is a monoterpene effective against seizures induced by pentylenetetrazole (PTZ) and it is known to reduce neuronal damage induced by pilocarpine (PIL) in mice. Previous studies have shown that GD acts as an antagonist of glutamate receptors. It also inhibits intracellular reactive oxygen species (ROS) generation and decreases the expression of inducible nitric oxide synthase (iNOS) and tumor necrosis factor-alpha (TNF-α) induced by the lipopolysaccharide *in vitro*. The present study evaluated GD mechanism of action using the chemical kindling and the acute aminophylline (AMPH) seizure models. Considering the strong relation between mitochondrial dysfunction and epilepsy, we also evaluated the effect of GD on mitochondrial complex I in cerebral cortex after AMPH seizure model. CF-1 male mice were injected (i.p.) with Bicuculline (2 mg/kg), a receptor $GABA_A$ antagonist, or DPCPX (2 mg/kg), an adenosine A1 antagonist, or ZM 241385 (3 mg/kg), an A2A antagonist, 15 min before treatment with GD (100 and 300 mg/kg). DZP (2mg/kg) was used in this study as a positive control. In the kindling model, 30 min after the treatments, mice received PTZ (40mg/kg

s.c.) once every third day, in a total of six treatments (16 days). The latency to the first clonic seizure and its occurrence were registered. In the AMPH model, a single dose of AMPH (280 mg/kg, i.p.) was administered and animals were observed for 60 min. The latency to the first seizure and the occurrence of tonic-clonic seizure were registered. The assessment of mitochondrial complex I activity was detected using spectrophotometer. The results were analysed using Fisher's exact test and Kruskal-Wallis analysis followed by Dunn's test. Tukey test was used to analyze the results of mitochondrial activity. The results showed that GD (300 mg/kg) increased the latency to first seizure and decreased seizures occurrence induced by PTZ or AMPH. Both the adenosine A2A receptor antagonist (ZM 241385) and $GABA_A$ receptor antagonist (Bicuculline) were not able to change GD behavioral seizure responses. On the other hand, the administration of adenosine A1 receptor antagonist (DPCPX) reverted GD effect as it was observed in both behavioral models used. Also GD decreased mitochondrial complex I activity in cerebral cortex. In summary, our results demonstrated that the anticonvulsive profile of GD observed in this study may be related to its action on A1 adenosine receptors.

Disclosures: P. Pereira: None. **G. Regner:** None. **L.L. Silva:** None. **L. Touguinha:** None. **M. Salvador:** None. **P. Pflüger:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

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Program #/Poster #: 289.18/I16

Topic: B.10. Epilepsy

Support: Swedish Research Council 2015-00353
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Jeansson Foundation
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Title: Crispr/cas9-mediated overexpression of cb1 receptors for the control of epileptogenesis

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Abstract: Epilepsy is one of the most common neurological disorders worldwide, affecting 1% of the general population. Epilepsy usually develops after an initial insult, such as head trauma or stroke, which triggers the generation of epileptic seizures. During epileptogenesis, the affected brain regions undergo massive changes in gene expression, including downregulation of the cannabinoid receptor I (CB1).

Recent developments in gene editing technologies, including the bacteria-derived CRISPR-Cas9 system, have opened new avenues for gene therapy. Particularly, the possibility of developing a reversible and precise regulatory system for endogenous genes with spatio-temporal control, overcomes several limitations of the classic gene therapy approaches. On this basis, this study aims to exploit the innovative CRISPR-Cas9 technology to prevent CB1 downregulation during epilepsy.
We generated an inducible CRISPR-Cas9 system to obtain spatio-temporal modulation of CB1. Precise spatial specificity was obtained using viral vectors carrying single guide RNAs (sgRNAs) specific for the promoter region of mouse CB1-receptor and dCas9 fused to either the transcriptional activator VP64 or VPR. To obtain temporal modulation of CB1 we used a Doxycycline sensitive system restricted to glutamatergic excitatory neurons. Real Time qPCR showed a significant upregulation of CB1 receptors in primary neurons infected with viral vectors, paralleled by an increase in protein expression as revealed by Western blot. In the mouse hippocampus in vivo, CB1 receptors were also significantly modulated in animals injected with dCas9-VPR and sgRNA carrying viruses.
Our results indicate that primary neurons and hippocampal neurons can be successfully manipulated with viral vectors expressing the CRISPR-Cas9 system to modulate target genes. These findings show potential for future experiments and will be the basis to apply this system to animal models of epilepsy, with the aim of delaying or completely preventing the development of spontaneous recurrent seizures.

Disclosures: V. Di Maria: None. **M. Ryde:** None. **L. Quintino:** None. **M. Ledri:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.19/I17

Topic: B.10. Epilepsy

Title: Novel KCNT1 inhibitors of wild-type and a P924L gain-of-function variant identified through comprehensive high-throughput drug repurposing screening

Authors: *G. R. STEWART[1], J. M. ANDRESEN[1], B. C. GAY[1], C. M. MAHER[1], A. C. GERLACH[2], T. A. ATKIN[3], M. D. FULLER[2], M. L. CHAPMAN[2], B. M. ANTONIO[2], D. B. GOLDSTEIN[4], O. DEVINSKY[5], S. PETROU[6]
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Abstract: KCNT1 epileptic encephalopathies arise due to mutations in a sodium-activated potassium channel, also known as $K_{Na}1.1$ or Slack, and present with seizures and profound developmental delay. In the present study, we developed an in vitro cell model expressing the P924L mutation and compared it to a cell line bearing the wild-type KCNT1 channel. Using patch-clamp electrophysiology, Slack potassium channels with the P924L mutation showed significantly increased potassium current compared to wild-type Slack channels, confirming a gain-of-function molecular phenotype associated with early infantile migrating focal seizures (EIMFS). We then performed a comprehensive high-throughput drug repurposing screen with 1,291 approved drugs to identify compounds that inhibited ion flow in the P924L or wild-type KCNT1 cell models. Using a rubidium efflux assay as an output, we identified 55 compounds in the wild-type and 40 compounds in the P924L cell model that inhibited efflux greater than two standard deviations beyond the group mean of all drugs. These hit compounds were then evaluated across a series of concentrations in the rubidium efflux assay and with electrophysiology to confirm activity and to derive an IC_{50} and maximal effectiveness. Compounds with a high degree of novel inhibitory activity in both cell models included ezetimibe (cholesterol-lowering), raloxifene (hormone modulator) and doxazosin mesylate (anti-hypertensive). Ritonavir (anti-viral) and carvedilol (beta-blocker) were two drugs with activity only against the P924L variant cell model. Although there has been interest in quinidine as an inhibitor of KCNT1 channels, the drug displayed only a modest level of inhibitory activity that was substantially less than several other compounds identified by the drug repurposing screen. In line with our previous work on SCN8A ion channels (Atkin et al, Epilepsia 2018), the KCNT1 study demonstrates the utility of comprehensive screening with a large library of approved drugs in order to identify compounds with significant activity against cellular models of epilepsy-related genes. These results provide an enriched starting pool of drug candidates for further development and therapeutic evaluation against gain-of-function KCNT1 epileptic encephalopathies.

Disclosures: G.R. Stewart: A. Employment/Salary (full or part-time):; Pairnomix, LLC. **J.M. Andresen:** A. Employment/Salary (full or part-time):; Pairnomix. **B.C. Gay:** A. Employment/Salary (full or part-time):; Pairnomix. **C.M. Maher:** A. Employment/Salary (full or part-time):; Pairnomix. **A.C. Gerlach:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pairnomix. **T.A. Atkin:** A. Employment/Salary (full or part-time):; Pairnomix. **M.D. Fuller:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pairnomix. **M.L. Chapman:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pairnomix. **B.M. Antonio:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pairnomix. **D.B. Goldstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent

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Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.20/J1

Topic: B.10. Epilepsy

Title: Optogenetic control of cerebellar output abolishes generalized seizures

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Abstract: Absence epilepsy (AE) is a form of generalized epilepsy, characterized by a brief loss of consciousness and behavioral arrest. The electrophysiological hallmarks, bilaterally synchronized 5-9 Hz spike-and-wave discharges (SWDs) occur spontaneously on an otherwise normal electroencephalogram. While genetic factors are most often the cause for developing AE, also trauma, stroke or tumors can be a factor in developing this type of seizures. The common dogma for the development of seizures (ictogenesis) consists of a reciprocally connected TCN that starts to produce hypersynchronous oscillations that spread over the whole cortex. The underlying mechanism of changes making the TCN prone to develop seizures (epileptogenesis) are hardly understood but researchers favoring the TCN to be the point of interest. This widely accepted theory is challenged by patients that developed a tumor in the cerebellum - a so far believed nonepileptic region of the brain - presenting with AE. Moreover, a highly invasive resection of the tumor was beneficial as a treatment, while other pharmacological treatments lacked sufficient seizure control. The favored drugs (e.g. ethosuximide, valproic acid) for the treatment of generalized absence seizures often target the thalamocortical network, but in some patients they lack efficiency indicating that other brain regions might be at least in some cases participating in epileptogenesis. Based on these studies, our laboratory created two conditional KO mouse models to test the cell type (Purkinje cells and granule cells) and area specific contribution of the cerebellum in AE and generate new animal models for the study of AE. Electroencephalography recordings in freely moving animals of both mouse lines showed no sex difference for AE similar to the widely used mouse models with a typical frequency between 4-9 Hz. Treatment with the commonly prescribed antiepileptic drug ethosuximide (intraperitoneal) significantly reduced the occurrence of ictal events in freely moving animals, while valproic acid lacked efficiency. By applying closed-loop optogenetic stimulation (ChR2 H134R) unilaterally

or bilaterally to the lateral cerebellar nuclei, we were able to stop ongoing seizures with a short (1s) light pulse. Taken together these results show the involvement of the cerebellar network in AE and that cerebellar stimulation could be a new therapeutic target for interventional therapies.

Disclosures: J. Schwitalla: None. **S. Heritze:** None. **M.D. Mark:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.21/J2

Topic: B.10. Epilepsy

Support: Merck Research Laboratories
Cavion, Inc.

Title: CX-8998 and CX-5395, potent, selective T-type calcium channel antagonists suppress seizures in genetic models of epilepsy

Authors: M. S. LEE[1], E. J. NEWBOLD[2], *S. PAPAPETROPOULOS[1]
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Abstract: T-type calcium (Cav3) channels are low threshold voltage-gated channels that regulate neuronal excitability. Cav3 gain-of-function mutants have been identified patients with childhood absence epilepsy (AE) and other generalized epilepsy syndromes. Overexpression of Cav3.1 results in an AE-like phenotype and mice lacking Cav3.1 show resistance to pharmacologically induced absence seizures. Currently approved drugs, including zonisamide and ethosuximide, have been reported to have non-selective Cav3 antagonist activity and while both drugs have shown evidence of efficacy in clinical studies, many patients experience lack of efficacy or intolerable side effects resulting in treatment discontinuation. Thus, selective targeting of Cav3 channels has the potential to improve efficacy and tolerability in indications such as epilepsy where Cav3 is an important component of disease pathophysiology. The objective of the study was to evaluate the efficacy of selective Cav3 antagonists in rodent genetic models of spontaneous AE that show enhanced Cav3 currents and burst-firing during seizures. Potent, selective and state-dependent Cav3 antagonists CX-8998 and CX-5395 were evaluated in two distinct rat models of genetic AE, inbred Wistar Albino Glaxo Rats from Rijswijk (WAG/Rij) and the Genetic Absence Epilepsy Rats from Strasbourg (GAERS). Rats were implanted with telemetric monitors to simultaneously record electrocorticograms. Cohorts of animals received oral vehicle, CX-8998 or CX-5395 at various doses and post-dose recordings were collected and compared to pre-dose baseline. Data were scored with seizure analysis software and results binned into epochs before and after drug administration. Each cohort was averaged and normalized to enable treatment comparisons. Both CX-8998 and CX-5395 dose-

dependently suppressed seizures while vehicle treatment had no effect. In WAG/Rij rats, the ED_{50} for reduction in cumulative time spent in seizure at 4 hours post-dose was 1 mg/kg for both compounds. Higher doses resulted in a longer duration of effect, indicating a minimum threshold for Cav3 inhibitory effects. Cav3 channels are a genetically and pharmacologically validated target for absence seizures and these results demonstrate that potent, highly selective Cav3 antagonists CX-8998 and CX-5395 show dose dependent efficacy in rodent models of AE. These results highlight the potential for selective Cav3 antagonists as a therapeutic option in AE and support their further investigation in a clinical setting. CX-8998 is currently being evaluated in a Phase 2 clinical study in generalized epilepsy syndromes with absences seizures (NCT03406702).

Disclosures: **M.S. Lee:** A. Employment/Salary (full or part-time):; Cavion, Inc. **E.J. Newbold:** A. Employment/Salary (full or part-time):; Cavion, Inc. **S. Papapetropoulos:** A. Employment/Salary (full or part-time):; Cavion, Inc..

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.22/J3

Topic: B.10. Epilepsy

Support: NINDS Grant NS082644

Title: TrkB activation reduces seizure activity in a mouse model of Dravet syndrome via enhanced interneuron function

Authors: *F. GU, I. PARADA, D. PRINCE
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Abstract: Dravet syndrome (DS) is one of the most severe childhood epilepsies and is mainly caused by loss-of-function mutations in *Scn1a* gene encoding Nav1.1 that is predominantly expressed in Parvalbumin-containing (PV) interneurons. Decreased Nav1.1 impairs PV cell function, contributing to neural circuit hyperexcitability and DS phenotypes. Therapy targeting defective PV interneurons is unavailable. The role of BDNF in development and maintenance of interneurons, and previous results showing antiepileptogenic effects of TrkB receptor agonist in a model of posttraumatic epilepsy via improved function of PV interneurons, lead us to hypothesize that early treatment with TrkB receptor agonist might prevent or reduce seizure activity in DS mice by enhancing PV interneuron function. Saline or LM22A-4 (LM), a partial agonist at the BDNF TrkB receptor, was given to DS mice (50mg/Kg I.P.+5mg/Kg intranasal once a day x7d) starting at P13 before spontaneous seizures start. Immunocytochemistry was used to assess the density of perisomatic PV-IR and colocalized PV/gephyrin-IR around layer V

pyramidal cells in the cortex, as well as Nav1.1- and synaptotagmin 2-IR. Whole cell recordings of mIPSCs and sIPSCs were obtained from layer V pyramidal cells to evaluate inhibitory synaptic transmission. Spontaneous seizures were assessed blindly in saline- and LM-treated DS mice monitored 2 days after the last dose of LM during P21-P25. Only seizures with Racine scale 3 and above were included for analysis. Results showed that LM treatment 1) enhanced PV-IR and colocalized PV/gephyrin-IR around pyramidal somata in layer V, indicating an increased number of PV interneuronal synapses; 2) increased Nav1.1- and synaptotagmin 2-IR in PV neurons; 3) increased inhibitory synaptic transmission, indicated by increased frequency of mIPSCs and sIPSCs; and 4) decreased frequency of spontaneous seizures in DS mice. Results suggest that chronic TrkB activation with a partial agonist may be a promising strategy to enhance PV interneuron function and thereby suppress epilepsy and potentially other phenotypes, such as cognitive and social deficits, in DS.

Disclosures: F. Gu: None. **I. Parada:** None. **D. Prince:** None.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.23/J4

Topic: B.10. Epilepsy

Title: Development of a clinically-relevant nonclinical model to investigate recovery of pilocarpine-induced convulsions by benzodiazepines

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Abstract: Benzodiazepines (BZs), such as lorazepam, are the standard-of-care across a broad spectrum of epilepsy types. A number of nonclinical models exist to evaluate the anticonvulsant efficacy of benzodiazepines, such as altered convulsion thresholds in acute chemo-convulsant models or preventing the onset of new convulsive events in recurrent seizure models. However, these models do not mimic the clinical treatment of status epilepticus events, where lorazepam is often administered by the intravenous (IV) route once seizures have already started. The goal of this work was to develop a novel model to assess BZ-mediated recovery from experimentally-induced convulsions that would more closely resemble the use of lorazepam in emergency settings. Pilocarpine, a muscarinic agonist, was selected as the chemo-convulsant because it reliably induces tonic/clonic convulsions in mice in a single experimental setting. Male CD-1 mice (n=18) were pretreated with scopolamine to minimize the peripheral toxicities associated with pilocarpine. Thirty minutes following scopolamine administration, mice were infused via the lateral tail vein with pilocarpine. Animals were simultaneously tethered, via a surgically

implanted jugular vein catheter, to a second infusion pump containing either lorazepam (n=8) or vehicle (n=10). During the pilocarpine infusion, animals were monitored for behavioral signs of convulsion and scored using the Racine Scale by experimenters blinded to the treatment condition. At the onset of tremor, the pilocarpine infusion was stopped and either lorazepam or vehicle infusion commenced immediately. Lorazepam or vehicle infusions continued until mice either recovered from tremors or progressed to clonic convulsions, or a total combined maximum IV volume of 50 mL/kg for pilocarpine and lorazepam was reached. The pilocarpine-threshold to the onset of tremor, latency to tremor recovery and percentage of animals that fully recovered was determined. Pilocarpine tremor thresholds were similar for the lorazepam (299.5 ± 25.4 mg/kg) and vehicle (274.6 ± 16.2 mg/kg) treatment groups. In lorazepam-treated animals, tremor recovery occurred faster and a greater percentage of animals fully recovered from pilocarpine-induced convulsive behaviors (5.1 ± 1.1 minutes and 87.5%, respectively) compared with vehicle (9.0 ± 0.9 minutes and 30%, respectively). These data indicate that it is possible to successfully recover a chemically-induced convulsion via intervention with IV lorazepam, which resembles the clinical treatment strategy for status epilepticus episodes and may be a valuable tool to evaluate new treatment options.

Disclosures: **J.K. DaSilva:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **C. Tyszkiewicz:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **K. Lee:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **D.L. Buhl:** A. Employment/Salary (full or part-time):; Previously Pfizer, Inc. **S.M.G. Goody:** A. Employment/Salary (full or part-time):; Pfizer, Inc.

Poster

289. Anticonvulsant and Antiepileptic Therapies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 289.24/J5

Topic: B.10. Epilepsy

Support: Grupo de Pesquisa e Pós-graduação GPPG/HCPA (Grant # 160265)
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)
Pro-reitoria de Pesquisa -PROPESQ- Universidade Federal do Rio Grande do Sul (UFRGS)
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
BIC-UFRGS

Title: Anodal and cathodal transcranial direct current stimulation (tDCS) effects on convulsions induced in the kindling model by pentylenetetrazole

Authors: ***I. L. TORRES**[1], G. G. REGNER[2], C. DE OLIVEIRA[2], V. L. SCARABELOT[2], D. E. S. RIOS[2], P. PFLÜGER[2], A. SOUZA[2], R. STRÖHER[2], P. PEREIRA[2]

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Abstract: Introduction: About 30 percent of patients with epilepsy are refractory to drug therapy. Thus, the search for non-pharmacological interventions such as transcranial direct current stimulation (tDCS) may be an alternative treatment, isolated or in the combination with anticonvulsants in lower doses. **Objective:** to evaluate the effect of anodal and cathodal tDCS (a-tDCS and c-tDCS, respectively) on seizures induced by pentylenetetrazole (PTZ) in the kindling model using diazepam (DZP) as the gold standard of anticonvulsant. **Methods:** 152 Male Wistar rats (60 days) divided in: Sal-PTZ, DZP3-PTZ, DZP0.15-PTZ, a-tDCS-Sal-PTZ, a-tDCS-DZP0.15-PTZ, c-tDCS-Sal-PTZ, c-tDCS-DZP0.15-PTZ and SHAM-Sal-PTZ. The tDCS groups were submitted to 10 sessions of anodal or cathodal tDCS (0.5mA / 20min) and every 3 days they received saline (SAL) or DZP (0.15mg / kg, ip, alone or in combination with tDCS), DZP (3 mg / kg, ip) 30 minutes before administration of PTZ (50mg / kg, ip), totaling 6 treatments. After PTZ administration, animals were observed for 30 minutes for convulsive behavior: latency for the first seizure (LFS) lasting more than 3 seconds and percentage of seizure. After the last treatment, animals were euthanized and the hippocampus collected to IL-1β, TNF-α, NGF and BDNF levels evaluation. The percent of seizure was analyzed by Fisher Exact test and the LFS by Generalized Estimating Equations (GEE). Biochemical data were analyzed by one-way ANOVA. ($P \leq 0.05$). **Results:** c-tDCS associated to DZP increased the LFS on the fourth and sixth days. IL-1β levels were reduced by c-tDCS alone or associated with DZP. TNF-α and NGF levels were not altered by c-tDCS or a-tDCS. a-tDCS associated to DZP reduced BDNF levels. **Conclusions:** c-tDCS associated to a benzodiazepine is more effective in suppressing seizures when compared to c-tDCS or the drug alone. IL-1β, but not TNF-α plays a role in the inflammation process as a good marker for fully developed seizures. BNDF is a neurotrophin involved in protection mechanisms during seizures in order to keep neurons damaged and even prevent cells from dying. Therefore c-tDCS associated with low dose of DZP has potential antiepileptogenic effect in the kindling model and provides neuroprotection against neuroinflammation.

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Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.01/J6

Topic: B.10. Epilepsy

Support: NIH CTSA TL1TR000141
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Title: High fidelity simulated driving paradigm for identifying EEG features of generalized spike-wave discharges that impair driving ability

Authors: *P. ANTWI[1], B. BANZ[2], C. A. ARENCIBIA[3], J. RYU[6], E. ATAC[7], S. TOMATSU[3], H. KRESTEL[8], J. WU[4], M. CROWLEY[4], F. E. VACA[5], H. BLUMENFELD[6]
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Abstract: Generalized spike-wave discharges (SWDs) are EEG hallmarks of generalized seizures and epilepsies. These epileptiform discharges, most commonly seen in absence seizures, typically last for 3-10 seconds and often impair behavior and/or cognition. Our previous work shows that the amplitude and duration of SWDs on EEG are predictive of performance on the Repetitive Tapping Task (RTT) and the Continuous Performance Task (CPT). The effect of generalized SWDs on more complex behaviors like driving has been investigated in very limited studies with either small sample sizes or by using computerized driving games. Evidence from these studies suggests that generalized SWDs prolong reaction time and impair drivers' abilities to maintain car positions. At the same time, these generalized SWDs may persist as subclinical epileptiform discharges even in "seizure-free" patients who continue to drive, posing a significant challenge to driver licensing authorities, clinicians and patients. Although not clinically observed and not perceived by patients, these subclinical discharges can be accompanied by transient cognitive impairments. There is a need to study the influence of generalized SWDs on driving behavior and safety in high fidelity simulated driving environments and to identify objective EEG features for predicting SWDs that impair driving ability. We have developed a feasible paradigm to test driving ability in patients with generalized SWDs and identify objective EEG features that reliably predict SWDs that impair driving safety. In this paradigm, subjects 15 years or older drive for an hour in a high fidelity, ½ cab driving simulator (miniSim^{TM}) fully instrumented for HD-EEG and video recording. A visual road obstacle is introduced in the driving course every 5 minutes and during every SWD, and the subjects are instructed to slow down and pull over when they notice the obstacle. The driving simulator continuously records vehicle speed (mph), brake force (lbs.), and rate of change for steering wheel angle (degrees/sec.). Further, we compute the reaction time (milliseconds) between obstacle presentation and driver's application of brakes. We compare the aforementioned variables between periods of no SWDs (as controls) and periods with SWDs. With testing of additional subjects, we aim to identify EEG features of SWDs that impair driving. We hypothesize that generalized SWDs that impair driving will have significantly longer duration and higher amplitude on EEG. Our knowledge of these features will advance our

efforts to develop EEG-based objective tools for determining driving safety in patients with epilepsy.

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Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.02/J7

Topic: B.10. Epilepsy

Support: ANPCyT PID 2012-0053
ANPCyT PICT-2014-1966
CONICET PIP 112 201301 00256
UNCuyo SeCTyP 05/C016
UNCuyo SeCTyP 06/C508

Title: Characterization of cross frequency couplings produced by harmonic and non-harmonic frequency bands during seizure activity from intracerebral recordings in patients candidate to epilepsy surgery

Authors: *D. DELLAVALE[1], E. URDAPILLETA[2], N. CÁMPORA[3], O. VELARDE[2], S. KOCHEN[3], G. MATO[4]
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Abstract: Cross frequency coupling (CFC) phenomenon has been proposed to be functionally involved in neuronal communication, memory formation and learning. Besides, experimental findings have shown that phase-amplitude (PAC) and phase-phase (PPC) couplings are important variants of CFC linked to physiological and pathological brain states. In particular, PAC and PPC have been observed in local field potentials (LFP) recorded during epileptic seizures. PPC represents the phase coherence across frequency bands and/or recording sites, which in general increases between nearby areas of the neural tissue recruited to the ictal event. In PAC, the amplitude of a high frequency band is modulated by the phase of another band with a lower frequency content. Recent works have shown that nested oscillations, associated to the

scale free neural activity, and sharp waveforms both produce PAC, however, they reflect two distinct neural mechanisms that are anatomically segregated in the human brain.
In this work, we study the CFC dynamics during the seizure activity in patients with focal epilepsy who were candidates for surgery treatment. The analysis was performed on LFP obtained from 5 patients undergoing intracerebral electroencephalography (stereo EEG) and 2 patients undergoing subdural electrocorticography (ECoG). To quantify the CFC dynamics during the seizure activity we use non-parametric methods: the Phase Locking Value (PLV) and the Modulation Index based on the Kullback-Leibler distance (KLMI). In addition, we have developed specialized tools to characterize the nature of the observed CFC patterns. Specifically, the Time Locked Index (TLI) and Harmonic Index (HI) were implemented to quantify the presence of harmonics associated to the emergence of CFC. Moreover, the correlation of LFP and CFC for a given recording site across seizures was evaluated in order to quantify the seizure stereotypy.
We have found that the ictal activity gives rise to different types of CFC, which were highly stereotyped during the seizure dynamics. Importantly, two essentially different PAC patterns produced by non-sinusoidal waveforms were identified. In the first one, the PAC was elicited by highly cyclostationary (pseudo-periodic) LFP signals, which were characterized by well-defined harmonic spectral components present in their Fourier spectrum. In the second one, the PAC was produced by sharp waveforms constituted by non-harmonic high frequency components. The proposed tools allowed us to better characterize the CFC patterns emerging during the seizure dynamics, which could pave the way to unveil the underlying neural mechanisms that initiate and propagate the ictal activity.

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Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.03/J8

Topic: B.10. Epilepsy

Title: Deep brain stimulation for seizure control: A role for white matter

Authors: *F. SCHAPER[1], B. R. PLANTINGA[2], A. COLON[3], L. WAGNER[4], P. BOON[4], E. GOMMER[1], G. HOOGLAND[1], L. ACKERMANS[1], R. ROUHL[1], Y. TEMEL[2]
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Abstract: *Background*: Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) can improve seizure control for patients with drug-resistant epilepsy. Yet, responder rates

vary highly which is possibly explained by crucial differences in brain stimulation sites.
Objective: We hypothesized that stimulation at the junction of the ANT and mammillothalamic tract (ANT-MTT junction) results in increased seizure control in DBS for drug-resistant epilepsy.
Methods: We retrospectively analysed the location of the active contacts and ANT-MTT junction of 11 patients treated with ANT-DBS for drug-resistant epilepsy. Coordinates and Euclidean distance of the active contact relative to the ANT-MTT junction were calculated and compared between 5 responders (≥50% reduction in seizure frequency) and 6 non-responders (<50% reduction in seizure frequency). Stimulation sites were mapped by modelling the volume of tissue activation (VTA) and generation of stimulation heat-maps.
Results: The mean Euclidean distance of the active contacts to the ANT-MTT was 30% smaller in responders to DBS. VTA models and heat maps indicate that the stimulation hot-spot of responders is located at the medio-ventral ANT in closer vicinity to the ANT-MTT junction compared to the hot-spot of non-responders, located at the dorsal ANT. The Euclidean distance between the centres of stimulation hot-spots was a substantial 3.8 mm.
Conclusions: Our findings suggest that there is a relationship between stimulation site and therapy response in ANT-DBS. The ANT-MTT junction is a potential brain stimulation site for increased seizure control.

Disclosures: B.R. Plantinga: None. **A. Colon:** None. **L. Wagner:** None. **P. Boon:** None. **E. Gommer:** None. **G. Hoogland:** None. **L. Ackermans:** None. **R. Rouhl:** None. **Y. Temel:** None.

Poster

290. Epilepsy: Human Studies

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Program #/Poster #: 290.04/J9

Topic: B.10. Epilepsy

Support: NIH R01 NS092760

Title: Using automated detection and classification of interictal HFOs to improve the identification of epileptogenic zones in preparation for epilepsy surgery

Authors: *T. SOBAYO, S. FARAHMAND, D. J. MOGUL
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Abstract: For more than 25 million patients worldwide who have drug-resistant epilepsy, surgical resection of brain regions where seizures arise is often the only alternative therapy. However, the identification of this epileptogenic zone (EZ) is often imprecise. Several studies have suggested that localized high frequency oscillations (HFOs) detected during iEEG

recording are a way to spatially locate the EZ. Traditionally, HFO detection is carried out through visual inspection of long hours of iEEG recordings. This is a very time-consuming and tedious process. In this study, an automated method for detecting and classifying HFOs based on noise-assisted, multivariate empirical mode decomposition (NA-MEMD) is proposed to identify the high-rate HFO areas in interictal, multi-channel, iEEG recordings. The NA-MEMD outperforms Fourier and Wavelet methods because it is adaptive and produces a set of finite narrowband components. NA-MEMD is also less susceptible than filtering to ringing artifacts. Interictal iEEG data recorded from 10 patients, who subsequently underwent epilepsy surgery at the University Hospital of Zurich, were used in this study. Recordings were made using subdural strip, grid and depth electrodes. Data acquisition was performed using a Neuralynx system with a sampling frequency of 2000 Hz and 0.5-1000 Hz band-pass filtering. Pre-processing of iEEG data involved the measurement of bipolar derivations from adjacent channels to eliminate the confounding effects of common reference signal and volume conduction. Bipolar-derivate signals were then divided into consecutive, non-overlapping, 1 s windows. For each window, NA-MEMD was performed on the time series to detect and classify HFO events; namely, fast-ripple (FR), ripple (R), and fast-ripple concurrent with ripple (FRandR). In each class, channels with high-rate HFO activity (as defined by a rate threshold) were selected as its corresponding HFO areas. To investigate the clinical relevance of the detected HFO areas, the resection ratio (RR) of all three classes of HFO were measured for each patient and then compared with his/her post-surgical outcome. The performance analysis of the proposed HFO detection and classification method resulted in sensitivity equal to 91.08% and false discovery rate (FDR) equal to 7.32%. Based on the obtained RR values for different HFO classes, it was found that patients with high RR for detected HFO-FRandR areas were seizure-free while those with low RR had recurrent seizures. These results support the feasibility of using this methodology to provide an automated algorithm that can be used in concordance with SOZs to better delineate the EZ.

Disclosures: T. Sobayo: None. **S. Farahmand:** None. **D.J. Mogul:** None.

Poster

290. Epilepsy: Human Studies

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Support: Joint US (NSF) German (DRG) Collaborative Research in Computational Neuroscience grant, IIS-1515168
NSF CAREER award, 1351112

Title: Validating cortical surface electrode localization uncertainty with simulation and clinical stimulation

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Abstract: Electrocorticography (ECoG) is an invasive technique currently used to perform seizure onset localization in patients with intractable epilepsy. The location of the ECoG electrodes with respect to a patient's neuroanatomy is critical for planning resection surgeries. However, during implantation of the arrays, brain shift occurs making registration of the preoperative MRI and postoperative CT challenging. Brain shift introduces uncertainty into electrode locations that can propagate through computational models. We aim to quantify the bounds of this uncertainty. We projected ECoG electrodes from the CT into the MRI space with three distinct segmentations approaches. For each segmentation, we used finite element method (FEM) simulations to solve the Poisson equation for the voltage distributions during bipolar stimulation in the brain. Electrode locations between three different segmentation models and their solutions to the bioelectric field model were compared at each of the recording electrodes and to the clinical stimulation recordings. We demonstrated the ability to project electrodes onto the cortical surface and account for brain shift. The Euclidean distance between projected electrodes for the three different models is 0.326 ± 0.057 mm. The projection method for the three different segmentations did not cause a large change in voltage solutions and these voltage profiles match well with the clinical recordings (Figure 1). The small difference in electrode locations for the three projection models did not introduce large uncertainty into the FEM simulations. In the future, further investigation of this uncertainty propagation needs to be addressed related to the spatial distribution of the voltage on the cortical surface instead of the electrode contacts. This will allow for more precise cortical targeting for brain-computer interfaces and improved therapeutic benefit.

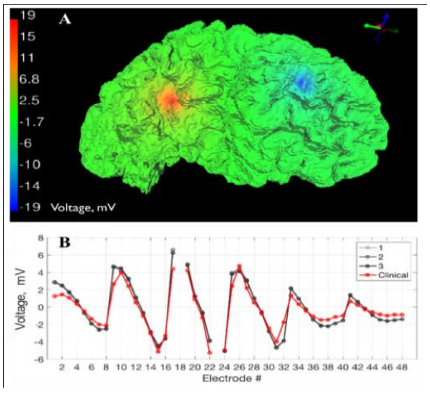

Figure 1. **A.** Representative FEM voltage solution for bipolar stimulation of two ECoG electrodes. **B.** Recorded voltage at each recording contact on the ECoG grids during stimulation for three different electrode projections (1-3) and the clinical recordings (red).

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Poster

290. Epilepsy: Human Studies

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Program #/Poster #: 290.06/J11

Topic: B.10. Epilepsy

Title: A portable 512-channel system for intracranial recording and mapping inclinical epilepsy research and other high-current neural stimulation applications

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Abstract: As the study and treatment of epilepsy progresses, researchers and clinicians require new, advanced tools to pursue important questions and improve the standard of care. The past decades have seen a trend towards increased channel counts in devices for intracranial monitoring, and an increased use of cortical stimulation mapping for surgical planning and research investigations. Many active areas of research into the electrophysiology of epilepsy, for example investigating the network dynamics of ictogenic regions, require the ability to precisely coordinate stimulation and recording across hundreds of implanted electrodes. Over the past ten years we have developed and extensively field tested a portable electrophysiology platform that enables researchers to record and stimulate on hundreds of electrodes. From the beginning, this system was designed to be modular, with a central processor that can be connected to one or more application-specific front ends, and compatible with human use. First generation front ends for this system support recording and stimulating on microelectrodes. Recently we have developed a new front end specifically designed for recording and stimulating on macro electrodes used in epilepsy treatment and research, including intractanial grids, for ECoG and μECoG, and sEEG electrodes. This front end is designed for both research and clinical use and comes in channel counts up to 128. Four 128-channel front ends can be connected to our central processor for a recording capacity of 512 channels. Each bank of 16 channels has a stimulation circuit capable of monopolar (to distant ground) or bipolar (electrode to electrode) stimulation. Stimulation output can be either current-controlled or voltage-controlled and outputs can be programmatically controlled to facilitate complex experiment paradigms. Current output can be specified in 100μA steps up to 15mA, with a max frequency of 10kHz. Voltage output can be specified in 100μV steps up to 15V, with a max frequency of 1kHz.We believe the combination of a large number of recording channels and high-current stimulation output in a single,

programmable interface sets this system apart from others available devices, enabling a wide range of new epilepsy research and offering the potential to substantially improve standard of care for patients.

Disclosures: T. Poulson: A. Employment/Salary (full or part-time):; Ripple LLC. **S. Barrus:** A. Employment/Salary (full or part-time):; Ripple LLC. **A.M. Wilder:** A. Employment/Salary (full or part-time):; Ripple LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple LLC. **S. Hiatt:** A. Employment/Salary (full or part-time):; Ripple LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ripple LLC.

Poster

290. Epilepsy: Human Studies

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Program #/Poster #: 290.07/J12

Topic: B.10. Epilepsy

Title: Dynamics of neuronal activity in the cerebral neocortex during human epileptic seizures revealed by microelectrode recordings

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Abstract: Little is known about the activity of individual cortical neurons during epileptic seizures in humans. We tested a microelectrode array (MEA) implant for safety and efficacy to record single units semi-chronically in epilepsy patients.
We implanted two patients undergoing invasive EEG monitoring with subdural electrodes as part of their workup for epilepsy surgery with an array of 96 microelectrodes arranged in a 4-by-4 mm square (Blackrock array). Recordings were obtained over 180 h (240h, 2nd patient), with short interruptions. Separable action potentials from one or several neurons were present on roughly 50%(60%). MEA recordings were synchronized with the clinical intracranial EEG.
In patient 1, the MEA was situated within the seizure onset zone. Complex activity patterns emerged during seizures. Many neurons showed increased, highly synchronized activity compared to interictal periods. On the other hand, a number of neurons had suppressed activity. Strikingly, activity of individual neurons was very similar across seizures within a cluster. The

patient's typical seizures occurred in clusters, and dozens of seizures were recorded. During discharges of interictal epileptiform activity, single-neuron activity was roughly locked to the spike component of spike-wave complexes. The patient underwent en bloc cortical resection of the right temporo-parieto-temporal junction, including the site of MEA implantation.
In patient 2, the array was located in the arm area of primary sensory cortex, 2 cm away from the seizure onset zone. One seizure was recorded with the MEA. The period leading up to the seizure was characterized by synchronous bursts of action potentials from units across the whole array. These bursts occurred with a frequency of 0.5-1 Hz and lasted until 10 s after seizure onset was detected from clinical EEG. Subsequent action potentials were less synchronized across the array. The MEA was explanted together with the subdural electrodes but no tissue was resected. The patient did not report abnormal somatosensory perceptions related to the array, before or after explantation.
Microelectrode arrays provide unprecedented access to the activity of multiple single neurons in the human neocortex and allow characterizing the dynamics of neuronal activity during epileptic seizures.

Disclosures: J.B. Zimmermann: None. **P. Megevand:** None. **A. Yulzari:** None. **A. Woodtli:** None. **L. Spinelli:** None. **S. Momjian:** None. **M. Corniola:** None. **G.R. Cosgrove:** None. **J.P. Donoghue:** None. **M. Seeck:** None.

Poster

290. Epilepsy: Human Studies

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Topic: B.10. Epilepsy

Support: Swebilius Grant 2018

Title: Noninvasive skin volatilomics for forcasting and diagnosing seizures

Authors: *K. DESHPANDE[1], D. D. SPENCER[4], R. B. DUCKROW[5], H. P. ZAVERI[2], L. HIRSCH[6], T. EID[3]
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Abstract: Purpose: Volatile organic compounds (VOCs) emitted by the mammalian body are typically small molecule intermediates or end products from metabolism of food, drugs, environmental agents and endogenous constituents of the body. Considering that metabolic perturbations are often associated with seizures we explored the utility of measuring VOCs, emitted through the patient's skin, as a novel, noninvasive and highly informative "volatilomic fingerprint" for forecasting of impending seizures and for diagnosis of ongoing, or recently

completed seizures. VOC can be collected in a rapid, easy and pain-free fashion, making the sample type particularly valuable for frequent monitoring of oscillating disease states such as epilepsy. **Methods:** Adult patients (>18 years) admitted to the Yale Comprehensive Epilepsy Program for long-term video-scalp electroencephalogram (EEG) recordings will be recruited for this study. Samples are collected by swabbing the skin with sterile gauze. Swabs will be collected multiple times in triplicates to establish each patient's baseline (interictal) VOC profile. Additional swabs are collected before and after electrographic seizures to capture seizure-associated VOC changes. Swabs will be analyzed by headspace solid phase microextraction-gas chromatography-mass spectrometry (HS-SPME-GC-MS). Multivariate and univariate statistics with correction for false discovery rate (FDR) will be used to identify statistically significant, "candidate markers". **Results:** We have previously shown the utility of this approach in a different species. In this study we identified 187 VOCs. Many of the VOCs correlated with the individuals' major histocompatibility complex (MHC) profile. In the present study we are establishing baseline VOC profiles as well as pre-seizure and post-seizure VOC profiles in patients with epilepsy and non-epilepsy control subjects. Our expectation is to identify a gradual change in the VOC profile in the hours leading up to a seizure and in the hours following a seizure. Some VOC changes are expected to be strongly associated with all seizures in all patients, suggesting that certain metabolic changes or pathways represent common seizure mechanisms. **Conclusions:** The discovery of easily measurable biomarkers of seizures will be significant because: (a) biomarkers of seizure forecasting will facilitate the development of novel, on-demand treatments for epilepsy, and (b) biomarkers of completed seizures, will fill a critical gap in the way seizures are diagnosed, by eliminating the need to capture a seizure by EEG.

Disclosures: K. Deshpande: None. **D.D. Spencer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; principal investigator of the FLARE study funded by Monteris Medical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US patents for the wireless transmission of intracranial electroencephalograms (8165684, 8738139, and 9326726 B2) and focal brain cooling (9849025).. F. Consulting Fees (e.g., advisory boards); member of the scientific advisory board for Monteris Medical. **R.B. Duckrow:** None. **H.P. Zaveri:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US patents for the wireless transmission of intracranial electroencephalograms (8165684, 8738139, and 9326726 B2) and focal brain cooling (9849025). F. Consulting Fees (e.g., advisory boards); member of the scientific advisory board and is a cofounder of Alva Health. **L. Hirsch:** None. **T. Eid:** None.

Poster

290. Epilepsy: Human Studies

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Topic: B.10. Epilepsy

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BMA Research Grants - 2013 Vera Down grant
Epilepsy Research UK (P1201)
Fulbright UK-US commission
NIHR Oxford Biomedical Research Centre

Title: LGI1-IgG levels, subtypes and clinical correlations in faciobrachial dystonic seizures

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Abstract: Autoantibodies to leucine-rich glioma-inactivated 1 (LGI1) are associated with a highly specific focal seizure semiology called faciobrachial dystonic seizures (FBDS), which often predates the onset of cognitive impairment. This condition is exquisitely sensitive to treatment with immunotherapy and early treatment can prevent the onset of cognitive impairment. Here we characterise the LGI1 autoantibodies involved in FBDS and correlate the levels and subtypes of autoantibodies in FBDS patients with or without cognitive impairment. Standardized questionnaires were distributed to an international network of clinicians between 2008 and 2013. Clinical data from 103 consecutive patients with a diagnosis of FBDS and serum LGI1 antibodies were included. LGI1-antibody determination with a novel flow-cytometry assay (FCA) was developed to quantify serum IgG-subclass deposition on live HEK293T cells with stable-express of membrane-tethered LGI1-EGFP. ADAM22 co-transfection and soluble LGI1 were used for internalisation experiments. All patients underwent informed consent (approval REC16/YH/0013). The novel flow-cytometry assay performed well in comparison to a cell-based assay (CBA) and allowed quantification of LGI1-IgG levels and subtypes. Patients with FBDS alone had LGI1 autoantibodies of predominantly IgG4 subtype and a near absence of the IgG1 subtype. Patients with FBDS and cognitive impairment showed a clear increase in the IgG1 subtype. Mechanistically, LGI1-IgGs are able to cause internalisation of its target membrane bound receptor ADAM22. We demonstrate that total LGI1-IgG autoantibodies and its IgG1 subtype are elevated in FBDS patients who present with cognitive impairment. This implicates complement activation and neuroinflammation as a possible mechanism, which ultimately leads to cognitive impairment in FBDS. Furthermore, patient serum is able to induce internalisation of

ADAM22, a membrane bound receptor of LGI1, suggesting the presence of a second and possibly reversible mechanism in the pathogenesis of FBDS.

Disclosures: M. Bi: None. **J. Thompson:** None. **A.G. Murchison:** None. **M. Makuch:** None. **S.R. Irani:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-applicant and receives royalties on patent application WO/2010/046716 entitled 'Neurological Autoimmune Disorders'.

Poster

290. Epilepsy: Human Studies

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Program #/Poster #: 290.10/K1

Topic: B.10. Epilepsy

Support: NSF 1539068
NSF 1701049
NIH P41EB018783 (NIBIB)

Title: Safety of transcranial focal stimulation (TFS) via tripolar concentric ring electrodes (TCREs) in people: Initial results

Authors: *L. M. MCCANE, P. STEELE[1], J. MERCIER[2], D. J. MCFARLAND[4], W. G. BESIO[3]
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Abstract: The incidence of epilepsy in the US alone is 1 in 26. Over 120 experiments using transcranial focal stimulation (TFS: 300 Hz biphasic pulses, 1-2 min) via tripolar concentric ring electrodes (TCREs) have demonstrated: reduced or abolished electrographic and behavioral activities of induced seizures and status epilepticus in three rat models (pilocarpine, PTZ, penicillin, (Besio, 2013)); prevention of electrical amygdaloid kindling in naïve cat brains (Valds-Cruz, 2015); pain blocking (Besio, 2016); and prevention of glutamate release (Santana-Gómez, 2015). TFS in rats did not cause skin damage or affect memory (Besio, 2013). Here, we report the initial, and encouraging, safety results of applying TFS in healthy people.
TFS safety is being tested on participant's skin and behavior during 3 sessions (S1, S2, S3) about 1-week apart. At S1, participants rate each step of the electrode application process on the arm and scalp for pain (0-10, none to worst) and the experimenter rates skin erythema (Draize scale, 0-4; no change-beet red, Guartienti, 2014) (NuPrep cleansing gel; Ten20 EEG paste; gel + paste; gel + paste + TCRE; gel + paste + TCRE + TFS or SH for 2 mins). Baseline (BL) performance on a working memory task (WMT: 5-min each of 2-back and 3-back) is recorded before scalp TFS or SH while 16 channels of EEG are collected at 512Hz (t-Interface 20, g.USB amplifier

and BCI2000) over the left prefrontal cortex (8 TCRE signals (tEEG), and 8 emulated EEG (eEEG, Makeyev, 2013)). TFS or SH is applied at F3. At S2 they perform a BL WMT, TFS or SH is delivered, then, they perform the WMT at 3 post-intervention time points (in mins: T0, T20 and T40). At S3, they perform the WMT at the 3 time points.
Ten healthy participants have completed the study (6M, 4W, mean age = 32, 6 SH, 4 TFS). Only 1s have been reported for pain (arm: 1 gel, 1 paste; scalp: 1 each for the last 3 scalp steps, 1 at SH at S2) and erythema (4 Draize 1s for NuPrep step: 3 at AF3, 1 arm). There is no significant difference between the TFS and SH groups (Wilcoxon rank-sum) in accuracy (%C) or reaction time (RT) of the WMT at the 3 BLs and 3 S2 and S3 time points (9 block %C (mean ± SD): SH, 86.1 ± 0.11, range 62-100; TFS: 81.6 ± 0.12, range 55-96; mean RTs: SH, 394ms ± 106 SD, range 201-650; TFS: 445ms ± 155, range 280-699). WMT %C and RT change from S2 to S3 between groups are not significantly different. Within subject t-tests of %C and from S2 and S3 are not significant. Significant differences (Wilcoxon rank sum) in tEEG amplitude at F3 (unfiltered, 3-40Hz) between TFS and SH were found for BL2 and S3 T0 ($p<0.05$). These preliminary results indicate TFS is safe in people. Further study will determine if TFS has beneficial effects in people with neurological disorders.

Disclosures: L.M. McCane: None. **P. Steele:** A. Employment/Salary (full or part-time):; CREmedical Corp. **J. Mercier:** None. **D.J. McFarland:** None. **W.G. Besio:** A. Employment/Salary (full or part-time):; CREmedical Corp. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CREmedical.

Poster

290. Epilepsy: Human Studies

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Topic: B.10. Epilepsy

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Doris Duke Foundation Clinical Scientist Development Award #2015096

Title: Temporal evolution of features of high-frequency oscillations in human epilepsy

Authors: *J. SCOTT, B. HUNT, S. GLISKE, W. STACEY
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Abstract: High-frequency oscillations (HFO) are a promising biomarker of human epilepsy. Increased HFO rates are associated with epileptogenic tissue, and many studies show improved surgical outcomes for resective surgeries targeting pathological tissue with high HFO rates. However, there has been only limited research on the role of signal features of the HFOs. One of the reasons for this is the difficulty in acquiring large numbers of HFOs to allow rigorous evaluation of signal features. In this study, we utilized a validated HFO detection algorithm to identify over 10 million HFOs in 40 patients with intracranial EEG recordings over multiple days. We used this database to analyze HFO rates and features as a function of time, and correlated results with sleep stage. The analysis used a variety of statistical and machine learning methods to determine any temporal correlation of HFOs through seizure onset and beyond. Our findings in general show a wide variation in temporal trends of HFOs between patients. We found that preictal HFO rates were not predictive of imminent seizure onset in most patients. There were no HFO features that consistently indicated seizure onset zone in different patients. However, in many patients there were specific HFO and EEG background features that correlated with seizure onset zone, and which evolved as seizures approached. These results suggest a temporal correlation between HFOs, EEG background activity, and the specific processes of ictogenesis in individual patients. Further work is necessary to correlate these temporal changes with ictogenic mechanisms.

Disclosures: J. Scott: None. **B. Hunt:** None. **S. Gliske:** None. **W. Stacey:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

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Program #/Poster #: 290.12/K3

Topic: A.10. Development and Evolution

Title: Anatomical evaluation of corpus callosum in MS patients mr images

Authors: *A. D. AYDIN KABAKÇI[1], M. BUYUKMUMCU[1], D. AKIN[2], N. POYRAZ[3], A. UCA[4]
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Abstract: INTRODUCTION
The corpus callosum (CC) is the largest interhemisferic commissural pathway which connecting cortial and subcortical areas of cerebral hemispheres. The brain structures especially CC have a tendency to be affected by morphological changes in the development and growth process. With the usage of tractography and functional MR; its much more easy to understand neurological development process and possible local effection of the brain by neurodegenerative diseases. This study had been planned to investigate morphological changes that can be occured on corpus callosum caused by MS.

MATERIAL AND METHODS
This study was conducted on restrospective images of 50 patients (20 males and 30 females) whom applied to University of Necmettin Erbakan, Faculty of Meram Medicine, Neurology Clinic with Relapsing-Remitting Multiple Sclerosis (RRMS) diagnosis, defined as RRMS or treated for RRMS. We measured many parameters related CC and distance between CC and surrounding structures on midsagittal MRI images. We assessed whether there was a relationship between the parameters CC was was divided into 7 sub-regions based on Witelson classification. The surface area of the each subregion was measured on midsagittal views.
RESULTS
In conclusion, morphometric changes and its statistical significant has been determined in both corpus callosum and its related surrounding structures ($p<0.05$). The results of our study suggest that CC tend to have frontal localization depending on course of diseaese in male and female patients. Also, positive and negative correlation relation has been determined in the conclusion of the study betweens many parameters. There was no correlation between sexes and measurements of subregion surface area, but there was a negative correlation between age and genu surface area measurement only.
CONCLUSION
When we consider the localization and its function, under the many factors CC may have structural changes. Especially for the diagnosis of the diseases, stractural changes of CC has Hint Point importance. We think that the obtained data from this study could be morphometric data sets for MS patients and a preliminary phase for future studies.
Key Words: Corpus callosum, magnetic resonance imaging (MRI), multiple sclerosis (MS).

Disclosures: A.D. AYDIN Kabakçi: None. **M. Buyukmumcu:** None. **D. Akin:** None. **N. Poyraz:** None. **A. Uca:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.13/K4

Topic: B.10. Epilepsy

Title: Stimulation levels determine amplitude and variability of cortico-cortical evoked potentials following single-pulse electrical stimulation

Authors: *T. DAVIS[1], J. D. ROLSTON[2]
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Abstract: Cortico-cortical evoked potentials (CCEPs) are an electrophysiological phenomenon used to explore functional connectivity in human cortex and cortical excitability in epilepsy

patients. CCEPs are typically produced by manually applying single pulse electrical stimulation (SPES) to electrocorticography (ECoG) electrodes. While these responses are used to infer function and connectivity, lack of automation and variable stimulation parameters limits our understanding of the dose-response features of CCEPs. To better understand these features, we systematically explored the SPES amplitude parameter space in five epilepsy patients. Monopolar stimulation was automatically delivered to 294 electrodes as a single biphasic pulse (0.5 ms/phase). Stimulation levels were varied from 2.5 to 10 mA in steps of 2.5 for a total of 10 trials per electrode at each level. Stimulation location and level were randomized across trials. Data were band-pass filtered at 0.3-250 Hz and recorded at 1 kHz. CCEP amplitude was measured by calculating the mean absolute value from 5 to 100 ms post-stimulation using the trial-averaged waveform. The Pearson correlation coefficient was used to calculate the similarity of CCEP waveform shape across trials and levels as a measure of waveform variability. Comparisons between CCEP amplitude, waveform shape, and stimulation level were made using ANOVA ($p<0.001$). CCEP amplitude approached an asymptote near 7.5 mA as levels increased from 2.5 to 10 mA. The median amplitude (and range) for levels at 2.5, 5, 7.5, and 10 mA was 108 (5-2138), 188 (14-2784), 214 (23-3545), and 222 (22-3194) µV, respectively. Inter-trial and inter-level correlation of CCEP waveform shape was found to be significantly lower (higher variability) at 2.5 mA compared to higher levels. No seizures were evoked at any of the levels in all five patients. Stimulation levels have a significant effect on CCEP amplitude and waveform variability. Amplitudes approached an asymptote at 7.5 mA, suggesting response saturation near this level. Amplitudes were smallest and variability highest at 2.5 mA, suggesting a more probabilistic and varied response at this level, likely from stimulation close to an activation threshold. These findings suggest that levels below 7.5 mA have the risk of generating low amplitude CCEPs with higher variability, which may adversely affect CCEP analysis.

Disclosures: T. Davis: None. **J.D. Rolston:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.14/K5

Topic: B.10. Epilepsy

Title: White matter tract development disrupted in youth with temporal lobe epilepsy

Authors: *W. I. MATTSON[1], M. MORNINGSTAR[1], J. VENTICINQUE[1], S. SINGER, Jr.[1], B. A. FULLER[1], S. GEDELA[3,2], E. E. NELSON[1,3]
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Abstract: Temporal lobe epilepsy (TLE) in adults is associated with profound effects on white matter integrity near seizure foci but also globally (Otte et al., 2012). It is less well understood how this impact is reflected in youth, where brain development is still in progress. Fractional anisotropy (FA), which uses the degree of restriction of water diffusion to infer the location and direction of white matter tracts, has been shown to continue to increase into early adulthood (Lebel et al., 2012). We employed FA to assess how the white matter development of children and adolescents differed between youth diagnosed with TLE and a comparison group without epilepsy. Specifically we were interested in how the association between FA and age was affected bilaterally in five major white matter tracts.

Youth with intractable TLE and comparison youth completed diffusion tensor image (DTI) as part of a larger imaging protocol. DTI imaging was acquired in 64 directions using multi-slice acquisition. Based on anatomical landmarks, DSI studio software was used to bilaterally identify the inferior occipito-frontal fasciculus (IFOF), inferior longitudinal fasciculus (ILF), uncinate (UNC), arcuate fasciculus (AF), and fornix (FX) tracts. Mean FA values for each of these tracts were extracted. Differences in the association between FA values and age were examined within each group and tract.

In preliminary findings from twenty-one comparison youth, age and FA values were associated for the right AF, left and right RIFOF, and right ILF, *r*s = 0.45 - 0.56, *p*s &lt .05, such that white matter integrity increased with age. In contrast, for the TLE group (*n* = 11) no tracts significantly increased in FA with age, *r* = -.39 - .15, *p*s &gt .27, except increasing age approached a significant association with *decreases* in right IFOF FA values *r* = -.53, *p* &lt .10.

These early findings suggest that youth with TLE experience heavily disrupted white matter tract development in comparison to youth without this diagnosis. Of particular concern is that the right IFOF—often linked to attention and visual processing—decreased in the TLE group, which might indicate potential atrophy during a period of major development. With elaboration, these results may elucidate alterations in the trajectory of brain development experienced by youth with TLE. Ultimately this may help identify periods where surgical intervention in intractable TLE patients might best improve clinical outcomes.

Disclosures: W.I. Mattson: None. **M. Morningstar:** None. **J. Venticinque:** None. **S. Singer:** None. **B.A. Fuller:** None. **S. Gedela:** None. **E.E. Nelson:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.15/K6

Topic: B.10. Epilepsy

Support: NRF-2017R1A2B4006903

Title: Increased spectral power and altered functional connectivity in patients with infantile spasms

Authors: G. KOIRALA[1], N.-Y. KIM[1], H. KIM[2], *D. LEE[2,3]
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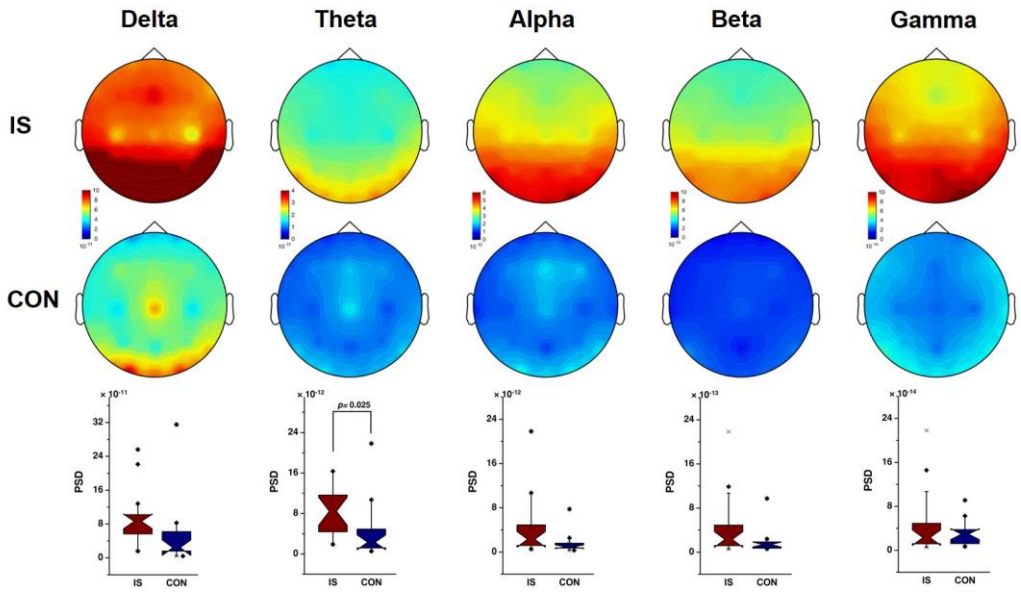
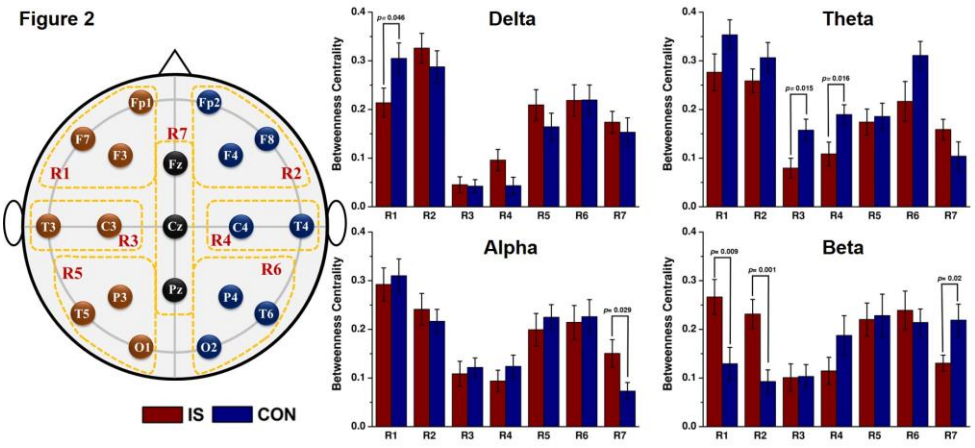
Abstract: This study aims to investigate the changes in spectral power and functional connectivity (FC) in patients with infantile spasms (IS). We examined 19-channel EEG time-series signals in 17 patients with IS and 16 age-matched controls. We extracted 160 noise- and artifact-free preprocessed 2 seconds epochs from each participant. Standard Fast Fourier Transform (FFT) was used to examine the changes in average power spectral density. FC was computed between 19 scalp electrodes using phase locking value. Average betweenness centrality (BC_{av}) in seven brain regions were computed in an acyclic network obtained by utilizing minimum spanning tree (MST) algorithm. Patients with IS showed increased spectral power and significantly increased power (F= 5.527, p=0.025) was observed in theta band (Figure 1). Higher $BC_{av}$was observed in frontal regions, which was significant in beta band and significantly lower (region R1) in delta band. At theta band, both left and right centrotemporalregions (R3 and R4) showed significantly decreased BC_{av}. There was a significant increase in BC_{av}at central node region (R7) in alpha band which was significantly decreased in beta band as shown in Figure 2. These findings suggest that the patients with IS have increased spectral power, especially at theta band and altered topological functional connectivity in different frequency bands as a sign of impaired functional organization of the brain.

Figure 1





Disclosures: G. Koirala: None. **N. Kim:** None. **H. Kim:** None. **D. Lee:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.16/K7

Topic: B.10. Epilepsy

Support: European Research Council (ERC) under the European Union's Seventh Framework Program (FP7/2007–2013)/ERC Advanced grant agreement no. 339244-FUSIMAGINE
ANR-10-IDEX-0001-02
INSERM
PremUp Foundation
Département de la Recherche Clinique et de l'Innovation, Assistance Publique–Hôpitaux de Paris

Title: Functional ultrasound (fUS) imaging of neonate brain activity at bedside characterizes the spatiotemporal propagation of epileptiform activity

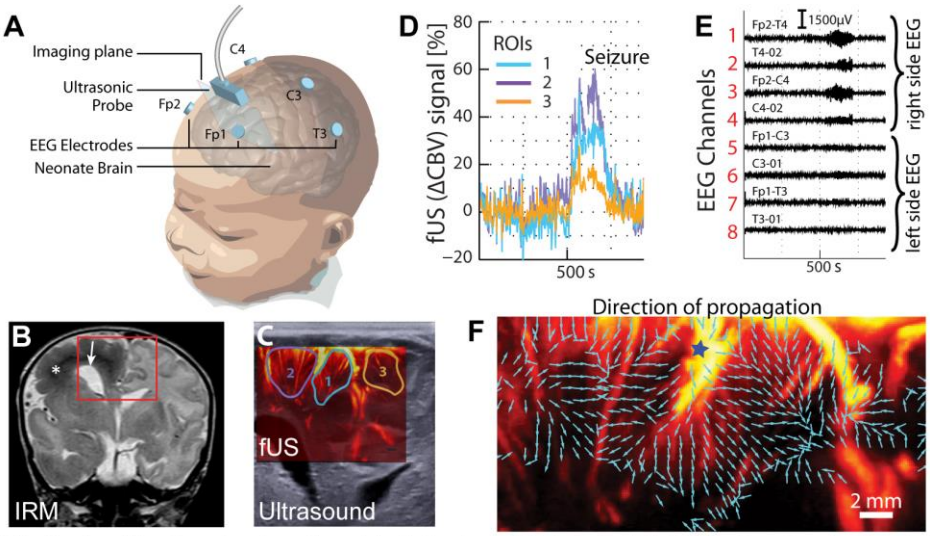
Authors: *C. DEMENÉ[1], J. BARANGER[1], M. BERNAL[1], C. DELANOE[2], V. BIRAN[3], M. ALISON[4], E. HARRIBAUD[2], M. PERNOT[1], M. TANTER[1], O. BAUD[3,5,6,7]
[1]CNRS UMR 7587, INSERM U979, ESPCI Paris, PSL Res. Univ., Inst. Langevin, Paris, France; [2]Neurophysiol. Unit, [3]Neonatal Intensive Care Unit, Assistance Publique–Hôpitaux de Paris, Robert Debré Univ. Hosp., Paris, France; [4]Assistance Publique–Hôpitaux de Paris, Robert Debré Univ. Hosp., Pediatric Radiology Department, France; [5]Promoting Res. Oriented Towards Early Central Nervous Syst. Therapies (PROTECT), INSERM U1141, Univ. Paris Diderot, Paris,

France; [6]Div. of Neonatology and Pediatric Intensive Care, Children's Univ. Hosp. of Geneva and Univ. of Geneva, Geneva, France; [7]Fondation PremUp, Paris, France

Abstract: Neuroimaging of human newborns remains challenging due to their vulnerability. The recent introduction of functional ultrasound (fUS) based on ultrafast imaging for ultrasensitive blood flow detection unveiled a new field of applications in Neuroimaging. Its very high sensitivity (flows down to 1mm/s), temporal (ms) and spatial (~240µm) resolution enabled to image the neurovascular coupling in unprecedented situations such as epileptic seizures [1] or spatial representation in a mobile animal [2]. However, to date those applications have been restricted to small animal studies. Here we present the first fUS imaging study on human neonates.

A custom light-weight ultrasonic probe (128 elements, 6.4MHz) mounted into an in-house newborn headset, and connected to an ultrafast ultrasound research scanner was used to acquire dedicated fUS sequences (650Hz, 370 frames), monitoring the Cerebral Blood Volume variations (ΔCBV) every 1s. The probe was placed on the anterior fontanel in coronal section along with 8 surface electrodes. EEG and fUS were synchronously recorded on 2 full-term neonates with abnormal cortical development associated with drug-resistant epileptic seizure occurring in one cerebral hemisphere.

During epileptic seizures, important blood inflow was detected (ΔCBV up to +70%) in the pathological cerebral hemisphere, whereas quite moderate activity was detected in the contralateral side, consistently with the lateralized ictal activity depicted on the EEG. Not only fUS enabled to observe precisely the seizure moving in different locations of the pathological cortex, but also, during the post-ictal phase associated with electrical spikes on the EEG, fUS imaging recorded slow waves of blood volume changes propagating from precise cortical locations with measured velocity ranging from 1.09 ± 0.11 mm.s^{-1} to 2.80 ± 0.32 mm.s^{-1}, consistent with values of epileptiform spread observed in neocortical brain slices after seizure. Localizing the precise origin of those waves could potentially lead to new therapeutic strategies for Epilepsy.



A Positionning of the ultrasonic probe on the anterior fontanel and EEG electrode. **B** T2-IRM showing enlarged pathological right hemisphere, with abnormal white matter (*) and dysmorphic ventricle (→). **C** Ultrasound Brain imaging (gray) overlaid with fUS imaging (red) and ΔCBV regions of interest (ROI). **D** ΔCBV in the 3 ROIs, with large increase in the right hemisphere (1 and 2) during the epileptic seizure starting at 500s, which is confirmed by the EEG right channels recording (**E**). **F** Based on the spatio-temporal characteristics of the ΔCBV recordings in the right hemisphere, directions of propagation of the epileptic neurovascular activity can be mapped on the brain.

[1] Macé *et al*, Functional ultrasound imaging of the brain, *Nature Methods*, 2011.
[2] Sieu *et al*, EEG and functional ultrasound imaging in mobile rats, *Nature Methods*, 2015.

Disclosures: C. Demené: None. **J. Baranger:** None. **M. Bernal:** None. **C. Delanoe:** None. **V. Biran:** None. **M. Alison:** None. **E. Harribaud:** None. **M. Pernot:** None. **M. Tanter:** None. **O. Baud:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.17/K8

Topic: B.10. Epilepsy

Support: National Institutes of Health NINDS [Award Number R01NS095369]
National Science Foundation DMS [Award #1451384]

Title: Characterizing the relationship between functional connectivity and neurocognitive deficits in benign epilepsy with centrotemporal spikes

Authors: *E. SPENCER[1], D. SONG[2], L. OSTROWSKI[2], C. CHU[2], M. KRAMER[1]
[1]Dept. of Mathematics and Statistics, Boston Univ., Boston, MA; [2]Dept. of Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Benign epilepsy with centrotemporal spikes (BECTS) is a common focal epilepsy disorder characterized by a self-limited period of spontaneous seizures as well as subtle

neurocognitive deficits in children. BECTS patients typically enter remission after adolescence, yet the neurocognitive deficits associated with the disease persist, including language and sensorimotor dysfunction. BECTS provides an interesting model to study functional network reorganization in epilepsy because, while there are no structural lesions, children have a period of abnormal electrical activity in a consistent focal cortical region followed by resolution, allowing for comparison across patients and at different stages of disease. We hypothesize that functional connectivity in the seizure focus is increased in during active periods of epilepsy compared to during in remission or comparable regions in healthy control subjects. Because the seizure onset zone includes the pre and post central gyrus and the superior temporal gyrus, we also hypothesize that functional connectivity in the pre and post central gyrus will correlate with performance on a sensorimotor task, and that functional connectivity within the superior temporal lobe will correlate with performance of a language performance. To examine these hypotheses, we construct functional brain networks from sourced electroencephalography recorded during sleep and compare them to performance in sensorimotor function and language tasks in children with active BECTS, patients in remission and healthy controls. We explore the relationships between functional connectivity and disease status, and between functional connectivity and task performance in the three subject groups. Understanding the functional network changes that accompany neurocognitive deficits in BECTS would further understanding of the disease itself and could provide potential diagnostic avenues for clinical application.

Disclosures: E. Spencer: None. **D. Song:** None. **L. Ostrowski:** None. **C. Chu:** None. **M. Kramer:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.18/K9

Topic: B.10. Epilepsy

Support: CIHR
NSERC

Title: Machine learning based responsive brain stimulation device: An epilepsy clinical trial

Authors: *G. O'LEARY[1], D. M. GROPPE[1], R. GENOV[2], T. A. VALIANTE[3]
[2]Electrical and Computer Engin., [1]Univ. of Toronto, Toronto, ON, Canada; [3]Toronto Western Hosp., Toronto, ON, Canada

Abstract: Purpose and hypothesis: A third of epilepsy patients are not successfully treated with current anti-seizure medications (England, 2012). Implanted closed-loop neurostimulation devices can be used to detect the onset of seizures and use electrical stimulation to prevent their

propagation in the brain. However, existing clinically approved devices use information-limited time-domain biomarkers with limited efficacy, where only 13% of patients achieve seizure freedom for at least a year (Sun, 2014). Recent work has found the use of phase locking values (PLV) between brain regions enable 83% seizure freedom with responsive stimulation in rodents (Salam, 2015), however, its efficacy is yet to be demonstrated in humans. A further challenge involves the patient-specific appearance of seizures due to differences in electrode placement and physiology. To overcome this, data-driven machine learning algorithms can learn temporal patterns in biomarkers on a per-patient basis to more accurately classify seizures and apply contingent neurostimulation. **Methods:** Our recent work has demonstrated NURIP, a neural interface processor for brain state classification, which utilizes the exponentially decaying memory support vector machine (EDM-SVM) algorithm to accurately learn the patient-specific nature of seizures (O'Leary, 2017). The device uses spectral energy (SE) and PLV biomarkers in combination with the EDM-SVM to anticipate seizures and trigger a preventative electrical stimulus. This device will be integrated with clinically approved neural recording and stimulation systems in a clinical trial with 50 patients. **Results:** Initial results using the EU intracranial EEG database (Ihle, 2012) has indicated a seizure sensitivity of 100% and a false positive rate (FPR) of 0.81 per hour over 24 hours. **Conclusions:** Patient-specific classifiers combined with information-rich biomarkers could lead to high-efficacy implantable neurostimulation devices, leading to higher rates of seizure freedom and an increased quality of life for those with drug-resistant epilepsy.

Disclosures: D.M. Groppe: None. **R. Genov:** None. **T.A. Valiante:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.19/K10

Topic: B.10. Epilepsy

Support: NSF DMS #1451384

Title: Linking data to models to estimate potassium ion concentration during a seizure

Authors: *E. SCHLAFLY, U. T. EDEN, M. A. KRAMER
Boston Univ., Boston, MA

Abstract: Potassium ion concentration plays an important role in neuronal excitability. Moreover, changes in extracellular potassium concentration are associated with seizures and other dysfunctional brain states. Yet it remains difficult to characterize these changes *in vivo* from human patients. To address this challenge we propose a computational method to track changes in ion concentration gradients throughout a seizure. This procedure comprises two steps.

First, we apply two automated spike-sorting methods to local field potential (LFP) data recorded during a seizure using a microelectrode array implanted in human cortex, and from these procedures isolate units sorted consistently by both methods. Second, we apply a particle filter algorithm to link these spike train data with a Hodgkin-Huxley-type biophysical model. The particle filter allows us to estimate model parameters, including the time-varying potassium conductance, from which we approximate the extracellular potassium concentration. We demonstrate the ability of the particle filter to estimate and track more than ten parameters in a simulated neuron. We also present parameter estimates from cells recorded during the early onset of a seizure. We propose that the resulting computational tool provides a technique for linking observed spike train activity to unobserved biological phenomena.

Disclosures: E. Schlafly: None. **U.T. Eden:** None. **M.A. Kramer:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.20/K11

Topic: B.10. Epilepsy

Support: NSF DMS 1451384

Title: Organization of high frequency oscillations by low freq activity within and between human seizures

Authors: *J. NADALIN[1], L.-E. MARTINET[3], C. CHU[4], S. S. CASH[5], U. EDEN[2], M. KRAMER[1]
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Abstract: High frequency oscillations (HFO, 140-180Hz) are an important rhythmic activity for brain function and dysfunction. However, the underlying mechanisms and organization of HFO remain largely unknown. Here, we investigate HFO organized in two ways by lower frequency rhythms First, we examine HFO coupling to the low frequency (4-7Hz)phase. We utilize a generalized linear modeling framework to characterize this cross-frequency coupling (CFC), which additionally takes into account the low frequency amplitude of the signal. Second, we examine HFO coupling to interictal epileptiform discharges (IEDs). We detect these IED-HFO events from long duration interictal recordings with an automated algorithm. We apply these analyses of high frequency oscillations tohumaninvivomultiscale recordings, including electrocorticography (ECoG)and microelectrode arrays (MEAs), within and between seizures. Our preliminary results show dynamic changes in cross frequency coupling at seizure onset and termination, notably arise and fall of both phase-amplitude coupling (PAC)and amplitude-

amplitude coupling (AAC), and suggest the co-occurence of HFO and IEDS may serve as a promising biomarker for seizure. A deeper understanding of high frequency oscillations during human seizure may provide insight into seizure mechanisms, and possibly suggest improved therapeutic strategies to treat epilepsy.

Disclosures: J. Nadalin: None. **L. Martinet:** None. **C. Chu:** None. **S.S. Cash:** None. **U. Eden:** None. **M. Kramer:** None.

Poster

290. Epilepsy: Human Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 290.21/K12

Topic: B.10. Epilepsy

Support: NIH NINDS Award R01NS095369

Title: Dynamic functional network analysis during human seizures

Authors: *L.-E. MARTINET[1], E. SPENCER[3], C. CHU[1], E. N. ESKANDAR[2], E. KOLACZYK[3], M. A. KRAMER[3], S. S. CASH[1]
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Abstract: Epilepsy, one of the most common neurological syndromes, is increasingly recognized as involving complex brain network dynamics, making understanding and treating this disease a unique challenge. To address this issue, we have created a data analysis framework to infer and track brain networks through time during spontaneous human seizures. Our method first infers time-dependent functional networks based on the correlation between voltage time series. Then, it applies to the inferred functional networks the Dynamic Plex Percolation Method (DPPM) - a recently developed graph theory algorithm - to identify and track through time well-connected subsets of nodes, known as communities. We apply this framework to invasive human brain voltage recordings (electrocorticogram or ECoG) obtained from patients with intractable epilepsy. We compute the functional networks and dynamic communities observed at seizure onset using both surface grid electrodes and depth electrodes; while the latter provide better subcortical sampling, the neocortical sampling is reduced. We show that our dynamic community tracking method detects network communities related to seizure onset, with consistent characteristics across a patient's seizures. We propose that dynamic network analysis of human seizure data may provide new approaches to improve patient care of medically refractory epilepsy, such as refinements to surgical target identification, surgical outcome prediction and alternative seizure control strategies.

Disclosures: L. Martinet: None. **E. Spencer:** None. **C. Chu:** None. **E.N. Eskandar:** None. **E. Kolaczyk:** None. **M.A. Kramer:** None. **S.S. Cash:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.01/K13

Topic: C.01. Brain Wellness and Aging

Support: Brain Research New Zealand Rangahau Roro Aotearoa
Faculty of Science Research Development Fund, University of Auckland, New Zealand.

Title: The effect of urolithin A on neuronal mitochondrial redox activity, mitochondrial respiration and mitochondrial network

Authors: *J. NG[1,3], T. L. MERRY[2], A. SCHEEPENS[1], W. C. ABRAHAM[4,3], A. J. R. HICKEY[1], N. P. BIRCH[1,3]
[1]Sch. of Biol. Sci., [2]Sch. of Med. Sci., Univ. of Auckland, Auckland, New Zealand; [3]Brain Res. New Zealand Rangahau Roro Aotearoa & Ctr. for Brain Res., Auckland, New Zealand; [4]Dept. of Psychology and Brain Hlth. Res. Ctr., Univ. of Otago, Dunedin, New Zealand

Abstract: Mitochondria play an important role in maintaining neuronal cell health. Dysfunctional mitochondria are a hallmark of the aging brain and are implicated in the onset of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Healthy neuron function is dependent on mitochondrial processes, which include the maintenance of mitochondrial redox state, membrane potential, networks, control of superoxide production and cellular bioenergetics. Therapeutics that target and improve these processes may impede the progression of aging-associated mitochondrial dysfunction. One source of therapeutics that targets brain health appears to come from dietary phytochemicals [1]. Urolithin A (UA) is a bioavailable human gut-metabolite of ellagic acid, which is abundant in pomegranates, and UA has been found to improve muscle mitochondrial function [2]. Here, we investigate whether UA improves neuronal mitochondrial function using an *in vitro* retinoic acid-differentiated human neuroblastoma SH-SY5Y culture model. Physiological human plasma concentrations were tested in the range of 0.2 µM up to 25 µM, and *in silico* predictions indicate that UA crosses the blood-brain barrier [3-4]. Using MTT reduction assays, we measured cell and mitochondrial redox activities. We observed a concentration-dependent biphasic response with an initial increase in MTT reduction at 6 h and 12 h of UA treatment and a decrease at higher doses (10 µM & 25 µM) after 24 h and 48 h of UA treatment. High-resolution respirometry following UA treatment (1 µM for 24 h) revealed increased endogenous cell respiration, mitochondrial complex I and II mediated respiration and maximum respiration, especially at complex II. Live-cell microscopy

shows that UA increases mitochondrial branch length and mean number of branches per mitochondrial network while decreasing the number of fragmented mitochondria. Measures of mitochondrial membrane potential and superoxide production were unaffected by UA. We propose that mitochondrial function is enhanced by UA, most likely at complex II, and UA remodels mitochondrial networks. Our findings suggest a beneficial effect of UA on neuronal mitochondrial fitness needed to prevent mitochondrial dysfunction associated with aging.
1. Vikneswaran M & Mattson M P. *Neurochemistry International* **2015**
2. Ryu D *et al*. *Nature* **2016**
3. Tomás-Barberán F A *et al*. *Molecular Nutrition & Food Research* **2017**
4. Yuan T *et al*. *ACS Chemical Neuroscience* **2015**

Disclosures: J. Ng: None. **T.L. Merry:** None. **A. Scheepens:** None. **W.C. Abraham:** None. **A.J.R. Hickey:** None. **N.P. Birch:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.02/K14

Topic: C.01. Brain Wellness and Aging

Title: Neurological effects of moving from an enriched environment to social isolation in adult mice

Authors: *V. HENG[1], M. J. ZIGMOND[2], R. J. SMEYNE[1]
[1]Neurosci., Thomas Jefferson Univ., Philadelphia, PA; [2]Neurol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: As social animals, our health depends on interactions with others. Yet millions suffer from chronic social isolation (SI), including those living in nursing/assisted living facilities as well as their caregivers. SI also manifests in our criminal justice system, where more than 80,000 people are housed in solitary confinement (SC); defined as segregation from the general prison population for at least 22-23 hours/day for a period longer than 30 days. This condition is known to have toxic physiological and psychological consequences, including depression, stress, cognitive deficits, memory loss, and impaired concentration. Despite these well-known consequences, little is known about the impact of SI on the brain itself. In this study, we have developed a mouse model of SC where animals (C57Bl/6J) are born and raised in an enriched environment (EE) and then as adults (4 months of age) are placed into isolated conditions. After 30 days of isolation, we examined the shape, size, and arborization of neurons in specific regions of the brain selected because of their relevance to known psychological effects induced by SC including alterations in memory (hippocampus), loss of sensory threshold and discrimination (somatosensory cortex) and deficits in motor function (motor cortex). We used a modified Golgi-

Cox method together with confocal microscopy and Neurolucida 360 image analysis to determine the total and average dendritic length per neuron, spine counts, the total neuronal volume, and the extent of dendritic branching. After 1 month of isolation significant differences were observed in the total neuronal volume, with the greatest effect in layer V of pyramidal neurons in the motor cortex. In addition, these changes were sex-dependent, with greater deficits in males. Despite these changes, we do not yet know whether these changes were dependent on the age at which isolation starts, the duration of isolation, are permanent, or alter behavior. We are currently examining the effect of more prolonged isolation (3 months) on these variables, as well as examining if any changes observed after short and prolonged isolation are permanent or can be reversed upon reintroduction to an EE. We hope that these results will then be used to inform public policy, including issues that affect the aging population as well as those that affect the current and future populations housed within the criminal justice system.

Disclosures: V. Heng: None. **M.J. Zigmond:** None. **R.J. Smeyne:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.03/K15

Topic: C.01. Brain Wellness and Aging

Title: Human plasma fraction prevents age-dependent decline in neuronal activity, neurogenesis, and neuroinflammation in C57BL6 mice

Authors: *M. K. CAMPBELL[1,2], C. TUN[2], A. LIU[2], H. HACKBART[2], S. REGE[2], I. GALLAGER[2], S. P. BRAITHWAITE[2], S. MINAMI[2], E. CZIRR[2]
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Abstract: Age-related cognitive impairment is a major unmet medical need that will continue to grow as human lifespan extends. Research using heterochronic parabiosis identified that the circulation of young blood in aged mice can counteract behavioral and histological deficits found in these aged animals. Recent findings from our group and others have shown that human plasma can have similar rejuvenating effects in mice. However, due to the immunogenic effects of plasma between species, these studies have been exclusively performed in immunocompromised mice. We have identified a fraction of human plasma (PF) that surpasses the beneficial effects observed with young plasma in aged NSG mice and show here, for the first time, that this fraction can be dosed safely in aged C57BL6 WT mice. We demonstrate that dosing of PF in WT mice improves neuronal activity, increases neurogenesis, and reduces neuroinflammation. By using WT mice, we are now able to address immune-related questions that were previously confounded by using immunocompromised mice. These findings are an essential step towards

deepening our mechanistic understanding of how circulating factors in the blood could potentially be used as a treatment to ameliorate age-related cognitive decline.

Disclosures: **M.K. Campbell:** A. Employment/Salary (full or part-time):; Alkahest. **C. Tun:** A. Employment/Salary (full or part-time):; Alkahest. **A. Liu:** A. Employment/Salary (full or part-time):; Alkahest. **H. Hackbart:** A. Employment/Salary (full or part-time):; Alkahest. **S. Rege:** A. Employment/Salary (full or part-time):; Alkahest. **I. Gallager:** A. Employment/Salary (full or part-time):; Alkahest. **S.P. Braithwaite:** A. Employment/Salary (full or part-time):; Alkahest. **S. Minami:** A. Employment/Salary (full or part-time):; Alkahest. **E. Czirr:** A. Employment/Salary (full or part-time):; Alkahest.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.04/K16

Topic: C.01. Brain Wellness and Aging

Support: NIH grants NS085568 (LW/SPY), NS091585 (LW), and NS075338 (LW)
VA National Merit grant RX000666 and RX001473 (SPY)

Title: A focal cerebral ischemic stroke model in the aged mouse: Comparative studies between 2-month and 18-month-old ages

Authors: *Z. Z. WEI[1], X. H. GU[1], C. QU[1], R. K. CHIN[1], L. WEI[1], S. P. YU[1,2]
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Abstract: Stroke is a leading cause of human death and disability. Aging and aged populations are the most vulnerable groups to strokes. Previous stroke investigations, however, have often been performed using young adult animals such as 2 to 3-month-old mice and rats. The establishment of an ischemic stroke model suitable for therapy developments using aging and aged rodents is important and necessary in basic and translational stroke research. A focal cerebral ischemic insult targeting the right sensorimotor cortex induces a restrained and well-defined cortical injury with excellent surviving rate and suitable for the examination of neural network repair and functional activities. In this investigation, we tested the similar focal ischemic insult in 18-month-old mice and compared with 2-month-old young adult mice. Animals were subjected to the permanent ligation of the distal branch of right middle cerebral artery (MCA) using a 10-0 suture, paired with bilateral ligations of the common carotid artery (CCA) for 7 min. Cerebral infarct was measured at 1 day and 3 days after stroke. Compared with young adult mice, aged mice had significantly larger infarct volume in the TTC assay. This is accompanied with less GFAP+ reactive astrocytes in the peri-infarct region of aged mice. Meanwhile, there

was significantly higher probability of spontaneous hemorrhagic transformation in the aged brain. The injury caused more severe sensorimotor deficits shown in the corner test and the cylinder test 1 and 3 days after stroke compared with young animals. Furthermore, aged mice with focal ischemia had significantly higher expressions of cytokines such as interleukin (IL)-1β, IL-6, MCP-1, and MIP-1α. Preliminary tests also indicate increased neuronal cell death and increased activation of microglia/macrophage in the ischemic region of aged animals. The RNA sequencing was performed to evaluate differentially-regulated genes and signaling pathways in the young and aged brains. Our data provide information and evidence to explain the distinctive neurological consequences after ischemic stroke at young and old ages. The significant morphological and functional deficits with lower mortality rates of this ischemic stroke suggest that it is an appropriate stroke model for aged rodents and suitable for evaluation of potential stroke therapies under clinically relevant conditions.

Disclosures: X.H. Gu: None. **C. Qu:** None. **R.K. Chin:** None. **L. Wei:** None. **S.P. Yu:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.05/K17

Topic: C.01. Brain Wellness and Aging

Support: Fondo Mixto del Estado de Jalisco FOMIXJAL 2014-01-250508

Title: Inhibitory effects of phenolic compounds on glioblastoma multiforme

Authors: *Y. K. GUTIERREZ-MERCADO[1], E. E. REZA-ZALDIVAR[2], M. A. HERNANDEZ-SAPIENS[2], S. E. OCHOA-HUGO[2], A. L. MARQUEZ-AGUIRRE[2,3], E. PADILLA-CAMBEROS[2], A. A. CANALES-AGUIRRE[2,3]
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Abstract: Introduction: Glioma is one of the most frequent primary brain tumor in adults, and the second one most common in children. Gliomas, especially Glioblastoma multiforme (GBM), is a public health problem affecting 5.6 per every 100,000 inhabitants; with 17,000 new cases per year. Despite advances in transcranial surgeries, radiotherapy and the use of chemical substances use, the average life expectancy after diagnosis is 8 to 15 months. Therefore, is important to find new molecules capable of crossing the blood-brain barrier, to reach the tumor site and promote a citotoxic effect. More than 60% of antitumoral treatments are obtained from natural compounds; some of these are the phenolic compounds (PC) and capsaicinoids, which are plant secondary metabolites. PC and capsaicinoids have antitumoral properties, as well as, anti-inflammatory and antiviral activity, among others. Both the capsaicinoids, which are pungent alkaloids, and the PC, possess high antioxidant activity stated by their chemical structure, due to its antitumor capacity

it is important its investigation to define its use as a possible treatment for GBM. Objective: Determine cytotoxic effect of some enzymatically synthesized PC, (methyl-o-coumaric, propyl-o-coumaric and ethyl-o-coumaric) and capsaicinoids (olvanil, dohevanil and punic acid) on GBM in 3D cell culture. Materials and methodsA 3D cell culture was carried out of the cell line U138 and U87 of GBM, and HBEC5i, L929 as controls; different doses of several enzymatic derivatives of coumaric acids (methyl-o-coumaric, propyl-o-coumaric and ethyl-o-coumaric) and capsaicinoids (olvanil, dohevanil and punic acid), (10, 50, 100, 200, 400, 800 µM) and temozolomide (TMZ) at the same doses as control in order to find LD50. MTT was carried out, as well as an immunofluorescence for caspase 3, TUNNEL and Anexin IV in all the cells lines. CD133, L1CAM was also determined, to verify its expression after PC and capsaicinoids treatment. Results: Some enzymatically synthesized PC, like some derivatives from coumaric acids, methyl-o-coumaric and propyl-o-coumaric, as well as, Dohevanil and olvanil (DL50 100µM and 200 µM respectively) showed a cytotoxic activity much higher tan TMZ (DL 50 800 µM) in order to reach cytotoxicity on GBM 3D culture cells.

Disclosures: E.E. Reza-Zaldivar: None. **M.A. Hernandez-Sapiens:** None. **S.E. Ochoa-Hugo:** None. **A.L. Marquez-Aguirre:** None. **E. Padilla-Camberos:** None. **A.A. Canales-Aguirre:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.06/K18

Topic: C.01. Brain Wellness and Aging

Support: NSFC (31320103906)

Title: Secreted alpha-Klotho overexpressed in the hippocampus alters social behavior and memory formation

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Abstract: Alpha-Klotho belongs to a gene family whose inactivation leads to a phenotype that resembles aging. Here, we present data showing that the expression level of alpha-Klotho protein in the hippocampal formation of mice decreases with age and that overexpression of secreted human alpha-Klotho alters social behavior and memory formation. Specifically, the expression of endogenous alpha-Klotho decreased significantly in the hilus and CA1 regions of the hippocampal formation within 13-month of life. Interestingly, overexpression of secreted human alpha-Klotho in the CA1 area changed the nest building behavior and improved object recognition, object location and conditional fear memories. Moreover, alpha-Klotho

overexpression increased hippocampal synaptic transmission in response to standardized stimulation strengths, altered paired-pulse facilitation of synaptic transmission and enhanced activity-dependent synaptic plasticity. These results indicate that the hippocampal alpha-Klotho expression is declining with age and that memory formation benefits from an augmented level of secreted alpha-Klotho.

Disclosures: D. Li: None. **Y. Chen:** None. **D. Jing:** None. **Z. Liu:** None. **T. Behnisch:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.07/L1

Topic: C.01. Brain Wellness and Aging

Support: CIHR-CVN Grant
Alzheimer Society of Canada Grant
CVN Scholar Award
Jeanne Timmins Costello Fellowship

Title: Inward rectifier potassium channels (K_{IR}) and impaired cerebrovascular dilatory function in mouse models of Alzheimer's disease and cerebrovascular disease

Authors: *M. LACALLE-AURIOLES, L. J. TRIGIANI, M. BOUROUROU, E. HAMEL
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Abstract: Background: Neurovascular coupling (NVC) refers to the tight relationship between local neuronal activity and cerebral blood flow. Neurons, astrocytes, smooth muscle cells (SMCs) and endothelial cells (ECs) all contribute to this process, but the specific mechanisms remain elusive[1]. Potassium (K^+) release by astrocytic endfeet, acting through vascular inward rectifier K^+ channels (K_{IR}), has been proposed as a key effector of NVC, as well as in the upstream signaling from capillaries to arteries[2].
Objectives: We investigated whether the vasodilation mediated by K_{IR} channels in cerebral arteries would be altered in mouse models of *i)* Alzheimer's disease (mice overexpressing a mutated form of the human amyloid precursor protein, APP mice) or *ii)* cerebrovascular disease (mice overexpressing transforming grow factor-β1, TGF mice) compared to wild-type (WT) mice; and whether K_{IR} channels are located only in SMCs or also in ECs.
Methods: Vasodilation was measured in isolated and pressurized segments of the middle or posterior cerebral artery in APP, TGF and WT mice (n=4-5 mice/group, ~7 months old). Dilatory responses were quantified as the increase in diameter in vessels submitted to a myogenic tone (80 mmHg) and exposed to increasing concentrations of K^+ (4-16 mM)[3].

Maximal dilation was determined in calcium free medium. In some vessels, the endothelium was removed to assess the cellular localization of K_{IR} channels in the vessel wall. In other experiments, vessels were incubated with antioxidant (catalase 1000U/mL) or anti-inflammatory (indomethacin, 10µM/L).
Results: In WT mice, K_{IR} channels located on ECs contributed to approximately 50% of the maximal dilation (90% at 16mM K^+). In APP and TGF mice, maximal dilation was reached at 8 mM K^+ (APP=35% and TGF=9%), and then vessels constricted to higher K^+ concentrations. In APP and TGF mice, dilation did not differ in intact vs. EC denuded arteries. Antioxidant treatment rescued K_{IR} channel function in APP mice only, whereas anti-inflammatory treatment was exclusively effective in arteries from TGF mice.
Conclusions: Impaired NVC observed in APP and TGF mice could be, in part, mediated by dysfunctional K_{IR} channels as a consequence of oxidative stress and inflammatory processes in APP and TGF mice, respectively. Our results confirm that K_{IR} channels exist in both SMCs and ECs of brain arteries, each contributing to K^+-induced dilation.
References: 1. Iadecola C, *Nat Rev Neurosci,* 2004;5 (5):347-60; 2. Longden TA et al, *Nat Neuroscience,* 2017; 20 (5): 717-26; 3. Erdös B et al, *Stroke,* 2004; 35: 964-969.

Disclosures: M. Lacalle-Aurioles: None. **L.J. Trigiani:** None. **M. Bourourou:** None. **E. Hamel:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.08/L2

Topic: C.01. Brain Wellness and Aging

Support: CONACyT Grant 572907
CONACyT Grant 252808

Title: Effect of the chronic administration of curcumin on the neuronal morphology and protein expression of the hippocampus and prefrontal cortex in senile mice

Authors: *A. E. GONZÁLEZ, SR[1], S. I. GONZÁLEZ CANO[1], D. GNECCO[2], G. FLORES[1]
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Abstract: In the last years, the number of older people (+65) has gradually increased at a rate of growth due to the advancement in healthcare, which leads to a longer life expectancy. For this reason, it's critical to improve the life quality in elderly, and health research aiming to geriatrics has increased its relevance. It has been postulated that treatments aimed at curbing aging could offer a much greater benefit than those focused on a specific disease. Therefore, it is possible to extend the useful life of an organism through dietary, pharmaceutical or genetic intervention that

modifies its metabolism. Several studies have shown the molecular mechanisms of many natural products and their therapeutic effects. For example, the turmeric (rhizome of the Curcuma longa plant), has different medicinal properties attributed. Curcumin (CUR) (the main active compound of turmeric) helps in the treatment of many diseases, such as Parkinson, Alzheimer, and dementia. The main pharmacological mechanisms attributed to CUR are its antioxidant properties as a scavenger of many oxygen-free radicals, including the superoxide anion and the hydroxyl radical. In this study, we evaluated the effect of a chronic administration of CUR in senile mice, measuring different behavioral and cytological markers related to cognitive processes, that is, Morris water maze and novel object recognition tests to evaluate learning and memory, Golgi-Cox staining to analyze dendritic spine density and neurological morphology, as well as Nissl staining for the stereological analysis of neuronal density and immunofluorescence assay for synaptophysin (SYP), glial fibrillary acid protein (GFAP) and metallothionein 3 (MT3) markers in the hippocampus and prefrontal cortex. The results obtained in the experiments, lead us to conclude that the chronic administration of CUR improved learning and memory capacities of the senile mice. Despite the CUR treatment had no effect in the number of neurons, it generated a restructuring of the cytoskeleton of the pyramidal neurons of the prefrontal cortex and the hippocampus, increasing the length of the dendrites and the density of spines, and increased the synaptic communication observed with the expression of SYP, as well as a decrease in oxidative stress and neuroinflammation. (Supported by: CONACyT grants No. 572907 to AEGG and 252808 to GF).

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Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.09/L3

Topic: C.01. Brain Wellness and Aging

Support: NRF (National Research Foundation of Korea) 2017R1D1A1B03030567

Title: Long term ingestion of drinking water containing sodium pyruvate prevents brain or neuronal damages in the models of epilepsy

Authors: *J.-Y. LEE, M. KIM, S. PARK, H. SON
Asan Inst. for Life Sci., Seoul, Korea, Republic of

Abstract: A large amount of study has demonstrated that sodium pyruvate (SP) has the potential neuroprotective activity in a variety of brain disorders. Most of the studies, however, showed that SP could significantly reduce brain damage or improve neurological impairments when it was

intravenously or intraperitoneally given at a large bolus dose immediately before or after the insults.
This study was performed to evaluate the effects of the long routine drinking of SP-containing water on brain or neuronal damages following epileptic insults. We found that pretreatment of neuronal cells with SP markedly increased cell viability or reduced cell death following exposure to kainate, glutamate, H2O2, etc. For in vivo animal study, we allowed mice free and routine access to SP-containing water for 6 months, and then subjected them to kainate-induced epileptogenesis. The progress or severity of seizure development, behavior or motor performance, and neuronal cell death were monitored and assessed following kainate treatment, in comparison with those of saline-ingestion groups. This study would uncover the preventive actions of long routine diet of SP against brain aging or neurological damages in brain disorders such as epilepsy or stroke.

Disclosures: J. Lee: None. **M. Kim:** None. **S. Park:** None. **H. Son:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.10/L4

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01 EB003268
CIHR Grant FRN 119312

Title: Investigating the potential of dexamethasone to modulate focused ultrasound-mediated increases in blood-brain barrier permeability

Authors: *D. MCMAHON[1,2], W. OAKDEN[1], K. HYNYNEN[1,2]
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Abstract: Therapeutic treatment options for diseases of the central nervous system are greatly constrained by the presence of the blood-brain barrier (BBB). Focused ultrasound (FUS), in conjunction with circulating microbubbles, can be used to induce a targeted and transient increase in BBB permeability, providing a unique approach for the delivery of drugs from the systemic circulation into the brain. Preclinical research has demonstrated the utility of FUS; however, recent work has shown that an acute inflammatory response accompanies this increase in BBB permeability. While the magnitude and duration of this response is relatively small when compared to alternative interventions, it may become a concern for the treatment of diseases that require multiple FUS exposures in short succession, as deleterious effects may accumulate. Dexamethasone (DEX), a corticosteroid, has anti-inflammatory properties and is known to

rapidly reduce BBB permeability in brain tumours. Work presented here demonstrates that DEX administration following FUS may have value in modulating the duration and degree of increased BBB permeability. For this work, male Sprague Dawley rats received unilateral hippocampal sonication; BBB permeability was assessed 15 minutes later by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI). Following imaging, animals received either DEX (10 mg/kg; intraperitoneal) or saline and were imaged again 2-3 hours later. Results indicate that a single dose of DEX induces a significant reduction in Ktrans hours after FUS, relative to Ktrans measured shortly following sonication. While further work is necessary, a more rapid return of BBB permeability to baseline, combined with the anti-inflammatory properties of DEX, may lead to a reduction in the magnitude of acute inflammatory response following FUS. This may provide greater clinical flexibility for FUS, allowing repeated treatments in short succession due to the reduced risk for deleterious effects to accumulate.

Disclosures: D. McMahon: None. **W. Oakden:** None. **K. Hynynen:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.11/L5

Topic: C.01. Brain Wellness and Aging

Support: BBSRC
MS Society of the UK

Title: The GSK3 inhibitor AR-A014418 promotes oligodendrogenesis in adult white matter

Authors: *F. PIEROPAN, A. M. BUTT, A. D. RIVERA
Univ. of Portsmouth, Portsmouth, United Kingdom

Abstract: Oligodendrocytes (OLs) are the myelin-forming cells of the central nervous system (CNS). Myelin insulates axons enabling rapid communication and its loss is the hallmark of demyelinating diseases such as multiple sclerosis (MS). Myelinating OLs are generated from precursors (OPCs) throughout life, under the control of multiple intrinsic and extrinsic factors. In the developing forebrain, OLs are generated from OPCs originating from neural stem cells (NSC) of the dorsal subventricular (SVZ). Previously, using a pharmacogenomic analysis of the dorsal SVZ, we determined that the GSK3β inhibitor AR-A014418 promotes oligodendrogenesis in the developing SVZ. Here, we have examined the effects of AR-A014418 on the generation of OLs in adult white matter of the mouse optic nerve. Sox10-eGFP mice were used to identify OLs and OPCs; mice were killed humanely in accordance with the Home Office Animals (Scientific) Act 2012 (UK), and optic nerves isolated with retina intact. Nerves were maintained ex vivo in organotypic culture in control medium or medium containing 20 μM AR-A014418. After 3 days

in vitro (DIV), optic nerves were analysed by confocal microscopy, immunohistochemistry, microarray, and qRT-PCR. AR-A014418 dramatically increased the number of Sox10+ cells in the adult nerve; Sox10 is expressed by both OLs and OPCs, but only the latter are proliferative, indicating that AR-A014418 promoted oligodendrogenesis in adult OPCs. Genomic analysis identified the Rho-GTPase pathway acting via Rac1 and Cdc42 as the key mechanisms of action of AR-A014418. The results demonstrate that AR-A014418 promotes oligodendrogenesis in adult white matter and indicates GSK3β inhibitors are potential therapeutics in demyelinating diseases such as MS. A.D. Rivera and A.M. Butt report to be shareholders in in the company GliaGenesis.Supported by the BBSRC and Multiple Sclerosis Society of the UK

Disclosures: F. Pieropan: None. **A.M. Butt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gliagenesis. **A.D. Rivera:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gliagenesis.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.12/L6

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant AG040261

Title: Interference with dopamine neurotransmission in substantia nigra affects movement frequency without striatal involvement

Authors: *M. F. SALVATORE[1], T. R. MCINNIS[2], K. E. LANZA[3], C. R. BISHOP[3]
[1]Inst. for Healthy Aging, Univ. of North Texas Hlth. Sci. Ctr., Ft Worth, TX; [2]Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX; [3]Psychology, Binghamton Univ., Binghamton, NY

Abstract: With aging, a significant risk of motor impairment, including bradykinesia, exists for those age 65 and older, affecting 15% of those age 65 to 30-50% by age 80. Unlike PD, the primary neurobiological basis for impaired movement initiation associated with aging may not be related to changes in dopamine (DA) biosynthesis in the striatum, given <15% loss of tyrosine hydroxylase (TH) in the human lifespan. We recently reported that calorie restriction prevented aging-related motor decline in male rats, which was associated with tyrosine hydroxylase (TH) expression decreased in striatum, but increased in substantia nigra (SN). Furthermore, pharmacological inhibition of TH activity in striatum did not reduce movement frequency in an open-field. Nigral neuron loss in older adults is associated with daily physical activity. We tested the hypothesis that nigral DA neurotransmission could affect motor performance in male rats by two approaches. First, we verified the TH inhibitor alpha-methyl p-tyrosine (AMPT) and DA

transporter inhibitor, nomifensine, reduced DA tissue content or increased extracellular DA levels in SN, respectively. The inhibition of TH emulated aging-related DA loss in young rats, without effect in striatum. In the opposite direction, nigral nomifensine increased extracellular DA, with no coincident change in striatum. In separate cohorts, bilateral guide cannula were implanted to target infusions to the ventrolateral SN to enable direct nigral infusion of AMPT or nomifensine. Movement frequency and speed were evaluated following nigral saline infusion (as the control) versus that following infusion of AMPT or nomifensine in a within-subjects design. In young 6 month old rats, movement frequency was significantly reduced following nigral AMPT infusion, consistent in a time period following AMPT -mediated DA reduction. Conversely, nigral blockade of DA uptake via nomifensine, in young and aged rats, increased movement frequency following infusion. Taken together, these results support an essential and unique contribution of nigral DA to movement frequency that may be important in age-related decline in motor impairment and, by extension, its improvement.

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Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.13/L7

Topic: C.01. Brain Wellness and Aging

Support: Dorothy Goodwin Scholars Program
University of Hartford

Title: Effects of probiotics on Alzheimer's disease progression: Assessing cognitive and cellular markers

Authors: *D. MEDEIROS, K. MCMURRY, N. BUITRAGO, C. LYONS, A. TANG, A. SILVER, P. SACCHETTI
Univ. of Hartford, West Hartford, CT

Abstract: Alzheimer’s disease (AD) is the sixth leading cause of death within the United States and the projected number of affected individuals is on the rise. Currently, no effective treatments have been identified, but the rise in costs and number of affected patients requires identification of easily accessible and affordable strategies to help manage symptoms. Recently, there has been growing interest in the gut-brain axis (GBA), a bidirectional communication system between the brain and the gastrointestinal system, for its potential impact on brain health. The gut microbiota, microorganisms populating the gut, plays an essential role in the host health and microbial imbalances (dysbiosis) have been correlated to several neurodegenerative disorders. We sought

to explore probiotics as a potential therapeutic treatment for Alzheimer's disease in a triple transgenic mouse model (3xTg-AD). In a preliminary study, probiotic treatment decreased cell death and normalized the number of $GFAP^+$ cells present in AD mice. Due to the abnormal behavior of control animals, we repeated the experiment with a new cohort of mice to confirm our original findings. Here, AD mice received a control diet (ADC; n=5) or a diet supplemented daily with probiotic strains *Lactobacillus curvatus* and *Lactobacillus plantarum* (ADP; n=5) and were compared to wild-type mice on control diet (B6129SF2J-1 - WTC; n=5). Behavioral analysis using the Barnes Maze indicated a decreasing trend in escape latency of ADP mice in comparison to ADC mice after 12 weeks. Upon completion of the probiotics treatment, mice were sacrificed and immunohistological analysis was performed on brain tissue. ADC mice showed an overall decrease in total number of $DAPI^+$ cells and a correlated decrease in neurons ($NeuN^+$), while increases in amyloid $beta^+$- and $GFAP^+$-cells were detected. In comparison, AD mice treated with probiotics showed higher cell counts for $DAPI^+$ and $NeuN^+$. Further assessment of the effects of probiotics on all cell populations is being conducted. Overall, our results point toward a beneficial effect of these probiotics on AD pathology progression, possibly driven by a mitigation of the previously reported dysbiosis in the current AD model.

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Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

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Program #/Poster #: 291.14/L8

Topic: C.01. Brain Wellness and Aging

Support: NIH AG040261
Institute for Healthy Aging, UNT Health Science Center

Title: Decreasing rest intervals within a moderate exercise regimen boosts efficacy to prevent aging-related motor decline

Authors: *E. A. KASANGA[1], T. MCINNIS[1], M. F. SALVATORE[2]
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Abstract: A physically active lifestyle can decrease the risk of aging-related impairments, including the prevention of motor decline similar to Parkinsonism. However, the extent to which a controlled exercise regimen will be beneficial, especially when started in well into the latter half of the lifespan, and the balance of exercise to rest periods needed to reduce aging-related locomotor impairment has not been fully elucidated. Furthermore, a number of exercise studies

show no change in striatal dopamine regulation despite motor improvement. A moderate intensity treadmill exercise regimen of equal exercise and rest periods, initiated at 18 months of age in Brown-Norway/Fischer 344 F1 hybrid (BNF) rats attenuates aging-related motor decline after 5 months of exercise. However, the same regimen initiated in 24 month old rats does not reverse motor decline, suggesting neurobiological changes associated with aging can limit exercise efficacy. Increasing the frequency of exercise is one variable that may be easily altered and evaluated for possible exercise benefit in older rats. A controlled longitudinal exercise study (without any negative reinforcement) was conducted with an increased frequency of exercise (15 days of exercise followed by 5 days of rest wherein we evaluated locomotor activity daily) in sedentary 18 month old BNF rats for 5 months to evaluate if an increased frequency and decreased rest period could lead to a more rapid and sustained recovery in motor function. Exercise attenuated the rate of decline in movement frequency. As compared to an identical exercise regimen, but with a longer rest period, the shorter rest period led to a faster onset and sustained effect of exercise to prevent locomotor decline. The exercise group exhibited a 25 % increase in nigral tyrosine hydroxylase (TH) with no significant effect on striatal TH. Taken together, our results indicate that exercise can be initiated in advanced middle age and reduce aging-related decreases in movement frequency, which may be related to the prevention of aging-related loss of TH in the substantia nigra. Our results suggest that moderate exercise, if practiced consistently, is an effective lifestyle strategy to prevent aging-related motor impairment.

Disclosures: E.A. Kasanga: None. **T. McInnis:** None. **M.F. Salvatore:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.15/L9

Topic: C.01. Brain Wellness and Aging

Support: P51 OD-011092
P30 AG008017
Intramural Research Program, National Institute on Aging
ARCS Foundation Oregon
AG-043640

Title: Calorie restriction prevents age-associated increase in amyloid beta in aged rhesus macaques

Authors: *G. A. STONEBARGER[1,2], H. F. URBANSKI[1,2], R. WOLTJER[3], K. VAUGHAN[4,5], E. M. TILMONT[4], J. A. MATTISON[4], P. L. SCHULTZ[6], S. M. CALDERAZZO[6], D. L. ROSENE[6], S. G. KOHAMA[1]

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Abstract: Calorie Restriction (CR) has been shown to extend maximum life span and reduce the prevalence of several age-related diseases in a variety of species. However, it is unclear whether CR can delay the onset of age-related neuropathologies, such as the accumulation of amyloid beta (Aβ) plaques found in Alzheimer's Disease (AD). To address this question, we used immunohistochemistry to examine Aβ levels in the prefrontal cortex (PFC) of rhesus macaques, aged 20-41 years (old to oldest-old). Postmortem brains were collected from animals belonging to a longitudinal CR study conducted by the NIA Intramural Research Program. Both male and female control (CON; n=6) and CR (n=8) monkeys were included. CON animals were fed approximately ad libitum, whereas CR-treated animals were fed at 80% of their normal intake of a nutritionally complete diet. We tested the hypothesis that CR would prevent accumulation of plaques using an antibody specific for Aβ (4G8). Like humans, old rhesus monkeys exhibit an age-associated increase in Aβ plaques in the gray matter of the PFC, a brain area that is especially susceptible to aging effects. Aβ density was quantified by calculating the percent area of gray matter surrounding the central sulcus that was occupied by Aβ. Using regression analysis, we found an age-related increase in percent area occupied by Aβ ($F[1,11]=6.54$, $p<0.03$, $R^2=0.37$); however, this increase was found to be driven by CON ($F[1,4]=15.39$, $p<0.02$, $R^2=0.79$). Critically, there was no statistically significant increase in Aβ in the CR-treated animals ($F[1,5]=0.33$, $p>0.10$, $R^2=0.33$). This suggests that chronic CR can have a protective effect against age-related increase in Aβ in susceptible brain regions in the nonhuman primate, and in the human may be able to delay development of AD.
Supported by NIH Grants: P51 OD-011092 (SGK), P30 AG008017 (RW) & AG-043640 (DLR). GAS is additionally supported by ARCS Foundation Oregon. Funded, in part, by the Intramural Research Program, National Institute on Aging, NIH.

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Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.16/L10

Topic: C.01. Brain Wellness and Aging

Support: USDA ARS
The Robert and Margaret Patricelli Family Foundation

Title: *In vitro* effects of a polyphenol-rich blue berry extract on adult human neural progenitor cells

Authors: *T. ZHENG, D. F. BIELINSKI, D. R. FISHER, B. SHUKITT-HALE, D. A. STEINDLER
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Abstract: The aging process affects all cells within the central nervous system, including neural stem cells. Significant declines in neurogenesis could contribute to neuronal dysfunction in aging. Pathology of aging and age-related neurodegeneration has been linked to increases in brain oxidative stress as well as inflammation, leading to interest in the protective effects of plant polyphenols, which possess both antioxidant and anti-inflammatory properties. Berries, including blueberry and strawberry, are rich in polyphenols and have been shown to improve cognition and memory in both aged animals and humans. While our previous studies have shown that blueberry and strawberry supplementations can increase neurogenesis in aged rodents, it is not clear whether this can be extrapolated to humans. We thus investigated the effects of berry fruit treatments on the viability, proliferation, and fate choice of adult human neural progenitor cells (AHNPs) that are neurogenic astrocytes potentially involved in memory and other brain functions. AHNPs from both control and Parkinson's disease (PD) patients, isolated and characterized previously in our lab, were used here as an *in vitro* model for testing the effects of berry extract on human neural progenitor cells. AHNPs were cultured in N2 medium plus 5% fetal bovine serum, bovine pituitary extract and growth factors. Blueberry extract was prepared by homogenizing blueberries with deionized water (1:1 w/v) followed by centrifugation and freeze-drying. AHNPs were treated with blueberry extract at concentrations from 0.1 to 0.5 mg/ml for 5-7 days. The viability of cells was examined using the Trypan Blue exclusion method, and proliferation was evaluated using the ethynyl-deoxyuridine (EdU) assay. A subset of treated cells was labeled with antibodies against neuronal markers to examine the differentiation of these cells. To determine whether blueberry could protect AHNPs from induced oxidative stress by dopamine (DA) present in the media, some pre-treated cells were exposed to DA for 2 hours; their viability, proliferation, and calcium buffering were then examined. Our data show that blueberry has beneficial effects on the viability and proliferation of both human control- and PD-AHNPs. The extract was also able to reverse a decrease in viability, proliferation, and calcium buffering following stress induced by DA. Polyphenol-rich berry extracts thus confer a neuroprotective effect on control and Parkinson's AHNPs, suggesting a role for dietary nutrients in helping to prevent and slow progression of neurodegenerative diseases.

Disclosures: T. Zheng: None. **D.F. Bielinski:** None. **D.R. Fisher:** None. **B. Shukitt-Hale:** None. **D.A. Steindler:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.17/L11

Topic: C.01. Brain Wellness and Aging

Support: USDA Intramural
WBANA

Title: The effects of intermittent wild blueberry feeding on inflammation and motor and cognitive behavior

Authors: D. R. FISHER, D. S. CAHOON, M. G. MILLER, D. F. BIELINSKI, *B. SHUKITT-HALE
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Abstract: Neuroinflammation has been identified as a major contributing factor in the behavioral declines seen in aging and neurodegenerative diseases. Previous studies from our laboratory have shown that continuous daily consumption of blueberry (BB) improved age-related declines in motor and cognitive function in old animals and animal models of accelerated aging and neuroinflammation. However, the optimal intake of BBs is currently unknown, and most people do not consume them every day. It is possible that intermittent consumption of BBs could: 1) have increased beneficial effects relative to continuous consumption, due to the repeated stimulation of cellular repair mechanisms; 2) have a reduced beneficial effect, as the total dose is lower; or 3) have the same effect as continuous consumption, if metabolites are retained in tissue. To evaluate the beneficial effects of blueberries on motor and cognitive function relative to the frequency of blueberry consumption, the diets of aged F344 rats (18 mo; n = 15/group) were supplemented with either a continuous control diet (modified NIH-31 diet), a continuous 2% wild blueberry diet, or an intermittent 2% wild blueberry diet for 2 months prior to behavioral testing. Rats in the intermittent 2% blueberry diet group consumed the 2% blueberry diet for 3 days, followed by a 4-day control diet (washout period) each week for the duration of the study. Serum samples were collected pre-diet and at the end of the study to assess inflammation. Results showed that continuous BB-fed rats performed better on the motor tasks and committed less errors in the radial arm water maze compared to control-fed animals. The intermittent-fed BB group had some positive effects, but did not perform as well as the continuous-fed BB group. A subsequent in vitro study using the serum showed that BB supplementation could enhance anti-inflammation capability, and frequency of intake determined level of protection. Based on these findings, daily consumption of BB may improve age-related deficits in motor function, cognition, and inflammation, and the frequency of eating BBs can have an effect on these measures.

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Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.18/L12

Topic: C.01. Brain Wellness and Aging

Support: MH085801

Title: Influence of dopamine compounds on mitochondria motility

Authors: *M. P. VAWTER[1], L. MORGAN, 92697[2], A. TRINH[3]
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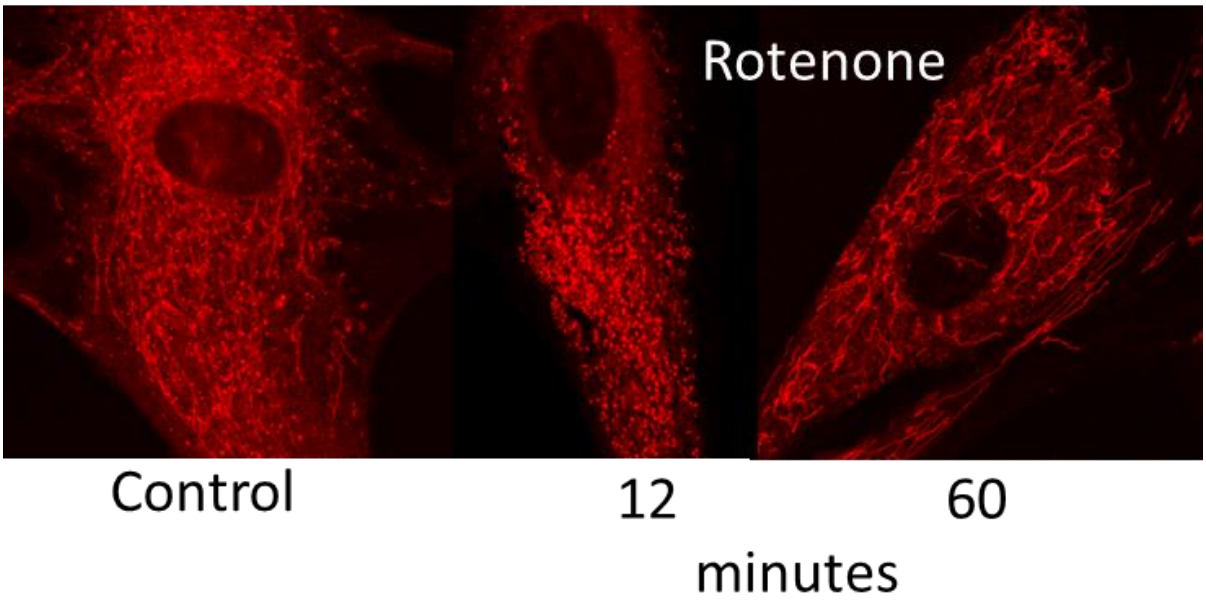
Abstract: The hypothesis that some psychiatric medications impair mitochondria functions has received support from our investigation of the dorsolateral prefrontal cortex and decreased Complex I activity in medicated subjects. To further this investigation, we are undertaking live imaging of mitochondria in human fibroblast cell lines. **Method:** The method involves plating fibroblast cells in 8 well imaging slide in varying densities. Acute treatments involve dopaminergic compounds, mitochondrial inhibitors, and alteration of calcium levels. Treated cells are stained with MitoTracker for 30 minutes, washed, and imaged after approximately 30 min. Imaging parameters are a collection of 100- 300 frames and using correlation analysis to track the amount of movement of thresholded mitochondrial images.
Results: Experiments are ongoing at this time, and we have shown that rotenone acutely decreases mitochondrial motility compared to control cells ($p = 0.049$; $N=8$ control cells and $n = 7$ rotenone-treated cells). Notably, rotenone altered the shape of mitochondria and is being studied to determine whether this alteration is reversible or can be blocked.



Conclusion: The preliminary results show possible modification of mitochondria biogenesis pathway by rotenone involving both the fission and fusion components.The information from this study will be able to identify whether dopaminergic compounds that we are studying inhibit mitochondrial motility and parameters of mitochondria biogenesis. This will be important for understanding the alterations of mitochondria in disorders that are treated with dopaminergic compounds. The ultimate goal is to further study induced dopamine cell lines and to monitor mitochondrial motility and biogenesis.

Disclosures: M.P. Vawter: None. **L. Morgan:** None. **A. Trinh:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.19/DP03/L13

Topic: C.01. Brain Wellness and Aging

Support: NIH

Title: Mitochondrial permeability transition pore-mediated mitochondrial stress is essential in age-related cognitive decline

Authors: *E. D. NOLTE, Q. YU, F. DU, F. AKHTER, S. S. YAN
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Abstract: As the average population age continues to rise, many diseases with aging as a primary risk factor have been identified, including Alzheimer's disease (AD), stroke, and cardiovascular disease. Understanding the behavioral changes of wild type mice with aging will help to inform translational models of aging and disease. Additionally, aging animal models can serve as a model for molecular changes that may explain non-clinically significant cognitive declines seen with aging.
As mice age from 3 to 24 months (n=19-24), clear, sex-based patterns develop. Female mice show significant increases in anxiety in an open field paradigm, while both sexes maintain general locomotion patterns. Locomotion patterns are not sex or age dependent, appearing consistent across both conditions. Both male and female mice show reduced ability in daily-task performance in a nest building behavioral test. Failure to perform daily tasks adequately is an early behavioral marker of cognitive decline often associated with dementia, and is a sensitive marker of cognitive decline.
Cyclophilin D (CypD) is a mitochondrial matrix protein that functions as the activator of the mitochondrial permeability transition pore (mPTP). Opening of the mPTP triggers mitochondrial failure and apoptosis, a common cause of neuronal death. In patients with AD, CypD is upregulated by 3 fold compared to healthy, age matched controls; this is also seen in animal models of Alzheimer's disease. Additionally, healthy persons experience a significant upregulation of CypD during the aging process, making it an attractive target for research in the aging phenotype. Overexpression of CypD leads to earlier onset of age related declines in mice and a more aggressive phenotype in AD mice. Blockage of CypD by genetic deletion or pharmacological inhibitor improves both mitochondrial dynamics and synaptic structure and function, leading to protection from age related cognitive declines. Thus, CypD is a key mitochondrial target for age- and AD-induced mitochondrial degeneration. Targeting mitochondrial mPTP through CypD may be a new therapeutic approach for halting age related dementia and cognitive dysfunction by powering mitochondrial function.
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Disclosures: E.D. Nolte: None. **Q. Yu:** None. **F. Du:** None. **F. Akhter:** None. **S.S. Yan:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.20/L14

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Phytohaemagglutinin (PHA)-induced oxidative stress in SH-SY5Y cells: A possible model to studyAβ toxicity and its modulation by pharmacological intervention

Authors: *K. RAFI[1], S. HUSSAIN[2], S. U. SIMJEE[1,2]
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Abstract: Alzheimer's disease (AD) is one of the leading causes of dementia worldwide. The neuropathological features associated with the disease are extracellular insoluble Aβ plaques and intracellular neurofibrillary tangles. Neuroinflammation and oxidative stress are involved in the onset and progression of AD. The production of inflammatory mediators, ROS and RNS causes synaptic dysfunction that is responsible for memory decline in AD. Therefore, the therapeutic options based on anti-inflammatory and anti-oxidant therapy are of important concern in targeting AD. The aim of this study was to develop a suitable *in vitro* model of Aβ deposition and to determine the role of novel neuroprotective agents for their therapeutic role thus targeting the disease at early stage or delay its onset.

Our preliminary studies were conducted to observe plaques formation using the cells stimulant PHA that releases cytokines upon stimulation. SH-SY5Y cells were incubated with PHA at the concentrations 5-40 µg/ml for 24 hours. After incubation, cells were observed using phase contrast microscopy. Oxidative stress was analyzed using 2',7'-dichlorodihydrofluorescein diacetate at concentrations of PHA 5-40 µg/ml by fluorimetric method. Immunocytochemistry was conducted to confirm the presence of Aβ plaques after stimulation with PHA. RT-qPCR was used to analyze the expression of α and β-secretase genes involved in the formation of plaques. Morphological analysis of PHA stimulated cells showed that 5 µg/ml of PHA did not cause any prominent changes in cellular morphology, while 10, 20 and 40 µg/ml concentrations caused visible aggregation when compared with unstimulated cells. Oxidative stress analysis of PHA stimulated cells demonstrated increased ROS levels upon stimulation with significant increased at 10 µg/ml of PHA. Later immunocytochemistry analysis at 10 µg/ml PHA concentration showed that expression of Aβ was increased significantly in stimulated cells. Quantitative gene expression analysis showed that expression of β-secretase gene was increased in PHA-treated cells.

Based on these observations, we suggest that PHA has a role in generating oxidative stress. Further we have screened different compounds for their neuroprotective effect to use for the treatment of PHA induced AD symptoms and neurodegeneration. In preliminary studies quinic acid and N-(2-hydroxyphenyl) acetamide were found to increase cell viability as compared to control cells. Next, we will use these compounds to check whether they are effective in reducing PHA induced Aβ generation and also, we will determine the molecular mechanism of action involved in the functioning of these compounds.

Disclosures: K. Rafi: None. **S. Hussain:** None. **S.U. Simjee:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.21/L15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministry of Science, ICT & Future Planning (grant number 18-BR-02-04)
NRF 2016R1A2B4011393

Title: As an FDA-approved drug, the small molecule suppresses LPS-induced neruoinflammatory responses in BV2 microglial cells and wild-type mice

Authors: *H.-S. HOE[1], H. NAM[2], J. NAM[4], J.-Y. LEE[3]
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Abstract: Background: As an FDA-approved drug, the small molecule B8 is an effective targeted therapy for patients with chronic lymphocytic leukemia (CLL). It inhibits Bruton's tyrosine kinase (BTK), a kinase involved in B cell receptor signaling. However, researchers have not comprehensively examined whether small molecule B8 regulates neuroinflammatory responses in the brain. **Methods:** BV2 microglial cells were treated with B8 (1 μM) or vehicle (1% DMSO), followed by lipopolysaccharide (LPS; 1 μg/ml) or PBS, and then we performed RT-PCR, immunocytochemistry, and subcellular fractionation to examine the effects of B8 on the neuroinflammatory response. In addition, wild-type mice were sequentially injected with B8 (10 mg/kg, i.p.) or vehicle (10% DMSO, i.p.), followed by LPS (10 mg/kg, i.p.) or PBS, and then we measured microglial and astrocyte activation using immunohistochemistry. **Results:** B8 significantly reduced LPS-induced increases in pro-inflammatory cytokine levels in BV2 microglial and primary microglial cells but not in primary astrocytes. B8 further suppressed LPS-mediated increases in pro-inflammatory cytokine levels when co-administered with a Toll-like receptor 4 (TLR4) inhibitor. B8 significantly decreased LPS-induced increases in p-AKT and p-STAT3 levels, suggesting that it attenuated LPS-induced neuroinflammatory responses by inhibiting AKT/STAT3 signaling pathways. In addition, B8 reduced LPS-mediated BV2 microglial cell migration. Moreover, B8-injected wild-type mice exhibited significantly reduced microglial and astrocyte activation. **Conclusions:** Our data illuminate the mechanisms of a potential therapeutic strategy for neuroinflammation-related diseases.

Disclosures: H. Hoe: None. **H. Nam:** None. **J. Nam:** None. **J. Lee:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.22/L16

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The *in vitro* effect of different coffees and extraction of coffee in Alzheimer's disease-associated cell line

Authors: *H. YANG[1,2], C. CAO[4,1], P. PHAM[3], U. KHAN[3], Y. HONG[1], X. LIN[1], N. SHEN[2,1]
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Abstract: Coffee is one of the most popular drinks in the world and naturally contains a variety of compounds including caffeine, antioxidants and diterpenes. Epidemiological data and recent scientific publications provide support for the neuroprotective effects of coffee against Alzheimer’s disease (AD). Our previous studies have shown that moderate caffeine administration protects/restores cognitive function and suppresses brain amyloid-β (Aβ) production in AD transgenic mice. We also proved that the function of coffee is different from caffeine and decaf coffee lost some of the beneficial functions compared with regular coffee. The aim of this study is to dig into the machoism that leads the difference between coffee and caffeine. In the present study, we compared the effect of different types of coffee on AD associated cell lines and gavage in mouse model. As result, we found that different brands of coffee showed differences after treatment. Even the effect of different types, such as instant, commercial or decaf coffee, of same brand coffee are varied. Furthermore, these differences showed no correlation with the concentration of caffeine in coffee. The result of Caffeine single treatment indicated that caffeine had stronger cell toxicity than coffee and the up-regulation function with Aβ level. Adding caffeine back into decaf coffee cannot restore the beneficial functions of regular coffee. We also found a mixture of several water-soluble compounds (WPI) which are extracted from coffee has antagonism with the toxicity of coffee and caffeine in AD-associated cell line. In conclusion, the toxicity of coffee is not related with the caffeine level but associated with the processing technology of coffee. The mechanism of coffee and the extraction of coffee still need to be explored.

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Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.23/L17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CoMRAD
Saskatchewan Health Research Foundation

Title: Effects of high-sucrose diet and multiple low-dose LPS injections on Alzheimer's disease-related pathological processes

Authors: *A. G. PACHOLKO, L. K. BEKAR
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Abstract: Alzheimer disease (AD) incidence is expected to more than double by the year 2050. Considering that less than 10% of AD cases are the result of genetic factors, external elements must be involved in this increase. Animal studies relying on humanized genetic mutations have been useful for studying the pathology of AD, but non-genetic models are now needed to elucidate the factors that contribute to the etiology of the far more prevalent late-onset sporadic form of the disease. These potential factors - diabetes, chronic stress, sleep deprivation and inflammation - are quickly becoming the norm in our society rather than the exception. Disturbingly, each of these conditions have been shown to contribute to mild neurodegeneration in isolation. Could these rising conditions be responsible for the growing AD epidemic, and what effects might they have when present in combination? By combining low-dose intraperitoneal injections (0.1 mg/kg delivered once per month for 3 months) of the endotoxin lipopolysaccharide (LPS) with the addition of 20% sucrose (hS) to animal drinking water (for 6 months), we explore the individual and cumulative effects of chronic inflammation and excess carbohydrate-based caloric intake on wild-type female mice. Given the fact that hS consumption can induce a brain insulin resistant state increasing GSK3β activity and that lithium is a potent GSK3β inhibitor, additional groups of mice received 0.001% lithium (by concentration) in their drinking water to assess the prophylactic potential of trace lithium in the management of diet- and inflammatory-induced conditions. Open field, forced swim and Barnes maze testing suggest an effect of high-sucrose on learning, memory and anxiety/despair. Interestingly, combined LPS and high-sucrose treatment increased anxiety-like behaviour relative to high-sucrose or LPS treatment alone. Sustained supplementation with trace lithium abolished the observed effect on the hS+LPS-mediated increase in anxiety-like behavior without effect on hS-mediated changes in immobility or learning and memory. Increased despair, increased anxiety-like behaviour, and impaired memory are behavioral patterns consistent with both brain insulin resistance and neuroinflammation. In addition to behavior, hippocampal neurogenesis, and various

neurochemical markers were also assessed to help further characterize this environmental animal model of neurodegeneration.

Disclosures: A.G. Pacholko: None. **L.K. Bekar:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.24/L18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BK21 PLUS
NRF-2016R1C1B2010206

Title: Levels of cerebrospinal fluid amyloid-β 40 and 42 are decreased in amyloid PET-negative idiopathic normal pressure hydrocephalus patients

Authors: *Y. KIM[1], J. CHANG[1,2]
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Abstract: The comorbidity of Alzheimer's disease (AD) with idiopathic normal pressure hydrocephalus (iNPH) is known to be associated with shunt unresponsiveness and is usually suspected by a decrease in the levels of β-amyloid (Aβ) 1-42 (Aβ42) in the cerebrospinal fluid (CSF). In the recent studies, it has been reported that the well-established CSF AD biomarkers could be misled in iNPH. In this study, we investigated levels of CSF AD biomarkers in amyloid PET (+) AD, amyloid PET (-) iNPH, and cognitively normal (CN) subjects. Ten patients diagnosed with probable AD, 10 probable iNPH, and 8 CN subjects were included in the experimental groups. To detect amyloid deposition, we performed 18F-florbetaben amyloid positron emission tomography (PET) and calculated the mean cortical standardized uptake value ratio (SUVR). We then analyzed the levels of Aβ40, Aβ42, total tau (t-tau), and phosphorylated tau (p-tau) protein in the CSF by using enzyme-linked immunosorbent assay. Amyloid PET gave positive (+) results for the ten AD subjects but negative (-) for the ten iNPH subjects. The mean cortical SUVR was significantly higher in AD than iNPH subjects (AD, 1.97 ± 0.25; iNPH, 1.37 ± 0.16; $p < 0.001$). Levels of CSF Aβ40 and Aβ42 were significantly decreased in iNPH subjects compared to CN subjects. The level of Aβ42 was significantly decreased in the AD group compared to iNPH and CN groups while there was no significant difference in the level of Aβ40 between AD and iNPH groups. Total tau and p-tau levels were significantly increased in the patients with AD compared to iNPH and CN. There was no statistical difference in the levels of total tau and p-tau between iNPH and CN groups. Our results suggest that the mechanism underlying the observed low CSF Aβ42 levels is different between amyloid PET (-) iNPH and

amyloid PET (+) AD subjects. Moreover, the proportionate decrease observed in both Aβ42 and Aβ40 levels in iNPH patients might be the result of defective amyloid metabolism and/or reduction in the clearance of amyloid species, due to glymphatic dysfunction. Future longitudinal studies should shed more light into these hypotheses.

Disclosures: Y. Kim: None. **J. Chang:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.25/M1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JPND 01ED1510A
Marie-Luise und Ernst Becker Stiftung

Title: Intensive interval training as promising approach to imporve cognitive function in mild cognitive impaired older persons

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Abstract: Background: Considering the rising prevalence of neurodegenerative diseases recent research focuses on early intervention strategies. Particularly Mild cognitive impairment (MCI), defined as prodromal stage of dementia, is of special interest. Continuous physical activity over a time period of 6 months is recommended by recent guidelines for the treatment of MCI to prevent further cognitive decline. However, which kind of physical activity is most effective to delay cognitive decline in older adults needs to be defined. First studies indicate that intensive interval training might be more beneficial than moderate aerobic exercise training to improve some cognitive functions in older adults. The aim of this study was to investigate the effect of intensive interval endurance training on the progression of cognitive performance of older adults with diagnosed MCI over a time period of 6 months. It was hypothesized that an intensive exercise load might reveal positive effects on cognition in a shorter training period than the currently proposed 6 month.
Method: 23 persons with diagnosed MCI (74.6± 6.9 years; MOCA: 22.8± 2) exercised 2-3 times/week on a cycle ergometer for a period of 35 min with 4x4 min of intensive load (80- 90% of their max. heart rate). Cognitive function was determined by using the Montreal Cognitive Assessment Battery (MOCA) and the Trail Making Test A and B (TMT A, B).
Results: A first data analysis after 12 weeks of training showed significant improvements of the MOCA total score (p= .008) and the MOCA memory index score (p= .0001) as well as in the

TMT A (p= .042) and B (p= .000) performance time.
Discussion: Regarding those results it seems that short but intensive exercise loads might be a valuable tool to improve cognitive function and influenced the ageing brain in a positively. These results are supported by data from animal models revealing a positive effect of short intensive interval training on neurogenesis in the ageing mouse brain.

Disclosures: S. Ruediger: None. **T. Stuckenschneider:** None. **S. Schneider:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.26/M2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CONACYT-MEXICO SCHOLARSHIP 339473

Title: Nutritional strategies against synaptic and metabolic alterations in obese rats

Authors: *T. SYEDA[1], L. PÉREZ-JIMÉNEZ[1], M. SÁNCHEZ-TAPIA[2], N. TORRES-TORRES[2], C. PEREZ-CRUZ[1]
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Abstract: Background: Mild-life obesity has been associated with alterations in expression of genes associated with cell metabolism, with a decreased metabolic expenditure and learning and memory deficits. Healthy life style and adherence to Mediterranean diet seems to reduce incidence of obesity and improve cognition. Bioactive components of our daily diet can modulate cellular metabolism and brain function. However, the mechanism of action of bioactive food (BF) remains unclear.**Objective:** To elucidate the mechanism by which bioactive food can improve synaptic and metabolic function in diet induced obesity. **Method:** BF diet contained dried nopal (5%), chia seed oil (9%), soy protein (19.4%), and turmeric (0.1%). High fat diet+5% sucrose was used for inducing obesity. AIN-93 was used as control diet. Two months old wistar rats were used for this study. Rats were randomly divided into 2 groups: 1) Rats fed control diet (AIN-93 group), and 2) Rats fed High fat+5% sucrose (HF group) for 4 months. After 4 months the HF group was divided into two group one group continued with the same diet, the other group were fed bioactive food along with High fat+5% sucrose for 3months (HF+BFgroup). Cognitive performance was assessed at the end of study by T-maze and novel object recognition test. We quantified spines ,inflammation markers and metabolic protein in the cortex. Short-chain-fatty acids (SCFAs) were analyzed by Gas chromatography.**Results:** There was a significant decrease in cognition in HF group, addition of BF improved cognition in HF-BF group. There was decrease in number of spines, increase in number of astrocytes and

microglia, increase in Tlr 4 receptor expression in HF group. There was decrease in short chain fatty acid, Butyrate in this group. Addition of bioactive food restored this parameters.
Conclusion: Our results shows that obesity caused cognitive alterations and decreased the number of spines, accompanied by a increase in inflammation and decreased Butyrate. The food combination used in the present study was able to improve cognitive performance and decrease inflammation. Several components of the BF diet have prebiotic properties and it been postulated that gut microbiota metabolites can modulate brain function (brain-gut axis). Interestingly, we observed that BF altered levels of Butyrate. Hence, a nutritional portfolio can be proposed as a therapeutic strategy against brain alterations induced by obesity.

Disclosures: T. Syeda: None. **L. Pérez-Jiménez:** None. **M. Sánchez-Tapia:** None. **N. Torres-Torres:** None. **C. Perez-Cruz:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.27/M3

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The VBrain system: Innovative training for cognitive diseases based on 3D and virtual reality

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Abstract: The VBrain system is an innovative solution for cognitive training based on 3D Virtual Reality (VR). Born as a fully immersive 3D Virtual Reality computerised system (based on a CAVE Virtual Environment), VBrain soon integrated a huge set of cross-visualization features. Nowadays VBrain can also operate on Tablet PCs, Personal Computers, Touch TVs, Touch Tables, Head Mounted Displays (Oculus VR, etc).
VBrain developed a complex device, inseparably interconnecting Reality and Virtuality through a simulation game, to facilitate the understanding of the territory-map link in people suffering for cognitive diseases and help them to learn what the digital interaction is and how it happens. The game will motivate young and elders to use VBrain, make learning easier and be a focusal experience in the process leading persons to understand the world. Reality and Virtuality will be integrated to build innovative settings for cognitive rehabilitation. Patients suffering for mental retardation will understand how to take part to cognitive rehabilitation and development of new cognitive resources activities.

VBrain is highly innovative thanks to dynamic evolution of software models for monitoring in tele-medicine and to the cognitive rehabilitation through VR. In fully immersive VR, the user manipulates virtual objects and feels haptic sensations thanks to instrumented gloves. That allows to evaluate functions in 3D space, visuo-spatial deficits in perception, attention and memory as well as the fine control of manipulation gestures in 3D and understanding of verbal instructions.
The VBrain system was designed and developed by a highly translational team where neuro-scientists worked together with engineers. It is tele-supervised by health professionals located in remote health structures (hospitals, research centres, etc.) for quantitative and qualitative evaluation and rehabilitation of motor-cognitive functions in patients suffering for Mental Retardation, Language and Communication Diseases, Alzheimer's and Parkinson's Diseases. The VBrain System, by its enormous potential, can totally change the current approach to cognitive diagnosis and rehabilitation.

Disclosures: C. Luciotto: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Commercial interest related to the topic, Action 4 Care Srls, Roma, Italy. **S.M. Pappalardo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Commercial interest related to the topic, Software Engineering Italia Srl, Catania. **D. Baratta:** None. **D. Puzzo:** None.

Poster

291. Brain Wellness and Aging: Pharmacological and Non-Pharmacological Interventions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 291.28/M4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BMBF 01ED1510A

Title: The effects of continuous aerobic and nonaerobic exercise on electrocortical activity in older adults with mild cognitive impairment

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Abstract: Background: Dementia will affect over 150 million older adults by 2050 (Prince, 2016). To prevent cognitive decline, the current focus has shifted to mild cognitive impairment

(MCI), which presents a prodromal stage of dementia (Petersen et al., 2017). The American Academy of Neurology (AAN) updated their guidelines for the treatment of MCI recently and stated that 6 months of exercise training is likely to improve cognitive measures shown by improvements in neuropsychological tests and changes in MRI scans (Petersen et al., 2017). Besides these methods, the electroencephalography (EEG), especially the P300 and N200 components of auditory event-related potentials (AERPs), have shown promise as a diagnostic tool for cognitive impairment (Morrison, Rabipour, Knoefel, Shepard, & Taler, 2018). However, the effect of exercise on AERPs in individuals with MCI is not known. It was hypothesized that exercise leads to an increased amplitude and a shortened latency. Method: 43 participants with MCI (72.5±5.3 years) were recruited from the NeuroExercise project (Devenney et al., 2017). They were either included in the exercise interventions (nonaerobic (n = 11) or aerobic exercise (n = 17)) or a standard care control group (n = 15). AERPs were recorded before and after 6 months and latencies and amplitude of N200 and P300 were determined at scalp sites Fz, Cz and Pz. Results: The control group tended to have a prolonged latency and a decreased amplitude after 6 months, whereas the intervention group showed an opposite trend. This development was particularly present in the CZ amplitude (P300: $p = 0.072$; N200: $p = 0.095$), but overall no significant differences were found. Discussion: The lack of significance might be due to differences in the exercise interventions, which might lead to different adaptations in the brain (Niemann, Godde, Staudinger, & Voelcker-Rehage, 2014). However, the described tendencies are supporting the findings of the AAN that exercise might improve cognitive function. As the EEG presents a cost effective, non-invasive method to assess cognitive function validly, future research should include this method in trials with bigger samples and a longer intervention period.

Disclosures: T. Stuckenschneider: None. **J. Weber:** None. **V. Abeln:** None. **T. Vogt:** None. **S. Ruediger:** None. **S. Schneider:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.01/M5

Topic: C.03. Parkinson’s Disease

Support: MINECO Grant BFU2017-82047-R
Dept Health Gov Navarra 046-2017
Programa Operativo FEDER 2014-2020 de Navarra
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Title: Glucocerebrosidase gene therapy induces alpha-synuclein clearance and stops disease progression

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Abstract: It has been recently uncovered a direct link between mutations in the GBA1 gene (the one coding for beta-glucocerebrosidase) and the development of synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Although the exact mechanisms through which glucocerebrosidase (GCase) regulates the homeostasis of alpha-synuclein still is not fully understood, the identification of reduced GCase activity as a common feature promoting the neuropathological findings underlying PD and DLB led to the development of novel strategies intended to increase GCase activity to further reduce alpha-synuclein aggregation and preventing neuronal death. Here we took advantage of neurospecific recombinant adeno-associated vectors coding for the mutated form of human alpha-synuclein (rAAV9-SynA53T) to further induce a bilateral progressive dopaminergic neuronal death together with the underlying pro-inflammatory microglial reaction in the substantia nigra pars compacta (SNc) in mice. Next, another rAAV coding for the GBA1 gene under the control of the constitutive promoter GUSB (rAAV9-GBA1) was delivered unilaterally in the left SNc. Animals have been sacrificed 3 weeks post-rAAV9-GBA1 delivery (e.g., 6 weeks after rAAV9-SynA53T injections). Obtained results showed that rAAV-mediated enhancement of GCase activity induced an almost complete clearance of aggregated alpha-synuclein, both in dopaminergic cells within the SNc as well as in nigrostriatal terminals. Unbiased stereological estimation of tyrosine hydroxylase-positive neurons revealed up to 70% of neuronal death 6 weeks after rAAV9-SynA53T delivery, in contrast with 17% of neuronal death observed in the SNc treated with rAAV9-SynA53T + rAAV9-GBA1. Furthermore, microglial reaction was tuned down and indeed microglial cells returned back to normal phenotype upon treatment with rAAV9-GBA1. Data reported here sustain the potential use of glucocerebrosidase gene therapy as a disease-modifying treatment for PD and related synucleinopathies.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.02/M6

Topic: C.03. Parkinson's Disease

Support: AA022448
AFPE Fellowship

Title: Variation in dopamine modulation by P2X4 receptor modulators, ivermectin (IVM) and moxidectin (MOX)

Authors: *A. M. WARNECKE[1], M. S. KANG[1], M. W. JAKOWEC[2], D. L. DAVIES[1]
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Abstract: Dopamine is a key neurotransmitter within the brain that plays a role in the mesolimbic pathway (associated with reward based behavior), and the nigrostriatal pathway (associated with motor control and reward based cognition). The ability to modify dopaminergic activities within these pathways provides a potential target for the treatment of dopaminergic disorders including Parkinson's disease and addiction. We previously found that IVM and MOX significantly reduced alcohol consumption in P2X4 knock-out (P2X4KO) mice and littermate controls. Notably, the degree of alcohol reduction was significantly less in P2X4KO mice, suggesting a role of P2X4Rs in IVM and MOX modulation. In addition, we found that IVM significantly enhanced the effect of levodopa (L-Dopa) on the motor system in both P2X4KO and littermate controls. Similarly, L-Dopa enhancement was significantly less in P2X4KO mice, suggesting another role for P2X4Rs. The current study tested the hypothesis that MOX would significantly increase L-Dopa rotations, a surrogate behavior marker of dopamine neurotransmission.
In the current study, we measured MOX enhancement of L-Dopa on motor activity in male and female C57BL6J mice. We unilaterally lesioned mice in the medial forebrain bundle with 6-hydroxydopamine. As positive controls, we administered amphetamine (2.5mg/kg) to the mice and measured the degree of ipsilateral rotational behavior followed by treatment with L-Dopa (5mg/kg, S.C) to measure contralateral rotation behavior. Mice were next allowed a 3 day washout (minimum) period followed by treatment with MOX (2.5mg/kg, I.P.) which was next followed by administration of L-Dopa injection (5mg/kg S.C.; 4 hours after MOX) and measured rotational behavior. After MOX washout (3 day minimum post-test), IVM (5mg/kg, I.P.) was administered 8 hours prior to L-Dopa injection (5mg/kg S.C.) as a positive control and mice were again observed for changes in rotational behavior. Unexpectedly, we found minimal changes in L-Dopa induced rotations when treated with MOX. On the other hand, IVM significantly increased L-Dopa induced rotational behavior in the same group of mice. Of note, there were gender specific differences in rotational behavior when mice were given IVM with L-Dopa; with female mice showing a significantly greater number of total rotations. Collectively, these findings suggest IVM superiority compared to MOX for L-Dopa adjunct therapy for Parkinson's disease. In addition, this work suggest differences in drug sensitivity that is sex specific in that females had an enhanced response to dopamine replacement therapy.

Disclosures: A.M. Warnecke: None. **M.S. Kang:** None. **M.W. Jakowec:** None. **D.L. Davies:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.03/M7

Topic: C.03. Parkinson's Disease

Support: Focused Ultrasound Foundation

Title: Immunohistochemical analysis of cellular transfection in the brains of rats given intranasal GDNF pDNA nanoparticles with focused ultrasound (FUS)

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Abstract: The potential of glial cell line-derived neurotrophic factor (GDNF) for Parkinson's disease (PD) is limited by its inability to cross the blood brain barrier (BBB), necessitating surgical delivery. We have shown that intranasal administration of PEGylated lysine 30-mer (CK30PEG10K) plasmid DNA nanoparticles (NPs) encoding hGDNF offers a non-invasive, non-immunogenic approach that bypasses the BBB and generates a long-lasting source of GDNF expression within the brain sufficient to provide neuroprotection in the rat 6-hydroxydopamine model of PD. We also showed with double-label immunohistochemistry (DL-IHC) that transgene expression in the rat brain is widespread, but the transfected cells were not neurons or astrocytes. They were consistently perivascular, located abluminal to the vascular endothelium, and resembled pericytes morphologically. In an attempt to enrich transgene expression in target regions for PD and improve tissue penetration, we next combined intranasal delivery of our DNA NPs with focused ultrasound (FUS). FUS with circulating microbubbles has been proposed as a way to enhance localized drug delivery to brain by temporarily widening tight junctions between cells. FUS did enrich transgene expression in the sonicated regions, but DL-IHC showed that it caused recruitment of cells to the sonication site that were neither astrocytes nor neurons, and not perivascular in location. We speculated that the transfected cells might be microglia. To test this hypothesis, we assayed brain tissue from rats given intranasal NPs encoding a reporter plasmid, which produces an eGFP-GDNF fusion protein, and used DL-IHC to assess whether GFP-positive cells co-expressed Iba1, a marker for microglia. FUS with microbubbles was applied to the right forebrain and midbrain just before and after intranasal administration, and rats were sacrificed one week later. Transfected (GFP-positive) cells were again found throughout the brain, commonly adjacent to microvessels in areas distant from apparent sonication sites. They were occasionally but not always Iba1-positive. However, at sonication sites, indicated by discrete clumps or clusters of transfected cells extending deep into

the parenchyma, essentially all GFP-positive cells were also Iba1-positive, identifying them as transfected microglia. Thus, we conclude that FUS with circulating microbubbles increases transfection of cells at sonication sites and improves tissue penetration, and the transfected cells are predominantly microglia. The implications of using FUS to promote microglial expression of a neurotrophic factor at disease target sites remain to be determined.

Disclosures: B.L. Waszczak: None. **A.E. Aly:** None. **Z. Li:** None. **T. Sun:** None. **Y. Zhang:** None. **O. Sesenoglu-Laird:** A. Employment/Salary (full or part-time):; Copernicus Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Copernicus Therapeutics, Inc.. **L. Padejimas:** None. **M.J. Cooper:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Copernicus Therapeutics, Inc.. **N.J. McDannold:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.04/M8

Topic: C.03. Parkinson’s Disease

Support: NRF-2016R1A2B4010692
NRF-2017M3C7A1031105

Title: Delayed treatment of capsaicin enhances functional recovery of dopamine neurons in MPP^+ model of Parkinson's disease

Authors: *K. Y. KYOUNG IN
Kyunghee Univ., Seoul, Korea, Republic of

Abstract: We recently demonstrate capsaicin (CAP) neuroprotection of dopamine neurons by astrocytic transient receptor potential vanilloid 1 (TRPV1) derived ciliary neurotrophic factor (CNTF) in MPP^+ rat model of Parkinson’s disease (PD). However, the neurorestoration of delayed CAP treatment several weeks after toxins remains elusive. To test this, we utilized MPP^+ model that the loss of nigrostriatal DA neurons was complete at 2 weeks post MPP^+ and that showed prolonged expression of astrocytic TRPV1 up to 10 weeks post MPP^+. Here, we report that astrocytic TRPV1 activation by CAP 9 weeks post MPP^+ improves amphetamine-induced rotation. In parallel, CAP increases level of CNTF and TH enzyme activity via CNTFR-a in substantia nigra (SN) and striatal dopamine level in MPP+ rat model. TH immunohistochemical analysis revealed that increase in biochemical indices was not accompanied by neurorestoration. Instead, delayed CAP treatment transiently improved dopamine function and behavioral recovery when astrocytic TRPV1-derived CNTF expression is switched on.

Disclosures: K.Y. Kyoung In: A. Employment/Salary (full or part-time):; 1Department of Neuroscience, Graduate School, Kyung Hee University.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.05/M9

Topic: C.03. Parkinson's Disease

Support: NINDS Grant R15NS093539

Title: Intranasal delivery of heat shock protein 70 reduces histopathology and smell loss in α-synuclein fibril-infused 20 month-old mice

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Abstract: Heat shock proteins (Hsps) constitute a network of chaperone molecules that mitigate the detrimental sequelae of proteotoxic stress by refolding misfolded proteins or enabling their clearance. Our prior work revealed that inhibitors of the stress-inducible heat shock protein 70 (Hsp70) exacerbate proteotoxic cell death in postnatal primary neurons from the sensorimotor neocortex, entorhinal allocortex, hippocampal allocortex, and olfactory bulb. Here we tested the hypothesis that exogenous delivery of recombinant Hsp70 might mitigate the proteinopathy of Lewy body disorders *in vivo*. We recently showed that infusions of preformed α-synuclein fibrils into the mouse olfactory bulb lead to the emergence of dense Lewy-like pathology in the limbic temporal lobe. In that model, intense Hsp70 immunoreactivity was present in some α-synuclein^{+} inclusions, suggesting that Hsp70 may be trapped within the aggregates and unable to perform some of its chaperone functions. These findings supported the view that providing additional, exogenous Hsp70 might be beneficial. Hsp70 has lipophilic properties and can enter the brain when administered intranasally. Following intranasal delivery, Hsp70 has been shown to improve cognition, reduce neurodegeneration, and extend lifespan in mouse models of aging and dementia, and to improve insulin sensitivity in mouse models of diabetes. However, intranasal delivery of Hsp70 has not been tested in models of Lewy body disorders to our knowledge. In a small pilot study, we infused yeast Hsp70 into the left nares every day for 28 days in aged male mice (20 months) following infusions of preformed α-synuclein fibrils in the left olfactory bulb. Two blinded investigators independently observed that daily intranasal Hsp70 delivery significantly mitigated 1) fibril-induced smell loss, measured as the latency to contact buried

food, and 2) fibril-induced α-synucleinopathy, visualized by immunostaining for pathologically phosphorylated α-synuclein (pSer129). Furthermore, we confirmed that Hsp70 entered the mouse brain from the nares within three hours post-infusion, as demonstrated by immunoblotting on tissue lysates from the olfactory bulb and the caudal recesses of the temporal lobe. Finally, inhibition of Hsp70 activity *in vitro* with the small molecule inhibitors MAL3-101 and/or VER155008 dramatically increased the number of $pSer129^{+}$ inclusions in primary neurons harvested from the rat sensorimotor neocortex, entorhinal allocortex, and hippocampus, suggesting a generalizable effect. These collective findings support further testing of the ability of intranasal Hsp70 to impede the propagation of Lewy pathology.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.06/M10

Topic: C.03. Parkinson’s Disease

Support: CONACYT

Title: Brain uptake of copper after systemic administration of copper gluconate in rats

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Abstract: Copper (Cu) is an important micronutrient in living beings due to its participation as an allosteric component or co-factor for various essential enzymes in several physiological processes. Cu homeostasis is strictly regulated by a large variety of proteins. Deficit or accumulation of this metal can trigger various diseases and even compromise the development of living beings. It has been suggested that neurodegenerative diseases such as Parkinson's are related to Cu concentrations in brain tissue. This study is aimed to determine the temporal course of an acute administration of Cu and its absorption in healthy rats. Oral administration of 79.5 mg/kg of Cu (as gluconate) was carried out in fed male Wistar rats weighing 250-290g (n=4).

Blood and liver, striatal and mesencephalic tissues samples, were collected at 0, 5, 10, 15, 30, 60, 90, 120, 180, 240, 300 and 360 minutes, digested in nitric acid (70%) and the Cu content was determined by atomic absorption spectrophotometry. A control group was administered with calcium gluconate and the Cu level was determined to establish basal content. Our data showed that Cu plasmatic concentration increases almost in 60% from basal levels 10 min after oral administration. Maximum plasmatic concentration was observed at 90 min post-administration increasing in almost 95% when compared to basal level. After 180 min of administration, Cu elimination starts and 360 min after administration metal levels return to baseline. In brain tissue increase of Cu level did not reach the percentages observed in plasma. Peak concentrations were observed 15 minutes after oral administration increasing basal levels in almost 36% in mesencephalon and in 49% in striatal tissue and basal values were observed again 90 min and 300 min after administration respectively. Additionally, maximum concentration of Cu determined in liver was observed 180 min after administration and it was 241.0% more when compared to basal value. In conclusion, the oral administration of 79.5 mg/kg Cu increase its plasmatic level, however, the observed increment is not proportional to concentration in brain tissues. On the other hand, liver seems to plays a relevant role regulating copper homeostasis after oral administration, since this organ shows significant retention of the metal when compared to levels observed in the rest of the tissues evaluated during this protocol.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

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Program #/Poster #: 292.07/M11

Topic: C.03. Parkinson’s Disease

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Title: 5-alpha reductase inhibitors dampen L-DOPA-induced dyskinesia by normalizing D1-receptor downstream signaling pathway

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Abstract: Although 1-3,4-dihydroxyphenylalanine (L-DOPA) is the mainstay therapy for treating Parkinson's disease (PD), its long-term administration is accompanied by the development of motor complication that dramatically affects patients' quality of life, particularly L-DOPA induced dyskinesia (LID). LID has consistently been related to an excessive dopamine receptor transmission, particularly at the down-stream signaling of the striatal D1 receptors, resulting in an exaggerated stimulation of cAMP-dependent protein kinase and extracellular signal-regulated kinase (ERK) pathway. We previously reported that pharmacological blockade of 5-alpha reductase (5AR), the rate-limiting enzyme in neurosteroids synthesis, attenuates the severity of a broad set of behavioral alterations induced by selective and non-selective dopamine receptor agonists, without inducing extrapyramidal symptoms. In light with these evidence, we hypothesized that inhibition of 5AR may also counteract dyskinesia in 6-OHDA-lesioned rats by normalizing the striatal D1 receptor signaling cascade. Thus, in this study we investigated the impact of the inhibition of 5AR on the development and expression of dyskinesia and related molecular alterations on D1 receptor downstream signaling. We used two 5AR inhibitors, already approved for clinical use, finasteride (FIN) and dutasteride (DUTA), that differ in affinity for two 5AR isoform. First, to characterize the therapeutic potential of FIN and DUTA on preventing of LID, we assessed the abnormal involuntary movements in hemiparkinsonian male rats chronically injected two weeks prior to L-DOPA administration. Furthermore, a battery of motor tasks was administered in order to verify the impact of 5AR inhibitors on the therapeutic efficacy of L-DOPA. Finally, in order to investigate a potential molecular alterations induced by the chronic treatment with FIN and DUTA, we analyzed striatal markers of dyskinesia in 6-OHDA lesioned rats treated with L-DOPA alone or in combination with FIN and DUTA. The results indicated that both FIN and DUTA preventive administration significantly reduced development and expression of LID; however, DUTA appeared more effective than FIN at a lower dose and produced its antidyskinetic effect without impacting the ability of L-DOPA to increase motor activation, or ameliorate forelimb use in parkinsonian rats. Moreover, we found that both 5AR inhibitors, prevented the increased phosphorylation of DARPP-32 and ERK1/2 induced by L-DOPA treatment. These results support 5AR as an intriguing target for LID and suggest DUTA as promising therapeutic agent for treatment of dyskinesia in PD patient.

Disclosures: S. Fanni: None. **F. Rossi:** None. **F. Traccis:** None. **P. Saba:** None. **S. Scheggi:** None. **E. Tronci:** None. **A. Melis:** None. **P. Devoto:** None. **M. Bortolato:** None. **M. Carta:** None. **R. Frau:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.08/M12

Topic: C.03. Parkinson's Disease

Support: Supported by a grant from Lundbeck A/S

Title: Co-treatment with rivastigmine and idalopirdine reduces the propensity for falls in a rat model of falls in Parkinson's disease

Authors: *A. KOSHY CHERIAN[1], A. KUCINSKI[1], R. WU[1], I. E. M. DE JONG[2], M. SARTER[1]
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Abstract: Falls in patients with Parkinson's disease (PD) are associated with cognitive, specifically attentional impairments and with losses in cholinergic projection systems. We previously established an animal model of the combined basal forebrain cholinergic - striatal dopaminergic losses of PD fallers (DL rats) and a behavioral test system (Michigan Complex Motor Control Task, MCMCT) to measure falls associated with traversing dynamic surfaces. Traversal through the rotating square rod surfaces requires limb coordination, carefully timed and placed steps, and persistent control of gait. We also demonstrated that treating DL rats with an acetylcholinesterase inhibitor (AChEI), donepezil, together with a $5HT_6$ receptor antagonist, idalopirdine, reduced fall frequency and improved associated performance of DL rats traversing rotating rods (Kucinski et al., 2017). Here we employed a longer and more taxing rotating beam apparatus to determine the potential therapeutic efficacy of idalopirdine when combined with the pseudo-irreversible, and thus relatively long-acting, AChE- and butyrylcholinesterase- (BuChE) inhibitor rivastigmine. As before, vehicle-treated DL rats fell more frequently, committed more slips and exhibited more movement stoppages than intact control rats. Semi-chronic administration of rivastigmine and idalopirdine significantly improved the performance of DL rats. Rivastigmine alone produced some trends for improved performance but the combination treatment was robustly more effective in reducing stoppages and stoppage-associated falls. As before, idalopirdine treatment alone was ineffective. These results extend the prediction that the combined treatment with idalopirdine and an AChEI enhances the fluency and efficacy of forward movement and thereby reduces the propensity for falls in patients with movement disorders.

Disclosures: A. Koshy Cherian: None. **A. Kucinski:** None. **R. Wu:** None. **I.E.M. de Jong:** A. Employment/Salary (full or part-time):; Employee of Lundbeck A/S. **M. Sarter:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; supported by a grant from Lundbeck A/S.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.09/M13

Topic: C.03. Parkinson's Disease

Support: Central Michigan University SRCEE Grant

Title: Luminopsin-mediated stimulation of transplanted dopaminergic cells in unilateral 6-OHDA lesion model of Parkinson's disease

Authors: *K. A. ANDERSON, E. D. PETERSON, A. PAL, R. A. BYRD, E. L. BURKETT, B. WHITEHEAD, A. S. HAULER, R. R. ANCOG, K. E. AZINGER, M. D. HILL, U. HOCHGESCHWENDER, M. I. SANDSTROM
Central Michigan Univ., Mt Pleasant, MI

Abstract: Of the treatments for Parkinson's disease (PD), stem cell transplantation demonstrates high potential. Preclinical data suggests a waning of benefit prior to or without significant disruption of the transplant. We theorize that a gradual adaptive response is occurring due to imprecise regulation of grafted cells that results in a constant, tonic release of dopamine (DA). While previous research in our lab has witnessed grafts such as this subtly reduce asymmetrical behavior using the unilateral 6-OHDA model, further improvements could center upon stimulating DA release to prevent gradual habituation and reveal more apparent reduction in asymmetry. Of the various tools for stimulating cellular activity, one recent development shows promise: bioluminescent optogenetics. Bioluminescent optogenetics makes use of luminopsins—pairs of proteins comprised of a luciferase and an opsin. This provides the ability to activate the opsin by administering a substrate compatible with the luciferase rather than with direct light. We created a stable transgenic cell line that expressed the luminopsin construct LMO3 and used these cells in a dopaminergic differentiation protocol followed by their *in vivo* transplantation into 6-OHDA lesioned rats. By using a repeated measures design where eight rats were injected with either the active substrate or an inert vehicle in randomized sequence, we compared benefits of transplants alone with those produced by stimulating luminopsin-expressing DA cells in restoring symmetrical limb use while the animals were swimming. This was done along with concurrent microdialysis to correlate DA release from the lesioned hemisphere with the animals' symmetrical limb use. We expected that stimulating DA release would rectify asymmetric behavior far more successfully than transplants left to their own devices. It was found that after stimulation, asymmetrical biases in behavior were reduced and in some cases reversed in direction. Results of vehicle stimulation were curiously mixed. It was found that vehicle injections that preceded the stimulation condition showed the expected, unreduced asymmetry, while vehicle injections that followed stimulations showed reduced asymmetry. Preliminary

results indicate no clear correlation has been seen between neurotransmitter levels and reduced asymmetry following either vehicle or substrate injection. Regardless, the behavioral data supports the notion that the transgenic cells can be stimulated via the luminopsin construct. This stimulation, however, may initiate a more complex dynamic that combines acutely driven release with residual levels of diffused dopamine.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.10/M14

Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS088554
Ply Gift Award

Title: Regulation of corticostriatal transmission and motor function by phosphodiesterase 9A: Implications for the treatment of Parkinson's disease

Authors: *A. R. WEST[1], F. ALTWAL[1], S. CHAKROBORTY[1], N. VOELKNER[1], R. MALIK[1], I. M. SANDOVAL[2], K.-Y. TSENG[4], F. P. MANFREDSSON[3]
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Abstract: While L-DOPA remains the gold standard treatment for Parkinson’s disease (PD), chronic administration is thought to restore dopamine (DA) tone in the striatum in a non-physiological manner which induces debilitating motor side effects termed L-DOPA-induced dyskinesias (LIDs). Thus, there is a critical need to identify novel non-DAergic targets as co-therapies for PD and LIDs. Among these, cyclic nucleotides and phosphodiesterases (PDEs) involved in their metabolism are emerging as promising targets for reversing striatal dysfunction associated with PD. The high affinity cyclic GMP (cGMP)-specific enzyme PDE9A exhibits moderate levels of expression in human and rodent striatal medium-sized spiny projection neurons (MSNs), however, it is not yet known how up or down regulation of cGMP signaling via PDE9A-specific manipulations may affect corticostriatal transmission or motor behavior in naïve animals and PD models. The current study investigated the effects of the selective PDE9A inhibitor PF-04447943 and genetic manipulations (knockdown or overexpression of PDE9A using rAAV2/9) on motor function and cortically-evoked activity recorded in naïve and

dyskinetic or non-dyskinetic hemi-parkinsonian rats. Augmentation of cGMP signaling following acute and chronic disruption of PDE9A did not affect motor behavior in naïve or untreated parkinsonian rats, and did not alter the prokinetic effects of L-DOPA or measures of LIDs in dyskinetic animals. However, electrophysiological studies performed in naïve animals showed that downregulation of PDE9A induced a significant decrease in the onset latency of cortically-evoked spikes recorded in striatal MSNs, indicating that increased cGMP tone facilitates corticostriatal transmission. Opposite genetic manipulations designed to down-regulate the cGMP signaling pathway in parkinsonian rats utilized viral vectors incorporating the PDE9A transgene and/or a dominant-negative form of PKG1-α (d-PKG1-α) or GFP as a control. Interestingly, overexpression of the PDE9A transgene in striatum significantly reduced the severity of LIDs and turning behavior in L-DOPA-treated PD rats. These findings point to new cGMP-dependent mechanisms for modulating striatal function to reduce the incidence and severity of LIDs, and potentially, improve motor control and quality of life in patients with PD. Moreover, as this gene therapy regime does not require striatal cell- or pathway-specific manipulations, it may be more readily translated to patients with PD than approaches requiring more restrictive genetic targeting.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.11/M15

Topic: C.03. Parkinson’s Disease

Support: pilot grant from RFUMS
The Ply Gift Award

Title: Multimodal serotonergic drugs for the treatment of L-DOPA induced dyskinesia in an experimental model of Parkinson’s disease

Authors: *F. ALTWAL, N. VOELKNER, R. MALIK, V. OLIVERA, A. PASTWA, A. R. WEST
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Abstract: Parkinson’s disease (PD) is a devastating neurodegenerative disorder affecting over one million Americans. The gold standard treatment for PD is levodopa (L-DOPA), which is effective for increasing dopamine (DA) tone and improving motor dysfunction, but unfortunately produces debilitating motor side-effects termed L-DOPA-induced dyskinesias (LIDs). Recent studies in dyskinetic parkinsonian models have implicated serotonergic raphe-striatal terminals

in the uptake and conversion of L-DOPA to DA, as well as the non-physiological release of DA and serotonin (5-HT) which may underlie the pathophysiological mechanisms of LIDs. Indeed, the utility of co-treatments with either selective 5-HT reuptake inhibitors (SSRIs) which block the 5-HT transporter (SERT), or selective 5-$HT_{1A/B}$ receptor (5-$HT_{1A/Br}$) ligands which stimulate 5-HT autoreceptors to potentially suppress DA release from 5-HT terminals, has been assessed in pre-clinical models and clinical trials. Many of the drugs tested were found to reduce LIDs, but unfortunately also reduced the prokinetic effects of L-DOPA. The goal of the current study was to identify a multimodal 5-HT drug which can act to attenuate the expression and severity of LIDs, without interfering with the antiparkinsonian efficacy of L-DOPA. Vortioxetine is of interest in this regard as it is known to exhibit potent SSRI, 5-HT_{1Ar} agonist, and 5-HT_{1Br} partial agonist properties, and can act as an antagonist at other 5-HT receptors. Unilateral 6-OHDA-lesioned rats modeling PD were treated with either vehicle and L-DOPA (2.5 - 5.0 mg/kg), vortioxetine (5.0 mg/kg) and L-DOPA, or escitalopram (3 mg/kg). Rats were treated for 5 consecutive days/week, for 2 weeks. On the second day of each week, stepping tests were performed prior to drug administration, and 60 minutes post L-DOPA treatment. Behavioral assessment of LIDs was performed (30-180 min) at the end of each week. Vortioxetine pretreatment (30 min) significantly reduced LIDs in 6-OHDA lesioned rats, but had no effects on forelimb akinesia or L-DOPA-induced prokinetic effects. Escitalopram pretreatment also induced a significant reduction in LIDs and did not affect the prokinetic effects of L-DOPA. Additional studies are ongoing to assess the impact of these treatments on corticostriatal transmission and striatal neuronal activity. The current results indicate that together with L-DOPA, multimodal 5-HT drugs such as vortioxetine may be safe and efficacious co-therapies for reducing side-effects such as hyperkinesia and dystonia in PD patients, potentially allowing for more flexibility in L-DOPA dose ranges and protracted chronic treatment.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.12/M16

Topic: C.03. Parkinson’s Disease

Support: Michael J Fox Foundation

Title: A gene therapy approach to knock-down Fyn in the striatum reduces levodopa induced dyskinesia in the 6-hydroxydopamine mouse model of Parkinson’s disease

Authors: *M. P. BORDONE[1], A. DAMIANICH[2], M. A. BERNARDI[1], S. SANZ-BLASCO[1], O. S. GERSHANIK[1], M. E. AVALE[2], J. E. FERRARIO[1]

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Abstract: Levodopa (L-DOPA) induced dyskinesia (LID) is the main side effect that appears after long-term treatment with that drug for Parkinson's disease (PD). To reduce the development and severity of LID is a significant challenge because to date there are no available pharmacological alternative therapies to PD with full clinical benefit. We have recently proposed Fyn as a novel target to control LID. Fyn is a Src tyrosine kinase located at the postsynaptic density zone that regulates the N-methyl-D-aspartate (NMDA) receptor by phosphorylation of the NR2B subunit at Tyr-1472 in response to dopamine D1 receptor stimulation. Here we propose to genetically manipulate Fyn expression aiming to downregulate LID in a mouse model of PD, by intra-striatal injection of lentiviral (LV) particles carrying a micro-RNA against Fyn (miR-Fyn). Four miR-Fyn sequences were designed, cloned in LV vectors, tested *in vitro* for silencing efficacy and selected the one with the highest silencing effect. Next, we generated the PD mouse model in C57 female mice (3 months of age) by injecting 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle, selected the animals with a remarked deficit of the contralateral forepaw in the cylinder test and challenged them with L-DOPA to induce LID before (n=16) or after (n=19) the intra-striatal injection of miR-Fyn or a control sequence (n=5 for each group). A group of non-injected animals with LV particles was run in parallel as a positive control for dyskinesia (n=9). LIDs were determined every 3 days for 2 weeks. *Postmortem*, we determined the degree of dopaminergic denervation by counting the number of tyrosine hydroxylase (TH) positive cells in the substantia nigra, to ensure an equal level of degeneration in all groups, and the level of striatal TH, Fyn silencing and the marker of LID, FosB-ΔFosB, all by Western blot. We found that the selected miR-Fyn reduces Fyn protein by ~50% in N2a neuronal cell line, and it significantly downregulated LID in a pretreatment paradigm of dyskinesia by ~60% or ~40% compared to the non-injected animals or the group injected with the control sequence, respectively. Also, the miR-Fyn was able to reduce the severity of already established dyskinesia (postreatment paradigm) by ~35% compared to both control groups. Our results demonstrate that Fyn is a potential target to control LID and set the grounds for a potential translation to therapeutic use in PD.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.13/M17

Topic: C.03. Parkinson's Disease

Title: NPT520-34 administration improves grip strength, limb posture, and balance and gait-related measures in a transgenic mouse model of Parkinson's disease

Authors: *D. L. PRICE, A. KHAN, M. MAILE, C. WITTMER, K. TATSUKAWA, E. STOCKING, W. WRASIDLO, D. BONHAUS
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Abstract: The accumulation of neurotoxic misfolded and aggregated proteins and the associated neuroinflammation are implicated in the pathogenesis of most neurodegenerative diseases. NPT520-34, a compound with good drug-like properties and an excellent in vitro safety profile, has demonstrated beneficial effects in multiple in vivo studies on alpha-synuclein (ASYN) protein accumulation, striatal dopamine transporter levels and a clinically translatable marker of neuroinflammation (Translocator protein - TSPO) in the Line 61 transgenic (Tg) mouse model of Parkinson's disease (PD). The Line 61 mThy1-ASYN Tg mouse develops extensive accumulation of ASYN neuropathology, inflammation, and motor and non-motor functional deficits recapitulating key features of PD.

The objective of the current study was to confirm the actions of NPT520-34 on neuropathology and grip strength and extend findings to measures of limb posture (clasping), and measures of gait and balance in a new 3 month administration study in the Line 61 Tg mouse model. Male Tg and non-Tg littermates received vehicle or NPT520-34 (0.5, 1, 5 or 10 mg/kg, IP) once daily for 3 months. Experimenters were blinded to genotype and treatment group.

Grip strength was evaluated at baseline (prior to treatments) and re-evaluated after 70 days of treatment. Consistent with previous 3 month studies, statistically significant grip deficits in Line 61 Tg mice were present at baseline and re-test. All doses of NPT520-34 from 0.5 to 10 mg/kg produced improvements in Line 61 Tg grip strength relative to vehicle-treated Line 61 Tg control mice.

Hind and forelimb clasping were evaluated (~day 70) as measures of striatal dysfunction and/or dysregulation of motor pathways. There were statistically significant increases in hind and forelimb clasping in vehicle-treated Line 61 Tg mice compared to vehicle non-transgenic control mice. Forelimb clasping was reduced in Line 61 tg mice treated with NPT520-34 (0.5 up to 5 mg/kg).

The effects of NPT520-34 at 10 mg/kg on gait and balance were evaluated (~day 20 and 70) in a separate cohort of Line 61 mice utilizing the automated CatWalk apparatus (Noldus Information Technology). Compared to non-transgenic mice, Line 61 Tg mice displayed multiple alterations in CatWalk indices of gait and balance, including statistically significant increases in abnormal lateral stance support (ipsilateral limbs) that were normalized in L61 tg mice treated with 10 mg/kg NPT520-34.

Taken together the present results confirm benefits of 10 mg/kg NPT520-34 treatment on Line 61 Tg grip strength and extends to findings of benefit on additional measures of limb posture, gait and balance with doses as low as 0.5 mg/kg.

Disclosures: D.L. Price: A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **A. Khan:** A.

Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **M. Maile:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **C. Wittmer:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **K. Tatsukawa:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **E. Stocking:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **W. Wrasidlo:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **D. Bonhaus:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc..

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.14/M18

Topic: C.03. Parkinson’s Disease

Support: Jerry T. and Glenda G. Jackson Fellowship for Parkinson’s Disease Research to the University of Arizona

Title: VEGF-B overexpression in PINK1 gene knock out rats improves motor function: Is this effect due to neuroprotection or to functional improvement of dopaminergic neurons?

Authors: *M. J. BARTLETT[1], S. CRISTIANI[2], S. I. B. SMIDT[2], D. C. FARRELL[4], K. P. DOYLE[5], M. L. HEIEN[6], S. J. SHERMAN[2], T. FALK[3]
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Abstract: Therapies to slow the progression of Parkinson’s disease (PD) or protect against the loss of dopaminergic neurons in the substantia nigra pars compacta (SN) remain a critically under met need. We have previously identified vascular endothelial growth factor B (VEGF-B)

as a novel therapeutic candidate and published neuroprotective effects of VEGF-B *in vitro* and *in vivo*. VEGF-B was shown to be upregulated in dopaminergic cells of a rat midbrain culture model upon exposure to rotenone, a suspected PD-inducing toxin, and to be neuroprotective against a rotenone insult (Falk et al. 2009). We have also demonstrated VEGF-B's neuroprotective effects in the progressive unilateral 6-hydroxydopamine rat PD model, after a single injection of VEGF-B in the striatum (Yue et al. 2014). In a first pilot study, we injected adeno-associated virus expressing human VEGF-B (AAV2/1-hVEGF-B) unilaterally into the SN and striatum of male PTEN-induced putative kinase 1 (PINK1) knockout (KO) rats at 5 months of age (n=4-5 per group). In this genetic PD model we saw a reduction in cumulative foot slip errors during monthly tapered balance beam (TBB) tests as compared to untreated PINK1 KO rats. The motor improvements were bilateral, in forelimbs (ipsilateral, *$p<0.05$; contralateral, **$p<0.01$), and hindlimbs (ipsilateral, **$p<0.01$; contralateral, *$p<0.05$). At 12 months of age these rats were euthanized and showed an ~30% increase in striatal dopamine (DA) content in the VEGF-B-injected hemisphere compared to the untreated PINK1 KO rats, analyzed via HPLC-EC (One-way ANOVAs; $p<0.05$; n=3-5). We also saw an increase in the VEGF-B-injected hemisphere in striatal levels of pigment epithelium-derived factor, a known negative regulator of apoptosis (*$p<0.05$). We expanded our previous pilot with a second cohort of male PINK1 KO rats, injected unilaterally with AAV2/1-hVEGF-B as above at 5 months of age (October 2017). AAV2/1-hVEGF-B treated PINK1 KO (n=8), untreated PINK1 KO (n=9) and wild type (WT; n=8) rats are currently being tested monthly under blinded conditions for changes in motor function with the TBB. At 12 months of age the rats (n=6/group) will be transcardially perfused. Unbiased stereology of dopaminergic cells in the SN and striatal terminals will be performed after co-staining for tyrosine hydroxylase and the neuronal marker, NeuN. The remaining rats will be used to increase the n number of the first pilot. The results will allow us to determine if VEGF-B's therapeutic effects on motor function and increased striatal DA content in PINK1 KO rats are due to a neuroprotective reduction in the loss of dopaminergic neurons, or a functional improvement in the surviving dopaminergic neurons.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.15/N1

Topic: C.03. Parkinson's Disease

Support: UdeG P3E2018.

Title: Effect of complete bee venom on fine-tune motor behavior in a 6-OHDA rat lesion model

Authors: *S. J. LOPEZ-PEREZ, A. K. LOMELI-LEPE
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Abstract: Bee venom has been historically used to alleviate human diseases, as arthritis and rheumatism, being currently popular as analgesic and anti-inflammatory, and experimental works have found neuroprotective effects in animal models of Parkinson´s disease, whose hallmarks can be replicated in rats throughout intra-striatal injection of 6-hydroxidopamine (6-OHDA). Animals whit this pharmacological manipulation lose fine motor capacity, as can be seen by the standardized "vermicelli handling test", consisting in manipulation and consumption of thin pieces of dried pasta. Intact animals regularly use one paw to hold the piece, and the other paw to guide the piece into the mouth. As the piece became shorter, the paws moved together into a symmetrical holding pattern. Unilateral 6-OHDA lesions resulted in atypical eating patterns and changes in movements used to manipulate the pasta, including increased movements made with the forepaw ipsilateral to the lesion, or even, incapacity to take the pasta. In this work, we analyzed the effect of "complete" bee venom on the capacity for handling pasta, to analyze its beneficial potential in the model of dopaminergic neurodegeneration by 6-OHDA. Male Wistar rats were injected with a single dose of 6-OHDA under isoflurane anesthesia, in the right striatum. After two weeks, damage was assessed by rotation induced test. Three weeks after lesion, a group was administered with filtered complete bee venom, obtained from beekeeping scholar group (CUCBA, University of Guadalajara, México). 6-7 weeks after lesion, vermicelli handling test was verified, providing the animals with 7 cm long segments of uncooked semolina spaghetti, and recording in video its behavior, in an acrylic cage. Intact animals took the segments with both forepaws, using one paw to hold, ant the other to push and guide the segment to the mouth, and ate the segments in 25.17 ± 98.2 seconds; 6-OHDA lesioned rats held the segments precariously, some released the segments in the middle of the procedure, and some were unable to get up off the floor of the cage, just sniffing the segments, without eating them. The animals that managed to eat them did so in a longer average time than controls. Animals treated with 6-OHDA and bee venom held and ate the segments in a similar time than controls, even thought its strategies to sustain and guide the pasta segments were different than controls. These results suggest that complete bee venom could have a protective effect on dopaminergic degeneration caused by 6-OHDA, maybe favoring a re-wiring of survival neurons, since animals use different strategies than intact subjects for stereotyped behavior.

Disclosures: S.J. Lopez-Perez: None. **A.K. Lomeli-Lepe:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.16/N2

Topic: C.03. Parkinson's Disease

Title: Pramipexole reverts the development of tactile allodynia in a rat model of Parkinson's disease

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Abstract: Pain is the non-motor symptom with the highest prevalence in patients with Parkinson's Disease (PD) affecting up to 85%. In studies with PD patients, it is contradictory if antiparkinsonian therapy is enough to alleviate this non-motor symptom. Although there is scarce researching about the pain mechanisms underlying this pathology. The aim of this study was to investigate the development of tactile allodynia after the nigrostriatal dopaminergic lesion induced by the unilateral 6-hydroxydopamine (6-OHDA) injection at different doses in the *sustantia nigra pars compacta* (SNc) and study the possible anti-allodynic effect of a dopamine agonist drug, Pramipexole (PPX) in rats. First, dopaminergic lesion was realized by the unilaterally injection of 6-OHDA into the SNc at different concentrations (6, 10, 13 and 16 µg/µL). To know the establishment of motor deficits, we measure number of turns, bradykinesia and forelimb-use asymmetry in the assays of rotational behavior (apomorphine, 0.1 mg/Kg, s.c.), open field and cylinder, respectively. On the other hand, to investigate the allodynia by 6-OHDA, we used the *up-down* method with von Frey filaments to measure the 50% of withdrawal response of both paws. In addition, the anti-allodynic effect of PPX was examined at different doses (0.03, 0.3 and 3 mg/Kg, s.c.) in an acute and chronic manner daily for 10 days. We found that the group of animals with the higher doses of 6-OHDA (10, 13 and 16 µg/µL) induced motor damage in the tests of open field and cylinder. Moreover, a greater number of contralateral turns by apomorphine were found in a dose-dependent manner in rats. Lesioned animals with the higher dose administered of 6-OHDA (16 µg/µL) presented significant tactile allodynia in both paws from day 16 to 32 days post-injury. The middle dose of PPX decreased significantly the 50% of withdrawal response of both paws without secondary effects. In conclusion the unilateral lesion with 6-OHDA is able to induce allodynia in both paws; interestingly the treatment with PPX reverses this nociceptive response then we suggest that PPX would have efficacy as an analgesic drug for patients with PD.

Disclosures: A.M. Austrich Olivares: None. **L. Mendieta:** None. **V. Gómez-García:** None. **A. Espinosa-Romero:** None. **A. Mata-Bermúdez:** None. **T. Pastrana-Quinto:** None. **B. Godínez-Chaparro:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.17/N3

Topic: C.03. Parkinson's Disease

Support: MJFF 6120.01

Title: Preclinical efficacy of systemically administered NPT189 in a mouse model of α-synuclein transmission

Authors: *K. MCDOWELL, E. ASP, M. PROSCHITSKY, M. LULU, C. ROCKWELL-POSTEL, J. WRIGHT, R. KRISHNAN, R. FISHER, J. LEVENSON
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Abstract: The key neuropathological feature of Parkinson's disease (PD) is the appearance of Lewy bodies, which are mainly composed of aggregated α-synuclein (α-syn). Studies have shown that as PD progresses, α-syn pathology spreads throughout the brain. Cell-to-cell transmission of proteopathic α-syn seeds appears to underlie the propagation of pathology, and this process can be recapitulated in preclinical models. We previously described the amyloid targeting activities of the general amyloid interaction motif (GAIM), a virus-derived protein that potently binds and structurally remodels fibrillar aggregates of misfolded proteins, such as amyloid beta, tau, and α-syn. GAIM also effectively reduces transmission of α-syn aggregates in a neuronal cell culture model. Here, we demonstrate the efficacy of systemically administered NPT189, a novel human-IgG1-Fc immunoglobulin fusion protein that is bivalent for GAIM, in a mouse model of α-syn transmission. Beginning 6 days after unilateral stereotaxic injection of α-syn seeds into the dorsal striatum, mice were treated intraperitoneally with NPT189 (15 mg/kg) or vehicle control twice weekly for 3-6 months. Three months after induction of pathology and treatment with NPT189, lower α-syn pathology loads were observed in both substantia nigra and amygdala, brain regions which exhibit high connectivity with dorsal striatum. Six months after induction of pathology, vehicle-treated mice exhibited a pronounced loss of tyrosine hydroxylase in the ipsilateral hemisphere of substantia nigra, whereas NPT189 treatment was associated with higher levels of tyrosine hydroxylase in substantia nigra relative to vehicle-treated mice. Our preclinical data suggest that NPT189 modulates α-syn-associated pathology by interfering with transmission of proteopathic α-syn seeds, which represents one putative mechanism whereby PD pathology progresses in patients.

Disclosures: K. McDowell: A. Employment/Salary (full or part-time):; Proclara Biosciences. **E. Asp:** A. Employment/Salary (full or part-time):; Proclara Biosciences. **M. Proschitsky:** A. Employment/Salary (full or part-time):; Proclara Biosciences. **M. Lulu:** A. Employment/Salary (full or part-time):; Proclara Biosciences. **C. Rockwell-postel:** A. Employment/Salary (full or

part-time):; Proclara Biosciences. **J. Wright:** A. Employment/Salary (full or part-time):; Proclara Biosciences. **R. Krishnan:** A. Employment/Salary (full or part-time):; Proclara Biosciences. **R. Fisher:** A. Employment/Salary (full or part-time):; Proclara Biosciences. **J. Levenson:** A. Employment/Salary (full or part-time):; Proclara Biosciences.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.18/N4

Topic: C.03. Parkinson's Disease

Support: CAPES-FCT
Maratona da Saúde
FAPESC
CNPq

Title: Adenosinergic drugs control striatal metaplasticity in mice with L-DOPA-induced dyskinesia

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Abstract: Objectives: The aim of this study was to evaluate the effects of adenosinergic drugs on striatal metaplasticity in dyskinetic mice induced by L-DOPA. Methods and results: C57BL/6 male mice (8-12 weeks) were treated with 6-hydroxydopamine (6-OHDA, 3 μg in 1 μL of 0.02% ascorbic acid diluted in 0.9% NaCl), in two different regions of the right mid-striatum (2 x 2 μL, 0.5 μL/min) to mimic a hemiparkinsonism. After 4 weeks, they were challenged with R(-)-apomorphine (0.6 mg/kg, subcutaneous), to confirm the lesion. During 30 days the animals received a daily intraperitoneal (i.p.) injection with L-DOPA (25 mg/kg) plus benserazide (12.5 mg/kg). The animals were then sacrificed and their brain removed to prepare striatal coronal slices (400 μm) used to measure corticostriatal transmission and synaptic plasticity assessed (WinLTP 2.20b Reanalyzes® software) 30 min after applying a high frequency stimulation protocol (HFS: 100 Hz, 3 times, every 20 seconds). We compared control and 6-OHDA-lesioned striatal slices in the absence and presence of either the selective adenosine A2A receptor antagonist SCH58261 (50 nM) or the analogue of adenosine 2-chloroadenosine (2-CADO, 100 nM) (n=8-12 independent preparations per group). The slices from mice with L-DOPA-induced dyskinesia displayed a shift in striatal plasticity to long-term potentiation (LTP) in control and 6-OHDA side in comparison to both sides in animals who received saline ($F_{3,76}$= 55,11, $p<0.05$). Notably, the incubation of striatal slices from dyskinetic mice with SCH58261 or 2-CADO

induced long-term depression (LTD). Conclusion: These findings demonstrate that animals with L-DOPA-induced dyskinesia display alterations in striatal metaplasticity that can be modulated by the blockade and activation, respectively, of adenosine A2A and A1 receptors. Altogether, these results reinforce the potential of adenosinergic drugs in the treatment of L-DOPA-induced dyskinesia.

Disclosures: A.E. Speck: None. **A.S. Aguiar:** None. **R.A. Cunha:** None. **R.D. Prediger:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

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Topic: C.03. Parkinson’s Disease

Support: Michael J Fox target validation grant (2014-2017)
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ISN-CAEN Category 1A (2017)

Title: A combined pharmacological strategy to block NMDA receptor function and reduce L-DOPA induced dyskinesias

Authors: *S. SANZ-BLASCO, L. ISAJA, M. P. BORDONE, A. K. STARK, O. S. GERSHANIK, J. E. FERRARIO
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Abstract: Levodopa (L-DOPA) induced dyskinesias (LID) are one of the most disabling side effects which appear after prolonged use of this drug for the treatment of Parkinson’s disease (PD). Finding a therapeutic alternative that could reduce LID is of great importance to improve the quality of life of PD patients. Moreover, gaining a more profound knowledge of the pathophysiology of LID is crucial for the development of more effective drugs and understanding the maladaptive changes taking place with the progression of the disease. Amantadine (or its analog, memantine) is a NMDA receptor (NMDA-R) antagonist which has been reported to reduce LID. However, its efficacy is limited and its safety and tolerability restricts its use in some patients. In this context, the aim of this work is to investigate pharmacological strategies, including novel target approaches, to reduce the use of amantadine. The inhibitor of the Src family kinases (SFKs) saracatinib (AZD0530), is an experimental drug currently under a phase 2a clinical trial for Alzheimer's disease, for its blocking effect on Fyn, one of the members of the SFKs. Fyn mediates the regulation of the NMDA-R by phosphorylating Tyr-1472 at the NR2B subunit and regulates NMDA-R redistribution after dopamine depletion and L-DOPA treatment. Recently, we have shown that saracatinib partially reduces dyskinesias in a mouse model of LID (Sanz-Blasco et al., Mol Neurobiol 2017),

suggesting a potential benefit of AZD0530 for PD patients under L-DOPA treatment. Here we have established an alternative approach targeting simultaneously the NMDA-R by two different strategies: reducing its availability at the membrane by inhibiting Fyn activity with saracatinib, and blocking the NMDA-R with amantadine. We have determined the intensity of LID on 6-OHDA lesioned mice treated with L-DOPA and challenged them either with saracatinib, amantadine or a combination of both drugs with the purpose of comparing their antidyskinetic properties at different concentrations. We have observed that, in dyskinetic mice with an equivalent severity of lesion, as determined by tyroxine hydroxilase immunohistochemistry, those treated with a combination of amantadine (at a lower dose than its effective concentration) and saracatinib (at a sub-therapeutic dose) showed reduced dyskinesia scores. LID reduction was greater when both drugs were administered in combination than when given individually at higher doses. Altogether, our results confirm the importance of the NMDA-R in the development of LID and point to a potential alternative strategy to control LID development in PD patients.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.20/N6

Topic: C.03. Parkinson’s Disease

Support: Lundbeck Postdoc Fellowship R171-2014-591

Title: Chronic caffeine treatment modulates disease progression in a transgenic α-synuclein prion-like spreading mouse model of Parkinson’s disease

Authors: *N. FERREIRA[1], C. BETZER[2], L. REIMER[1], M. ROMERO-RAMOS[3], P. H. JENSEN[4]
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Abstract: Introduction Compiling amount of evidence suggest that cell-to-cell transmission and the self-propagation of pathogenic aggregated α-Synuclein (αSyn) plays a central role in the initiation and the progression of Parkinson’s disease (PD). Epidemiological studies suggest that prolonged caffeine intake may confer neuroprotection against the underlying dopaminergic neuron degeneration, and influence the onset and progression of PD. The present study sought to investigate the chronic protective effects of caffeine intake in a tg αSyn prion-like spreading mouse model of PD.

Methods A53T-mutant ($M83^{-/+}$ and $M83^{+/+}$) Tg mice were injected bilaterally in the upper hind limb muscles (biceps femoris) with fibrilar mouse αSyn and treated in the absence or presence of caffeine (0.3 mg/mL) in the drinking water.
Results Chronic caffeine treatment resulted in significant delay (up to 3 weeks) of the onset of clasping behavior and also increased lifespan (up to 40%) in both $M83^{-/+}$ and $M83^{+/+}$ compared to vehicle treated controls. In addition, western blot analysis of brains homogenates of both $M83^{-/+}$ and $M83^{+/+}$ mice showed significantly reduced levels of total α-syn and pathological P-α-syn in the urea-SDS soluble fraction of caffeine-treated mice compared to controls. The mechanism for the observed protection is being investigated in cell models.
Conclusion Taken together, our data strongly suggest caffeine as modulator of α-syn spreading. Understanding the mechanism of action of caffeine will open the relative narrow therapeutic window for patients suffering from α-synucleinopathies.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.21/N7

Topic: C.03. Parkinson’s Disease

Support: Michigan Parkinson Foundation

Title: The role of dysfunctional BDNF in remodeling of the parkinsonian striatum following dopamine neuron grafting in val68met (rs6265) knock-in rats

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Abstract: We recently reported that early-stage Parkinson’s disease (PD) subjects possessing the met allele of the rs6265 *Bdnf* variant exhibit reduced therapeutic efficacy of oral levodopa. Up to 40% of the population possesses the rs6265 *Bdnf* met allele, which results in diminished neuronal release of BDNF. BDNF plays an important role in spine dynamics of striatal medium spiny neurons, sculpting the structure and function of synapses. We hypothesize that BDNF is an unrecognized contributor to the discordant finding of abundant survival of grafted dopamine (DA) neurons and lack of behavioral efficacy reported in a subpopulation of PD subjects and aged parkinsonian rats. To test this hypothesis, we generated a CRISPR knock-in rat model of the human rs6265 BDNF variant to evaluate the impact of reduced host BDNF release on the

function and synaptic integration of new DA terminals in the parkinsonian striatum. In this study we will compare graft survival, integration, and behavioral improvement between val68val wild-type ('WT', BDNF normal) and homozygous met68met ('MET', BDNF reduced) young adult parkinsonian rats. Rats were rendered unilaterally parkinsonian with intranigral 6OHDA and primed with levodopa (12mg/kg, s.c.; M-Fr) 4 weeks after 6-OHDA to induce stable expression of levodopa-induced dyskinesias (LID). This complex behavioral malady was chosen as the primary behavioral endpoint. Amphetamine-induced rotational behavior served as a second behavioral endpoint. Five weeks following levodopa priming, WT and MET rats received a sham graft (WT N=8; MET N=8) or primary embryonic mesencephalic neurons (200,000 cells, E14 WT donors; WT N=7; MET N=8); parameters that we have previously established to significantly improve amphetamine-induced rotations and ameliorate LID in young WT parkinsonian rats. Data thus far reveal significant differences in pre-graft amphetamine rotational asymmetry and LID profiles in WT rats compared to MET rats. Specifically, while both genotypes show a similar time course of LID onset and peak dose LID severity, MET rats show a faster 'wearing off' compared to WT ($p=0.02$). MET rats also display significantly less amphetamine-induced rotational asymmetry (MET 8.5 ± 0.3/min; WT 11.6 ± 0.8/min; $p=0.002$). These findings suggest differences in DA neurotransmission due to the rs6265 met allele. Behavioral responsiveness to mesencephalic grafts between genotypes is currently ongoing. Post mortem analyses will include quantitative assessment of: 1) graft survival; 2) graft volume; 3) neurite outgrowth; 4) synaptic connectivity between grafted dopaminergic neurites and host neurons. Supported by Michigan Parkinson Foundation.

Disclosures: K. Steece-Collier: None. **R.L. Dangremond:** None. **C.E. Sortwell:** None. **T.J. Collier:** None. **I.M. Sandoval:** None. **B.F. Daley:** None. **M.F. Duffy:** None. **N.M. Mercado:** None. **J.A. Stancati:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

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Program #/Poster #: 292.22/N8

Topic: C.03. Parkinson's Disease

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National Health Research Institutes, Taiwan

Title: Post-treatment with PT302, a long-acting Exendin-4 sustained release formulation, reduces dopaminergic neurodegeneration in a 6-Hydroxydopamine rat model of Parkinson's disease

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Abstract: We previously demonstrated that pretreatment with Exendin-4, a glucagon-like peptide-1 (GLP-1) receptor agonist, reduces 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -mediated dopaminergic neurodegeneration. The use of GLP-1 or Exendin-4 for Parkinson's disease (PD) patients is limited by their short half-lives. The purpose of this study was to evaluate a new extended release Exendin-4 formulation, PT302, in a rat model of PD. Subcutaneous administration of PT302 resulted in sustained elevations of Exendin-4 in plasma for >20 days in adult rats. To define an efficacious dose within this range, rats were administered PT302 once every 2 weeks either before or following the unilaterally 6-hydroxydopamine lesioning. Pre- and post-treatment with PT302 significantly reduced methamphetamine-induced rotation after lesioning. For animals given PT302 post lesion, blood and brain samples were collected on day 47 for measurements of plasma Exendin-4 levels and brain tyrosine hydroxylase immunoreactivity (TH-IR). PT302 significantly increased TH-IR in the lesioned substantia nigra and striatum. There was a significant correlation between plasma Exendin-4 levels and TH-IR in the substantia nigra and striatum on the lesioned side. Our data suggest that post-treatment with PT302 provides long-lasting Exendin-4 release and reduces neurodegeneration of nigrostriatal dopaminergic neurons in a 6-hydroxydopamine rat model of PD at a clinically relevant dose.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.23/N9

Topic: C.03. Parkinson's Disease

Support: Clinical and Translational Science Institute (CCTSI) TL1 fellowship TL1TR002533
University of Colorado Movement Disorder Center

Title: Short chain fatty acid drug sodium butyrate delays Parkinson's disease progression in transgenic mice comparable to sodium phenylbutyrate treatment outcomes

Authors: *S. M. GARCIA[1], W. ZHOU[2], C. LOZUPONE[2], C. FREED[2]
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Abstract: Background: Current therapies for Parkinson's disease (PD) temporarily improve motor function but cannot impact disease progression. Previously, we reported that sodium phenylbutyrate treatment attenuates alpha synuclein (aSyn) neuropathology and improves behavioral deficits in transgenic mice expressing human mutant aSyn Y39C. However, sodium phenylbutyrate for human use costs about $10,000/kg and has several side effects including allergic skin rash in about 10% of people.
Objective: To bypass obstacles associated with sodium phenylbutyrate therapy, we assessed if sodium butyrate can similarly delay disease progression in aSyn Y39C mice.
Methods: 12-month aSyn Y39C mice were separated into 3-groups (n=6) based on rotarod performance and treated with either sodium phenylbutyrate, sodium butyrate, or sodium chloride (vehicle) for 3-months by water supplementation. Disease progression was determined by behavioral and neuropathology outcomes. Rotarod and Morris water maze testing assessed motor and spatial learning abilities. Whole-brain aSyn (SYN-1 antibody) and neuroprotective DJ-1 protein levels were assessed by Western blotting. Cortical brain tissue sections were evaluated by immunohistochemistry analysis to identify Lewy body-like inclusions containing intracellular human aSyn (LB509 antibody) and pathological aSyn (pSerine129) protein aggregates. Feces was collect at 12 and 15-months to perform 16s rRNA sequencing and QIIME1 analysis to identify gut-microbe shifts associated with treatment.
Results: Both sodium phenylbutyrate and sodium butyrate improve motor and spatial learning abilities, attenuate Lewy body-like inclusions, decrease whole-brain aSyn oligomerization, increase DJ-1 protein, and increase plasma aSyn compared to vehicle treatment. Though sodium phenylbutyrate and sodium butyrate treated mice displayed similar motor and cognitive abilities at 15-months, sodium phenylbutyrate more effectively reduced brain aSyn oligomerization. Microbial composition shifts were not associated with treatment, age, or transgene expression.
Conclusions: Sodium butyrate and sodium phenylbutyrate similarly delay disease progression in

a transgenic mouse model of age-related Parkinson's by elevating neuroprotective protein DJ-1 levels resulting in reduced neuropathology and behavioral deficits. Butyrate treatment may promote the clearance of brain aSyn to the cerebral spinal fluid and plasma to delay disease progression. Since sodium butyrate is up to 50-times cheaper than sodium phenylbutyrate, sodium butyrate or calcium magnesium butyrate should be considered for future clinical investigations.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

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Topic: C.03. Parkinson's Disease

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Title: Neuroplastic effects in the striatum contribute to the suppression of the development of L-DOPA-induced dyskinesia by sub-anesthetic ketamine

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Abstract: Sub-anesthetic ketamine infusions are an effective therapy for the treatment of depression and chronic migraine headaches. Parkinson's disease (PD) and L-DOPA-induced dyskinesia (LID) share a commonality with both disorders, hypersynchrony in brain networks, and ketamine alters oscillatory brain activity. We have demonstrated a long-term therapeutic effect of ketamine in PD patient case studies with LID (Sherman et al. 2016). In a preclinical model (Bartlett et al. 2016), we have reported that established LID, measured by abnormal involuntary movements (AIMs) in this model, are reduced by low-dose ketamine infusion (10-hr infusion paradigm with 20 mg/kg, five *i.p.* injections 2 hrs apart). Here, we test if low-dose ketamine can suppress development of LID. Male Sprague-Dawley rats were unilaterally injected with 6-hydroxydopamine to create a PD model. In a first cohort (n=9/group), rats were primed for 4 weeks with escalating daily L-DOPA doses and treated for 10 hrs with ketamine once per week, as described above. Total limb, axial, and oral AIMs were scored every 3-4 days

under blinded conditions. Ketamine treatment led to a 50% reduction in the development of AIMs ($p<0.05$; One-way ANOVAs, Tukey *post-hoc* tests), even on testing days without ketamine, indicating a neuroplastic effect. In striatal tissue an increase in phosphorylation of mTOR, a master regulator of neuroplasticity, was seen after ketamine (intact, $p<0.001$, lesioned, $p<0.05$; two-tailed *t*-test). In a second cohort (n=10/group), PD rats were primed with daily injections of L-DOPA for 14 days, and treated with ketamine on days 0 and 7 for 10 hrs, ketamine plus the tropomyosin receptor kinase B (TrkB) antagonist, ANA-12, or vehicle. On day 14, ketamine treated rats showed a 50% reduction in their AIMs scores as compared to vehicle ($p<0.01$; One-way ANOVAs, Tukey *post-hoc* tests). However, this sustained effect of ketamine was blocked in rats co-treated with ANA-12 ($p<0.05$). The rats were euthanized, and dendritic spines in the striatum were analyzed after a Golgi stain, showing a 2-fold increase in multi-synaptic mushroom spines on the lesioned side of vehicle-injected rats, that is not seen in the ketamine-treated group ($p<0.0001$). In the ketamine+ANA-12 group the mushroom spines on the lesioned side approach the level seen in the vehicle group proving a block of ketamine's effect by ANA-12 ($p<0.0001$). In conclusion, the sustained anti-dyskinetic effect of ketamine is inhibited by blocking the brain-derived neurotrophic factor (BDNF) receptor (TrkB) and involves changes in striatal spine density. Combined, this data suggests a novel use for low-dose ketamine as a therapy to suppress LID development.

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Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.25/N11

Topic: C.03. Parkinson's Disease

Support: Michael J Fox Foundation
Advance Queensland Research Fellowship

Title: Neuroprotective efficacy of nilvadipine in experimental models of Parkinson's disease

Authors: *R. GORDON[1], A. HICKS[2], J. CONROY[3], K. Z. HANTON[2], C. S. FONG[2], V. KUMAR[4], M. A. COOPER[5], K. SCHRODER[5], T. M. WOODRUFF[3], J. D. O'SULLIVAN[2]
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Abstract: Abstract Parkinson's disease (PD) pathology is characterized by a profound loss of nigral dopaminergic neurons that is accompanied by chronic neuroinflammation and extensive α-

synuclein inclusions in the form of Lewy-bodies. L-type calcium channel blockers (LCC) have been shown to have protective effects in multiple models of neurodegeneration. However the mechanisms by which these calcium channel blockers could exert their neuroprotective effects remain unclear. In this study, we evaluated the neuroprotective efficacy of the clinically approved antihypertensive drug nilvadipine and its effects on neuroinflammation in experimental models of Parkinson's disease. We found that pre-treatment with nilvadipine caused a dose-dependent reduction in microglial inflammasome activation and neuroinflammatory mediators induced by pathological synuclein aggregates. Further, nanomolar doses of nilvadipine also protected against neuronal death induced by MPP^+ and 6-OHDA in dopaminergic N27 cells. Our *in vivo* studies confirmed that nilvadipine can enter the CNS at therapeutically relevant concentrations with daily dosing. Crucially, daily dosing with nilvadipine (8 mg/kg) protected against behavior deficits, dopamine depletion and neuropathology in the 6-OHDA model of Parkinson's disease. Our results demonstrate for the first time that nilvadipine can mitigate inflammasome activation and microglial neuroinflammation that are closely linked to disease progression in PD. Collectively, our results suggest that nilvadipine could have potential to be repurposed as a disease-modifying therapy for the management of PD.

Disclosures: R. Gordon: None. **A. Hicks:** None. **J. Conroy:** None. **K.Z. Hanton:** None. **C.S. Fong:** None. **V. Kumar:** None. **M.A. Cooper:** None. **K. Schroder:** None. **T.M. Woodruff:** None. **J.D. O'Sullivan:** None.

Poster

292. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 292.26/N12

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation
Iowa Neuroscience Institute Pilot Funding

Title: Modulation of miR-181 influences dopaminergic neuronal degeneration in a mouse model of Parkinson's disease

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive loss of dopaminergic (DA) neurons of the substantia nigra (SN), which project to the striatum where dopamine release stimulates neuronal circuits controlling voluntary movement. Loss of nigrostriatal dopamine results in classic motor symptoms of PD, such as tremor, rigidity, and bradykinesia. PD pathogenesis is not fully understood and mechanisms are thought to involve

oxidative stress, defective autophapy/mitophagy, and neuroinflammation. Currently no treatments are available to halt PD progression. MicroRNAs (miRs) are a diverse class of small, non-coding RNAs that target mRNAs for translational inhibition and degradation, and several recent studies demonstrate that certain miRs may represent viable therapeutic targets. In this work, we asked whether the microRNA miR-181 family, which has previously been implicated in regulating apoptosis and mitophagy, plays a role in PD pathogenesis. The miR-181 family is abundantly expressed in brain and has been shown by two independent studies to be up-regulated in PD patient brain tissues and cerebrospinal fluid. For our PD mouse model, we employed an AAV5-based vector encoding human α-synuclein (αSyn) driven by the neuronal-specific synapsin I promoter (AAV5-syn1-αSyn) to over-express αSyn in mouse SN via direct injection. Within 14 weeks post-injection, loss of SN neurons was evident; staining for tyrosine hydroxylase (TH), a DA neuron marker, indicated significant loss of SN neuronal bodies and striatal projections (up to 70% striatal TH loss, relative to AAV5-syn1-eGFP controls; n=10/group, $p<0.01$). To evaluate the effects of miR-181 in this model, AAV5 vectors expressing either miR-181 or inhibitory RNAs that sequester and inactivate endogenous miR-181 were co-injected with AAV5-syn1-αSyn. Based on TH staining, we determined that <4-fold over-expression of miR-181 markedly exacerbated SN neuronal loss, while inhibition of endogenous miR-181 almost completely blocked αSyn-induced neurodegeneration, relative to controls (i.e. scrambled inhibitory RNA; n=10/group, $p<0.01$). In addition, follow-up studies showed that miR-181 overexpression in SN alone was capable of eliciting measurable loss of TH staining, whereas miR-181 inhibition was well-tolerated. These new data are intriguing and suggest that miR-181 provokes DA neuronal cell death and accelerates aSyn-induced neurotoxicity, thus warranting future studies to 1) delineate the underlying mechanisms, 2) better define miR-181 regulation in DA neurons and 3) advance pre-clinical testing of miR-181 inhibition as a therapeutic strategy for PD.

Disclosures: R.L. Boudreau: None. **N.H. WItmer:** None. **C.S. Stein:** None.

Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.01/O1

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIA T32 AG00216-23

Title: Behavioral consequences of neuronally - derived exosomes cargo proteins *in vivo*

Authors: *C. N. WINSTON[1], E. M. ROCKENSTEIN[2], M. MANTE[2], J. FLORIO[2], B. SALEHI[2], A. ADAME[2], E. MASLIAH[3], R. A. RISSMAN[4]

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Abstract: Background: Exosome cargo proteins acutely predict the conversion of mild cognitive impairment (MCI) to Alzheimer's disease (AD), however the pathogenic potential of exosomes has yet to be fully elucidated. We recently reported neuronally-derived exosomes (NDEs) isolated from demented patients acutely (1m) induced AD-like neuropathology in normal mouse CNS. Here, we extended our previous studies to investigate the chronic neuropathological and behavioral consequences of plasma NDE cargo proteins *in vivo.*
Methods: Plasma exosomes derived from stable MCI patients and MCI converting to AD patients (ADC) were extracted, precipitated, and enriched against a neuronal source (L1-CAM) by fluorescent activated cell sorting (FACS) and characterized by Nanosight. Exosome preparations were injected unilaterally into normal mouse CNS and locomotor activity, anxiety, and spatial learning and memory was assessed 6m and 12m post-injection. Neuropathological changes were visualized by immunostaining at 3m, 6m, and 12m post-injection.
Results: We observed no signs of astrogliosis and microglioses however, pathological forms of tau, as measured by PHF1, and oligomeric amyloid beta (oAβ) as measured by 6E10, was observed bilaterally in the entorhinal cortex, hippocampus, and subcortical post-thalamic regions, at all three timepoints. Anxiety-like behavior was not observed, and normal locomotor activity was similar in all groups at all three timepoints. Spatial learning and memory deficits, as assessed by the Morris Water Maze, was observed in
MCI and ADC NDE-injected mice at 6m post-injection, with ADC NDE-injected mice exhibited worsening cognitive deficits as compared to controls. Surprisingly, at 12m post-injection, MCI and ADC NDE-injected mice performed similarly in all behavioral tasks as compared to controls. The attenuated cognitive decline may be a synergistic consequence of age, as demonstrated by degenerating cognition in the 12m control mice as compared to 6m control mice; and increased protein clearance of plasma NDE cargo proteins in MCI and ADC NDE-injected mice.
Conclusion: We are the first to report the pathogenic potential of plasma NDEs *in vivo*. Neural exosomes package and traffic toxic AD-related proteins to the blood where they mediate protein prorogation and induce learning and memory deficits in normal mouse CNS.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.02/O2

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: JPND INSTALZ grant
LabEx (Excellence Laboratory)
DISTALZ (Development of innovative Strategies for a Transdisciplinary Approach to Alzheimer's disease)

Title: Re-expression of differentiation factors in the neuronal DNA damage response: Alteration in tauopathies

Authors: *C. SCHIRMER, Y. DJENIDI, M.-L. REYNAERT, L. BUÉE, B. LEFEBVRE, M.-C. GALAS
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Abstract: No treatments are currently able to effectively prevent the progression of tauopathies, such as Alzheimer's disease, which are the most common neurodegenerative diseases in the elderly. Therefore it is urgent to understand the early mechanisms involved in the etiology of these pathologies to highlight new therapeutical targets. Tauopathies are characterized by the aggregation of hyperphosphorylated forms of Tau protein into neurons. Tau is mainly described as a cytosolic protein involved in microtubules stabilization. However, Tau protein is also located in neuronal nuclei where its functions are still unclear. We previously demonstrated that, *in vivo*, nuclear Tau protects the integrity of neuronal DNA and that, in the Thy-Tau22 mouse model of tauopathy, Tau oligomerization alters its DNA protective function. Tau deletion-induced DNA damage is associated with an alteration of neuronal heterochromatin structure leading to aberrant genes re-expression which could participate to neurodegeneration. Our hypothesis is that the accumulation of neuronal DNA damage could activate the expression of genes playing a crucial role in differentiation. These factors would participate to the neuronal DNA damage response in mouse and human brain. We speculated that their expression could be regulated by Tau. By a combination of RT-qPCR, western blotting, and immuno-fluorescence analyzes we characterized, in N2A cells lines, in WT, KO-Tau and Thy-Tau22 mouse brains and in Alzheimer's brains the re-expression of essential differentiation genes in response to neuronal DNA damage. We also highlighted the deleterious effect of the deletion of Tau and pathological forms of Tau on their expression and functionality. Dysregulated expression of differentiation factors related to Tau-induced neurodegeneration opens the way for promoting efficient tau-based therapies in tauopathies.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.03/O3

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: Academy of Finland (no. 267788 and 305710))
Jane and Aatos Erkko Foundation
Sigrid Juselius Foundation
Helsinki Institute of Life Sciences Proof-of-Concept grant

Title: Prolyl oligopeptidase is a novel and critical regulator for protein phosphatase 2A

Authors: *T. T. MYÖHÄNEN, R. SVARCBAHS, U. JULKU, M. JÄNTTI
Univ. of Helsinki, University of Helsinki, Finland

Abstract: Background
Protein phosphatase 2A (PP2A) is the main phosphatase in mammalian cells. It is the key regulator of cell cycle but regulates also several kinases, proteins and receptors. Downregulation of PP2A has been connected e.g. to Alzheimer's disease, where it leads to Tau hyperphosphorylation and aggregation. This has made PP2A a tempting drug target but its complicated holoenzyme structure and strict regulation has made the development of PP2A activators difficult. Now, we have found that a serine protease, prolyl oligopeptidase (PREP), negatively regulates PP2A and that small-molecule PREP inhibitors or PREP deletion induces PP2A activity.
Methods
Protein-protein interactions were studied by protein-fragment complementation assay (PCA) in HEK-293 cells, using split Gaussian luciferase (hGluc) tagged constructs for PREP, PP2A catalytic subunit (PP2Ac), a PP2A endogenous inhibitor, protein phosphatase methylesterase 1 (PME-1) and an endogenous PP2A activator, protein phosphatase 2 activator (PTPA). KYP-2047 was used as a PREP inhibitor with concentrations of 1-10 µM. PP2A phosphatase activity assay was used to determine PP2A activity. Levels of PP2Ac/p(Y307)PP2Ac, PME-1, PTPA, regulatory subunit PPP2R2A (B55), p(S2448)mTOR/mTOR, p(T308)Akt/Akt and p(T183/T183/T221)JNK/JNK1+2+3 were determined by Western blot. Generation of PREP-knock-out HEK-293 cells (PREP-KO cells) and PREP-KO mouse have been described earlier. N=3-4 in all assays.
Results
In PCA assays, PREP showed interactions with PP2Ac, PME-1 and PTPA. After 4h PREP inhibition by 1-10 µM KYP-2047, the interaction between PP2Ac, PME1 and PREP was increased but interaction between PP2Ac and PME-1 reduced. In phosphatase assay, PREP inhibition significantly increased PP2A activity, and this was supported by significantly reduced p(Y307)PP2Ac and PME-1 levels. PREP inhibition elevated total PP2Ac, B55 and PTPA levels and dephosphorylated PP2A targets, such as mTOR, Akt and JNK, and PREP overexpression had opposite effects. p(Y307)PP2Ac and phosphorylation levels of several PP2A targets were reduced in PREP-KO cells and in the cortex of PREP-KO mouse.
Conclusions
Our current data shows that PREP regulates functions of both endogenous inhibitor PME-1 and endogenous activator PTPA via direct protein-protein interaction. PREP inhibition modulates these interactions, leading to PP2A activation. Our results with PREP-KO systems indicate that

this regulation is conserved and important for PP2A. When taking in account that PREP inhibition is considered safe even in clinical trials, our findings support the potential of PREP inhibitors as PP2A activators.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.04/O4

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH: 9R01NS096785-06
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The Amyotrophic Lateral Sclerosis Association
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Title: Ubiquilin-2 regulation of tau and α-synuclein in neurodegenerative disease

Authors: *J. GERSON[1], S. S. PISTORIUS[2], J. WELDAY[1], L. M. SHARKEY[1], H. L. PAULSON[3]
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Abstract: Protein dyshomeostasis is a common factor in the most prevalent age-related neurodegenerative diseases. The protein, ubiquilin-2 (UBQLN2), helps ensure protein homeostasis by shuttling ubiquitinated substrates to the proteasome for degradation and by modulating autophagy. UBQLN2 is implicated indirectly in various disorders, including tauopathies and synucleinopathies, due to its accumulation in neuropathological deposits. More recently, UBQLN2 has been directly connected as a cause of frontotemporal dementia when mutated, and our laboratory has linked the toxicity of UBQLN2 to its aggregation. To evaluate whether UBQLN2 regulates tau and α-synuclein expression, aggregation or clearance, we assessed levels of tau or α-synuclein in cells and compared results with UBQLN2 to highly homologous, UBQLN1, which is not robustly correlated with disease. The ability of UBQLN2 to regulate other common aggregate-prone disease proteins was also evaluated. Co-expressed UBQLN2 markedly lowered levels of α-synuclein and tau. Conversely, knockdown of UBQLN2 significantly elevated levels of α-synuclein and tau. In contrast, UBQLN1 did not exhibit the same ability to decrease tau and α-synuclein levels. Likewise, UBQLN2 selectively had an effect on levels of TDP43 and Huntingtin. UBQLN2 expression in mice also lowered levels of tau and α-synuclein. The possibility that UBQLN2 undergoes alterations in disease was evidenced by the

fact that more UBQLN2 was insoluble in human disease and transgenic mouse models of synucleinopathy and tauopathy than in controls, while UBQLN1 levels were highly variable across both control and disease samples. Our findings highlight a new role for UBQLN2—but not UBQLN1—in managing tau and α-synuclein levels. While UBQLN2 and UBQLN1 are highly homologous, our results suggest they are not simply redundant proteins and differences between the two ubiquilins may depend on domains unique to UBQLN2. However, lowered soluble UBQLN2 in disease brain suggests that UBQLN2 may be dysfunctional in synucleinopathies and tauopathies, due to its intrinsic aggregation or accumulation in disease aggregates.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.05/O5

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Activity-dependent release of human tau from transgenic *Drosophila* neurons

Authors: *S. K. ISMAEL[1], R. A. COLVIN[2], D. LEE[3]
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Abstract: Alzheimer's disease (AD) is the most prevalent neurodegenerative disease characterized by accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT), causing neuronal death. It is known that the tangles are composed of microtubule associated protein tau (MAPT), which is hyper-phosphorylated and aggregated. In recent years, an intriguing concept of prion-like spreading of pathogenic proteins such as tau has emerged. A prion-like mechanism involves the transfer of hyper-phosphorylated and/or aggregated tau between synaptically connected neurons, and underlies the seeding and spread of tau pathology. The first step to understand tau propagation between neurons is to study tau release from neurons. It is well known that disruption of neuronal activity is involved in AD pathogenesis. This finding is directly related to the fact that neuronal excitability increases at the early stage of AD as patients with mild cognitive impairment have shown hyperactivity in the hippocampus. Therefore, we asked whether stimulation of neurons increases 'toxic' tau release. *Drosophila* primary neuronal culture expressing human tau was used to develop a model system to study release of toxic tau, toxicity and propagation of human tau. We found human tau can be released into the media and this release was induced chemically by 50mM KCl depolarization. Additionally, intracellular calcium ion chelation reduced the amount of tau release while extracellular calcium chelation did not affect tau release in our system. We also utilized

optogenetic technique, which allows us to stimulate 'genetically targeted' neurons using blue light (470nm). In this experiment, we have expressed channelrhodopsin (ChR2) in fly neurons. Our results show that one-hour stimulation of neurons that express ChR2 by blue light is enough to induce tau release into the media. Taken together these results strongly support that tau release is activity dependent. *Drosophila* neurons showing activity-dependent release of tau can be an excellent model to study the role of tau toxicity and propagation in AD. Future studies aim to test the effect of different protein kinases on tau toxicity and release.

Disclosures: S.K. Ismael: None. **R.A. Colvin:** None. **D. Lee:** None.

Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.06/O6

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant AG050471
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Title: Rna binding protein tia1 is involved in tau propagation and subsequent neurodegeneration

Authors: L. JIANG[1], P. ASH[1], H. BALLANCE[1], B. MAZIUK[1], S. BOUDEAU[1], L. PETRUCELLI[2], *B. L. WOLOZIN[1]
[1]Pharmacol, Boston Univ. Schl Med., Boston, MA; [2]Neurosci. Div., Mayo Clin., Jacksonville, FL

Abstract: Background: The pathophysiology of tauopathy appears to result from both intrinsic dysfunction of tau metabolism in neurons, as well as extrinsic propagation of aggregated tau among neurons. Recent studies point to pathological stress granules as a significant mechanism contributing to the accumulation of tau pathology in neurons. However, fundamental questions about tau propagation remain unclear, including whether the inclusions induced by propagated tau contribute to the neurodegeneration and whether propagated tau affects stress granule metabolism. We sought to answer these compelling questions by comparing induction of stress granules, tau aggregates and neurotoxicity among different pools of pathological tau.
Methods: *In vitro*, C57BL/6 primary hippocampal cultures were transduced with human wild type 4R0N or mutant P301L Tau via AAV, and then treated with S1p (oligomeric Tau) or P3

(fibrillary Tau) fractions purified from PS19 mice brain tissues. Neurotoxicity were detected by LDH assay, neuronal markers (MAP-2, SYP, NeuN) western blot and cell count. Tau aggregation was measured by tau phosphorylation markers PHF-1 and CP13, and stress granules were imaged with TIA1, eIF3 and PABP. *In vivo*, S1p and P3 fractions are stereotaxically injected into hippocampal CA1 of P301S/TIA1++ and P301S/TIA1+- mice, respectively, at 3-month old. Tauopathy, pathological stress granules and neuronal loss of entorhinal cortex were examined at 3 months after injection.
Results: Oligomeric (S1p) and fibrillary (P3) tau fractions induced similar amounts of tau aggregation after treatment. In contrast, only oligomeric Tau induced neurotoxicity, with treated neurons exhibiting a 5-fold increase in LDH level, and 40% decrease of neuron number in S1p treated cultures. Our previous studies demonstrated that RNA binding protein TIA1 co-localizes with tau inclusions during neurodegeneration in P301S mice. We proceeded to investigate the effects of TIA1 reduction by shRNA in primary neurons over-expressing 4R0N WT or P301L tau. Interestingly, TIA1 reduction reduced the accumulation of tau aggregates and subsequent neuronal loss. These results were confirmed *in vivo*. We observed 30% rescue of neurons in entorhinal cortex of P301S::TIA1+/- compared to P301S::TIA1+/+ mice, which has a 48% neuronal loss after S1p injection.
Conclusions: Our findings suggest that oligomeric tau is more toxic than the fibrillar tau, and that the tau-induced neurotoxicity was unrelated to levels of tau aggregates in tauopathy neurons. Finally, TIA1 reduction appears to play a protective role in oligomeric tau propagation and subsequent neurotoxicity.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.07/O7

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Mitochondrial trafficking and clearance in tauopathies

Authors: *V. BHARAT, X. WANG
Dept. of Neurosurg., Stanford Univ., Palo Alto, CA

Abstract: Mitochondria are an essential organelle supporting a wide range of cellular functions by producing ATP, maintaining Ca^{2+} homeostasis, generating reactive oxygen species and signalling apoptosis. Defects in mitostasis - maintaining healthy mitochondria - in neurons has been implicated in the pathogenesis of many neurodegenerative diseases, including tauopathies which includes Alzheimer's disease (AD), frontal temporal lobar degeneration and parkinsonism

(FTLDP), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and Pick's disease (1,2). The outer mitochondrial membrane protein, Miro, helps in anchoring mitochondria to microtubule motors for motility and is also removed to stop motility in order to facilitate mitophagy. Recently, we have found a cellular defect in removing Miro protein from damaged mitochondria in skin fibroblasts of Parkinson disease (PD) patients. This defect can delay damaged mitochondrial clearance, causing energy shortage and oxidative stress, and consequently lead to neurodegeneration in neurons (3). Here we discovered the failure to remove Miro from damaged mitochondria in additional PD fibroblast lines which harbour mutations in MAPT gene encoding tau protein. This result suggests that mutant tau protein affects Miro removal from depolarized mitochondria and consequently interrupts mitophagy. Proving the functional relevance of mitochondrial transport and mitophagy in tauopathies, we discovered impaired mitochondrial trafficking in a human neuron model of Alzheimer's disease. Our work links tauopathies to mitochondrial transport and mitophagy in neurons and provides novel targets for therapeutic intervention.

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3. C. H. Hsieh et al., Functional Impairment in Miro Degradation and Mitophagy Is a Shared Feature in Familial and Sporadic Parkinson's Disease. Cell Stem Cell 19, 709-724 (2016).

Disclosures: V. Bharat: None. **X. Wang:** None.

Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.08/O8

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Deficits in nonsense-mediated RNA decay contribute to neurodegeneration in tauopathy

Authors: *G. ZUNIGA, G. CORNELISON, B. FROST
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Abstract: Cells utilize the nonsense mediated RNA decay (NMD) pathway for post-transcriptional control of gene expression and degradation of aberrant RNA that could otherwise encode potentially toxic proteins. Preliminary data suggests that transgenic expression of pathogenic tau, a protein that accumulates in Alzheimer's disease and related "tauopathies," promotes neurodegeneration by increased nuclear export of polyadenylated RNA through nuclear envelope invaginations in *Drosophila* and human tauopathy. These invaginations

penetrate deep into the nuclear interior and may protect RNAs from NMD by sequestering RNA away from NMD machinery. We have performed bioinformatic analysis of the transcriptome in tauopathy, which points toward a role for NMD in shaping the transcriptome in *Drosophila*, mouse, and human tauopathy. We find that genetic manipulation of NMD machinery significantly modifies tau-induced neurotoxicity in *Drosophila*, suggesting a causal role for reduced clearance of RNA by NMD as a driver of tau-induced neurodegeneration. We have used fluorescent *in situ* hybridization to examine the relationship between nuclear envelope invaginations, polyA RNA, and NMD machinery, and to determine if reduced clearance of RNAs by NMD may be in part due to physical barriers between polyA RNA and NMD machinery. We are currently utilizing an NMD-sensitive reporter to further investigate the extent of RNA clearance by NMD in *Drosophila* models of tauopathy, and to determine if reduced clearance of RNA by NMD is age-dependent. Our preliminary studies suggest a critical role for NMD in safeguarding the transcriptome and preventing accumulation of RNA transcripts that contribute to neuronal death in tau transgenic *Drosophila.*

Disclosures: G. Zuniga: None. **G. Cornelison:** None. **B. Frost:** None.

Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.09/O9

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

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UCSD RN192H-YUAN

Title: Tauopathy associated PERK alleles increase neuronal vulnerability to ER stress via loss of function

Authors: *S. H. YUAN[1], N. HIRAMATSU[2], Q. LIU[3], X. SUN[2], D. LENH[3], P. CHAN[2], K. CHIANG[3], E. H. KOO[4], A. KAO[5], I. LITVAN[6], J. H. LIN[2]
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Abstract: Tauopathies are neurodegenerative diseases defined by misfolded hyperphosphorylated tau protein deposits as neurofibrillary tangles (NFT) in the brain.

Endoplasmic reticulum (ER) stress has been implicated in neurodegenerative diseases including tauopathies; however the mechanism is still not clear. *EIF2AK3 (eukaryotic translation initiation factor 2 alpha kinase 3)*, also known as *PERK* (*protein kinase R-like endoplasmic reticulum kinase*), was identified as a genetic risk factor in tauopathies and Alzheimer's Disease (AD) in genome-wide association study (GWAS). The risk single nucleotide polymorphism (SNP) identified in GWAS, rs7571971, is in the same haplotype (haplotype B), which includes three exonic SNPs: S136C, R166G, and S704A. We hypothesized that the SNPs in haplotype B altered normal PERK function; therefore, increased the risk for neurodegeneration. We found that tauopathy-associated *PERK* alleles showed reduced activity in response to ER stress due to decreased kinase activity and increased instability. The human patient induced pluripotent stem cells (iPSC) derived neurons carrying *PERK* risk alleles were highly vulnerable to ER stress-induced injury and were associated with increased tau and p-tau level. Furthermore, iPSC derived neurons carrying normal PERK alleles were susceptible to ER stress and tau protein pathology when treated with PERK inhibitor. Our results suggest that impaired PERK activity sensitizes neurons to ER stress and may underlie the increased risk for neurodegenerative tauopathies. These findings may have implications on designing personalized therapeutics and clinical trials in patients with tauopathy.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 293.10/O10

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH/ NIA R01AG054559
Alzheimer's Association (MNIRDG
Cure PSP & CBD
BrightFocus Foundation

Title: Higher-order polyamines and ssat ablation impacts the tau neuropathology

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Abstract: Tauopathies comprise of an increasing spectrum of neurodegenerative disorders, in which no disease modifying therapies exist. Although tau is disordered, its recognized function

consists of stabilizing microtubules in support of neuronal function, yet simple modifications to tau promote neuropathology. Current targeted approaches include posttranslational modifications, activating clearance, aggregation inhibitors, and microtubule stabilizing agents, among others. Polyamines (PA) control growth, support neuronal function, axonal integrity and interact with macromolecules electrostatically and covalently promoting different cellular effects. Polyamines harbor positively charged (+2, +3, +4) nitrogen atoms at physiological pH, which make them "supercations"; yet they distribute the charge along the entire length of the carbon chain permitting unique and distinct bioactive moieties. This intrinsically changes protein, DNA, RNA, and macromolecule folding dynamics. We identified a unique interaction between polyamines and tau biology. Higher-order polyamine (longer chain length) inhibits tau fibrillization and also stabilizes microtubules. Conversely, acetylated (inactive) polyamines fail to inhibit tau and can promote aggregation. Acetylated polyamines also fail to facilitate microtubule polymerization. Using gene therapy approaches that promote prosynthetic polyamine enzymes that endorse higher-order polyamines and genetic knockout models that prevent accumulation of acetylated polyamines, we find that many components of the tau phenotype are reversed in mice. Several models of tauopathy induce spermidine spermine N-acetyl transferase (*SSAT*) and the accumulation of acetylated polyamines, we refer to as the tau-polyamine stress response (tau-PSR). However, *SSAT* ablation mitigates the PSR signature, and reduces acetylated polyamines. Additionally, mice with tauopathy sequester acetylated polyamines in cells but them following increased neuronal activity compared to non-transgenic littermates. Our data signifies an unrecognized crosstalk between the polyamine system and tau neurobiology. Identifying limited entry points within the polyamine system might subvert some components of the tau phenotype and provide therapeutic strategies for tauopathies.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 293.11/O11

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant R01AG054025
NIH Grant R01NS094557

Title: The mechanism of tau oligomer internalization

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Abstract: The microtubule binding protein, tau, aggregates pathologically into neurofibrillary tangles during Alzheimer's disease (AD). A smaller, soluble aggregate of tau known as oligomers, are comprised of a heterogeneous group of biochemically and structurally distinct aggregates. Tau oligomers have been shown by our lab and others to be toxic and self-propagate by seeding endogenous tau. Several studies have also shown that tau oligomers will propagate from cell-to-cell along anatomical connections. In addition, tau oligomers have been shown to be internalized while large fibrils are not efficiently taken up into a cell. Tau forms different aggregates which display distinct conformation (strains), the mechanism for internalization of these strains remains to be elucidated. Thus, we investigated three potential mechanisms for the internalization of recombinant and brain-derived seeded tau oligomers using primary mouse neuron cultures. Using a variety of cell imaging and toxicity measurements in combination with commercial internalization inhibitors for clathrin, caveolae, and macropinocytosis, we studied the mechanisms of exogenous tau oligomer internalization. We were able to observe the internalization of recombinant tau oligomers and attenuate tau oligomer uptake with inhibitors of clathrin-mediated endocytosis. Further, tau oligomers prepared with AD brain-derived tau oligomers showed a consistent mechanism of internalization. In determining the mechanism by which tau oligomers enter naïve cells, especially neurons, we can discover novel drug targets. Disrupting the spread of tau may stop disease progression by preventing the spread of toxicity, inflammation, and synapse loss that lead to cognitive decline in AD and related tauopathies. In addition, tau oligomeric strains may have strain specific internalization mechanisms which will influence their toxicity and ability to spread. This may explain the individual and disease-specific patterns of progression as well as rate of progression.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 293.12/O12

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: CurePSP Foundation Grant 600-6-15
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Title: The molecular tweezer CLR01 ameliorates pathology in the P301S-tau mouse model

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Abstract: Tau self-assembly into neurotoxic oligomers and fibrils underlies the pathophysiology in tauopathies. Molecular tweezers (MTs) act as unique, artificial nanochaperones and are the first small molecules whose activity as modulators/inhibitors of abnormal protein self-assembly has been discovered using a rational approach. Previously, we evaluated the effect of a lead MT, called CLR01, in the 3×Tg mouse model, which overexpresses mutant human PS1(M146V), APP(KM670/671NL), and tau(P301L). Immunohistochemistry (IHC) showed 30-50% reduction of amyloid plaques, neurofibrillary tangles, and microgliosis. Because tau hyperphosphorylation is downstream of Aβ insults, the question whether CLR01 affected tau directly or indirectly remained open. Therefore, we asked if CLR01 could be used for treatment of tauopathies in the absence of amyloid pathology and set up to answer this question using the P301S-tau mouse model. The study included 5 groups of mice, each comprising 8 males and 8 females. The treatment groups included three Tg groups, administered 0, 0.3, or 1.0 mg/kg per day CLR01 and two wild-type littermate groups receiving 0 or 1.0 mg/kg per day CLR01. CLR01 was administered for 35 days via osmotic minipumps implanted subcutaneously at 6-6.5 months of age. The mice were weighed out and grip-strength and open field tests were performed in the beginning, middle (grip-strength only), and end of the treatment. No adverse effects were observed in any of the groups. CLR01 prevented a decline in grip-strength observed in vehicle-treated Tg mice. However, Tg mice did not show deficits in any open-field test precluding evaluation of drug effect. Following completion of the treatment, the mice were sacrificed and the brains were collected and divided into the two hemispheres. One hemisphere was fixed and sectioned for IHC analysis and the other was dissected into regions of interest. Brain regions were snap-frozen and extracted into soluble, membrane-bound, and insoluble fractions. Analysis of seeding activity, phosphorylation, and oligomerization of tau is underway. Initial results show that CLR01 treatment reduced hyperphosphorylated tau and astrocytosis compared to control, suggesting target engagement and beneficial therapeutic effect.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 293.13/O13

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NINDS/NIH R01NS082730
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BrightFocus Foundation

Title: Inherited tauopathy mutation alters the interaction between tau and protein phosphatase 1

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Abstract: The tau protein is implicated in a variety of neurodegenerative disorders characterized by progressive degeneration of axons and neurons closely associated with pathologically-modified forms of the tau protein. The majority of the cases are sporadic but an important subset is caused by mutations within the tau gene, collectively these are known as frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). Due to the highly toxic nature of these mutations they are often used to model tau dysfunction but the mechanisms of the toxicity remain poorly understood. By identifying the effect of mutant tau we hope to better understand toxic mechanisms engaged by pathological tau in sporadic and inherited tauopathies. Several lines of evidence link tau toxicity to disruptions in axonal transport that may induce degeneration of axons, a common and early hallmark of disease. Previously, we showed that conformation changes in pathological tau activate a protein phosphatase 1 (PP1) and GSK3β signaling cascade that inhibits axonal transport in the squid axoplasm but exactly how tau engages this pathway remained unknown. We hypothesized that FTDP-17 mutations enhanced the tau-PP1 interaction and activation of PP1. To study this, we used WT full-length tau and a P301L mutant version of the protein to determine the nature of tau's interactions with the PP1 gamma isoform by using pulldown assays and bioluminescence resonance energy transfer (BRET) assays. We also used phosphatase activity assays to examine the effects of tau on PP1 enzymatic activity in vitro and from mammalian cell lysates. We found that tau directly interacts PP1 while the P301L mutation significantly enhanced the interaction. We also found that tau increases PP1 phosphatase activity but no significant differences existed among WT and P301L tau. Ongoing studies are evaluating the effects of WT and P301L tau on transport in primary rat hippocampal neurons. The results presented here support a direct interaction between tau and PP1 that can enhance phosphatase activity. This may have direct implications in tau-mediated axonal transport disruption and suggests some FTDP-17 mutations may confer toxicity through altering tau's interaction with PP1.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

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Program #/Poster #: 293.14/O14

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NRF-2016M3C7A1905074
2016R1A2B4009409

Title: Nitric oxide synthase-associated tau phosphorylation in CTE mouse model

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Abstract: ABSTRACT
Aims: Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease thought to be caused by repetitive traumatic brain injury (TBI) and sub-concussive injuries. While hyperphosphorylation of tau (p-Tau), which is attributed to astrocytic tangles (ATs) and neurofibrillary tangles, are known to be involved in CTE, there are limited neuropathological or molecular data. By utilizing repetitive mild TBI (rmTBI) mouse models, our aim was to examine the pathological changes of CTE-associated structures, specifically the ATs.
Results: Our rmTBI mouse models showed symptoms of depressive behavior and memory deficit, alongside an increased p-Tau expression in their neurons and astrocytes in both the hippocampus and cortex. rmTBI induced oxidative stress in endothelial cells and NO generation in astrocytes, which were mediated by hypoxia and increased HIF1α. There was also a correlated decreased regional cerebral blood flow, mild activation of astrocytes and NFκB phosphorylation, increased expression of inducible nitric oxide synthase (iNOS), increased endothelial nitric oxide synthase (eNOS) uncoupling with decreased tetrahydrobiopterin, and increased expression of nitrotyrosine, Nox2/Nrf2 signaling proteins. Combined, these effects induced peroxynitrite formation and hyperphosphorylation of tau in the hippocampus and the cortex towards the formation of ATs.
Innovation: Our model features molecular pathogenesis events of CTE with clinically-relevant latency periods. In particular, this is the first demonstration of an increased astrocytic iNOS expression in an in vivo model.
Conclusion: Our results propose a novel mechanism of uncoupled eNOS and NO contribution to Tau phosphorylation and AT formation in rmTBI brain, and contribute towards an increased

molecular understanding of the pathophysiology of human CTE (NRF-2016M3C7A1905074, 2016R1A2B4009409

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

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Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH/NIA F31 Grant AG057104-01
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Title: Developmental impact of exon 10-positive tau is lost with the P301L mutation

Authors: *J. GAMACHE[1], L. KEMPER[2], K. LEINONEN[1], E. STEUER[1], W. XIA[5], K. BENZOW[1], M. KOOB[3], K. HSIAO ASHE[4]
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Abstract: Tauopathies are a family of neurodegenerative diseases characterized by abnormal regulation of the microtubule-associated protein tau. It is thought that hyperphosphorylation of tau causes it to mislocalize from the axon to dendritic spines, where it can cause internalization of glutamatergic receptors and, consequently, cognitive deficits. The P301L mutation in tau is the most common mutation underlying familial tauopathies. To study the pathogenic effects of P301L tau in the mammalian brain, we generated two genetically matched transgenic mouse lines harboring a single copy of a Tet-Off regulatable human tau transgene containing exon 10 (E10). Importantly, the transgene is located in a non-disruptive genomic locus, outside of the coding regions of endogenous genes. These mouse lines express E10 tau in forebrain excitatory neurons either with (rT2) or without (rT1) the P301L mutation. Unexpectedly, we observed cognitive deficits in rT1 mice but not rT2 mice at five months of age. This led us to hypothesize that E10 tau without the P301L mutation is pathogenic during development. At eight weeks of age we observed higher levels of tau in rT1 than rT2 mice, explained by a slower clearance rate of E10 tau without the P301L mutation, especially in the biochemically isolated postsynaptic fraction. We also observed that at eight weeks of age, tau in rT1 mice was hyperphosphorylated compared to rT2 mice at sites previously shown to be necessary for tau's pathogenic effects at dendritic spines. To support the idea that E10 tau may indeed cause internalization of glutamatergic receptors in spines, we have shown that within the postsynaptic fraction E10 tau

without the P301L mutation is hyperphosphorylated compared to E10 tau with the P301L mutation. These findings indicate that E10 tau with and without the P301L mutation can be toxic via distinct pathways: 1) without the P301L mutation E10 tau is toxic during development, whereas 2) the P301L mutation is associated with aging-related tauopathy. Indeed, we have shown that by eight months of age, rT2 mice develop cognitive deficits while rT1 deficits remain unchanged. These distinct pathogenic pathways of tau may be explained by enhanced binding of E10 tau to microtubules, a quality lost with the P301L mutation. Future experiments will test whether this is the case, and whether suppressing human tau expression during development ameliorates the rT1 phenotype. This work is important to understand the molecular phenotypes associated with different forms of tau, and reveals abnormal dynamics of E10 tau including a slowed clearance rate and hyperphosphorylation observed at a young age.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

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Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

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Title: Retinal degeneration in PS19 tau transgenic mice

Authors: P. CHAN[1], K. CHIANG[2], N. HIRAMATSU[3], A. P. CHEN[1], E. H. KOO[2], *J. H. LIN[1,4]
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Abstract: Tau overexpression in the central nervous system has obvious deleterious effects on both spinal cord and brain, however its effect on the optic nerve and the retina is less clear. PS19 tau transgenic mice, which overexpress the human 1N4R tau isoform bearing a P301S mutation, were previously shown to express abundant levels of pathological hyperphosphorylated tau in the optic nerve and retinal ganglion cells. Furthermore, increased dystrophy was present in the optic nerve axons of PS19 mice as compared to wild-type controls. In this study, we performed

electroretinography (ERG) tests, spectral domain optical coherence tomography (SD-OCT), and histology to further characterize the retinal structure and function of aged PS19 mice. ERG showed that aged PS19 mice displaying motor symptoms exhibited reduced photopic and scotopic responses, with scotopic a- and b-wave amplitudes at lower intensities showing the greatest decreases compared to wild-type mice. SD-OCT analysis demonstrated decreased retinal thickness and increased frequency of retinal detachment in PS19 mice compared to age-matched controls. Retinal histology was performed to assess photoreceptor degeneration, levels of tau and hyperphosphorylated tau, and activation of glial cells. Western blotting and qPCR analyses of brains and retinas showed no changes in levels of the ER chaperone, BiP/Grp78, or induction of PERK in PS19 mice compared to controls In conclusion, PS19 mice exhibit surprisingly severe retinal degeneration whie ER stress-induced markers were not detected in diseased retinas.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.17/P1

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Investigating how tau overexpression in the retina of a triple repeat tau transgenic mouse model impacts visual-spatial learning

Authors: *J. NGOLAB[1], E. M. ROCKENSTEIN[1], M. MANTE[1], J. B. FLORIO[1], J. GRUNDMAN[1], N. NANDANKAR[1], E. MASLIAH[1,2], R. A. RISSMAN[1,3]
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Abstract: Symptoms of visual impairment usually precede cognitive symptoms in patients with dementia such as Alzheimer's Disease (AD). Thinning of the retinal fiber layer along with deposits of amyloid beta and hyper-phosphorylated tau, pathological hallmarks of AD, in the retina of AD patients suggest impairment may occur at the level of the retina. However, it is unclear how either amyloid beta or tau affects retinal function. Abnormal levels of phosphorylated tau and decrease of total tau have been observed in the inner plexiform layer (IPL) in the retinas of glaucoma patients, suggesting that dysregulation of tau expression may play a role in visual impairment. To understand the role of tau overexpression in the visual pathway, we utilized a transgenic mouse line overexpressing three-repeat tau (3R tau) at different ages: 3 months, 6 months, 9 months and 12 months. Visual-spatial learning was measured in both 3R tau and non-transgenic littermates by performance in the visual probe trial of the Morris Water Maze. Histological analysis of the outer nuclear layer of the retina and expression of

3RTau was assessed through immunohistochemistry. 3R tau mice at 6 months of age took longer to locate the platform in the visual probe trial of the Morris Water Maze compared to non-transgenic mice. There were no differences in outer nuclear layer (ONL) thickness between wildtype and transgenic mice, suggesting 3R tau overexpression does not induce photoreceptor degeneration. However, 3R tau expression in the retina was observed through immunohistochemical analysis as early as 3 months, mainly in the ganglion cell layer (GCL) and the IPL. Expression of 3R tau precedes visual impairment in 3R tau mice. It is possible that early 3R tau expression may alter vision processing at the level of the IPL. The IPL is a stratified structure that houses synapses of the multiple retinal cell types responsible for processing vision. Further investigation into tau expression the IPL may provide further insight into the molecular mechanism of visual impairment and retinal pathology in tauopathies.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 293.18/P2

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Discharge and synaptic input profiles of striatal neurons in models of neurodegenerative disease

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Abstract: *Objective*: Many neurodegenerative tauopathies lack validated animal models. In order to validate animal models it is necessary to understand the impact on individual neurons in affected brain regions. Here we compared electrophysiological properties of striatal neurons of wildtype mice with an existing transgenic model of Pick's disease (K3 mice) and an occasional Parkinson's model, rotenone injected mice.
Methods: All experiments were approved by the Animal Ethics Committee of the University of Sydney. The electrophysiological discharge properties (n = 55) and synaptic input properties (n = 5) of mouse striatal neurons were characterized in three experimental groups; *wildtype* mice (n= 27), K3 transgenic mice (n= 16), and rotenone-treated mice (n= 12), all on the C57BL/6 background. Recordings were made from coronal slices (200 μm) distributed evenly across the entire striatum in whole-cell current-clamp and voltage-clamp mode at room temperature. Voltage-clamp recordings to interrogate synaptic input profile were carried out under pharmacological blockade using known excitatory and inhibitory receptor blockers.

Results: The proportion of striatal neuron discharge profiles in *wildtype* mice was significantly altered when compared with the K3 transgenic and rotenone- treated groups (p= 0.006). In general this alteration was characterized by a shift towards burst firing discharge profiles in the K3 transgenic and rotenone treated mice. Further, both the K3 transgenic, and rotenone treated mice showed significantly higher subthreshold EPSP activity at rest (p= 0.03). The passive membrane properties including input impedance and capacitance of striatal neurons were not significantly different between the three mouse groups. Preliminary results suggest that the synaptic input profile of striatal neurons is predominantly excitatory in nature.
Conclusion: Neurons in the striatum of K3 transgenic mice display a hyper-excitable state that can be mimicked at least in part by injection of rotenone.

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Poster

293. Tauopathies and Synucleinopathies: Cellular and Molecular Mechanisms

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Program #/Poster #: 293.19/P3

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: IMI2 IMPRiND No.116060

Title: Zebrafish proteinopathy models for target validation

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Abstract: Accumulation and toxic gain of function of misfolded protein assemblies, such as α-synuclein and Tau, are major pathological features of Parkinson's and Alzheimer's disease, respectively. The IMPRiND project aims to map critical steps in the aggregation and propagation of these misfolded proteins. To address these features, Servier is developing zebrafish models for the stable expression of human wild type and mutated variants of α-synuclein and Tau. Zebrafish models are well poised to bridge the gap between *in vitro* models and traditional *in vivo* rodent models, providing an *in vivo* vertebrate system amenable to accelerated throughput. To generate the stable transgenic animals, we designed plasmids for the overexpression of these proteins in zebrafish motor neurons and use biochemical, imaging and electrophysiological based approaches to characterize the lines. Plasmids were individually injected into embryos at the single cell stage and subsequently integrated into the zebrafish genome resulting in stable transgenic zebrafish overexpressing human Tau and α-synuclein protein. Transgenic animals underwent biochemical evaluation to assess Tau and α-synuclein expression levels and the

presence of pathogenic aggregates. The coexpression of either Tau or α-synuclein with GFP allows for the analysis of changes in neuronal morphology due to the presence of these proteins. We are optimizing throughput for live fluorescence imaging of zebrafish larvae *in vivo* by coupling a microfluidics device to a confocal microscope. With this system, individual fish are shuttled into an imaging capillary and automatically positioned prior to image acquisition. Once the images are acquired, the 3D neuronal structure is reconstructed. Axon length and branching can subsequently be quantified and with the addition of a fluorescent postsynaptic marker it is possible to quantify synapse number and size. These metrics will be used to assess the effect of the presence of pathogenic protein aggregates. To characterize functional consequences of wild type and mutant Tau and α-synuclein overexpression, we are investigating their effects on synaptic transmission electrophysiologically. Whole cell patch clamp recordings of postsynaptic muscle fibers and presynaptic motor neurons are employed to quantify changes in neurotransmitter release properties. We present our progress for the development of zebrafish proteinopathy models, focusing on Tau. Altogether, these zebrafish proteinopathy models aim to provide a means by which we may accelerate the screening of therapeutic molecules in vivo and validate new targets generated through the IMPRiND consortium.

Disclosures: **J.M. Hubbard:** A. Employment/Salary (full or part-time):; Institut De Recherches Servier. **N. Ribeiro Palha:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **A. Dekeyne:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **W. Boucheron:** A. Employment/Salary (full or part-time):; Institut de Recherche Servier. **N. Rogez:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **S. Veiga:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **R. Billiras:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **V. Pasteau:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **S. Caignard:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **S. Guenin:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **A. Francois:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **E. Schenker:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **R. Jeggo:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.01/P4

Topic: C.08. Ischemia

Support: NSFC Grant 81571277

Title: Expression change of lipocalin-2 and BIM in ischemic cerebral protection induced by remote preconditioning

Authors: *C. REN[1], M. LIU[2], J. CHEN[2], S. ZHANG[2]
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Abstract: Objective: Our study focused on observing whether RPC was capable of regulating the expression level of LCN2 and BOCT in ischemic, and whether the expression level of the corresponding downstream molecule Bim would be affected. **Methods:** 1, male SD rats (weight between 270 and 330 grams) were randomizedly divided into ICS groups and RPC groups, with each group included five subgroups: sham control, 6 h, 24 h, 48 h, 72 h. Rats in ICS group were treated with focal cerebral ischemia, while rats in RPC group were treated with RPC before receiving focal cerebral ischemia. 2, TTC staining: The core area and salvage area was defined according to the results of the TTC staining. 3, Western blot analysis was used to determine the expression level of LCN2, BOCT, and Bim protein in the brain tissue.. 4, immunofluorescence staining method was used to detect the colocalization of LCN2 with GFAP, BOCT with NeuN, Bim with NeuN. DAPI staining was used for location of the nucleus. **Results:** 1. TTC staining showed that cerebral infarction area could be decreased by RPC($P<0.05$). 2, RPC downregulated the expression levels of LCN2 after cerebral ischemia at the time point of 24 h($P < 0.05$) and 72 h($P < 0.05$), shown by western blot analysis result. The double immunofluorescence staining results further indicated that the RPC could reduce the number of LCN2-positive astrocytes ($P < 0.01$) at all time points, indicating that the RPC could downregulate the expression of LCN2 by astrocytes after cerebral ischemia. 3, the western blot analysis results indicated RPC had no obvious regulation effect on BOCT expression, except the time point of 72 h. Double immunofluorescence staining results further indicated that the RPC had no obvious regulation on the number of BOCT-positive neurons after cerebral ischemia except the time point of 72 h. 4, The western blot analysis result showed that RPC could downregulate the expression levels of Bim after cerebral ischemia at the time 6 point of 24 h ($P < 0.05$).Double immunofluorescence staining results further indicated that RPC could decrease the number of Bim-positive neurons after cerebral ischemia ($P < 0.01$) at all time points, indicating that the RPC can downregulate the expression of Bim neurons after cerebral ischemia. **Conclusion:** Our research results showed that the RPC could reduce the production of LCN2 astrocytes after cerebral ischemia, while having no obvious regulation on BOCT expression except at the time point of 72 h. We further found RPC could downregulate the expression level of Bim in neurons after cerebral ischemia. Our results speculated that downregulation of LCN2 and Bim by RPC may be one of the neuroprotection mechanisms of RPC exerted after ICS.

Disclosures: C. Ren: None. **M. Liu:** None. **J. Chen:** None. **S. Zhang:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.02/P5

Topic: C.08. Ischemia

Support: APVV-15-0107
VEGA 1/0128/16

Title: Proteomic study to uncover neuroprotective mechanisms linked to ischemic preconditioning in rat hippocampus

Authors: *A. TOMASCOVA[1], Z. TATARKOVA[1], D. KALENSKA[1], B. TÓTHOVÁ[2], J. LEHOTSKY[1]
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Abstract: OBJECTIVES: Global ischemic brain injury, for example as a result of cardiac arrest, is among the most common causes of disability and mortality worldwide, and so there is constant effort to find effective neuroprotective strategy. One of the highly studied approaches of improving an outcome of ischemic damage is an endogenous mechanism of neuroprotection called ischemic tolerance. Ischemic tolerance following exposure to brief period of ischemia near to but below the threshold of damage is known as ischemic preconditioning. Such preconditioned tissue then develops a resistance to similar noxious stimuli. Preconditioning is an attractive experimental strategy to identify endogenous protective mechanisms that can be therapeutically induced or supplemented.
MATERIALS AND METHODS: Adult male Wistar rats were randomly divided into control, ischemia-reperfusion (IR) and preconditioned (IPC) groups, 5 animals per group. Global ischemia was induced by 15 min of standard 4-vessel occlusion followed by 24-hour reperfusion. Preconditioning was induced by 5 min ischemic insult 48 hours prior to global ischemia. Proteomic analysis of rat hippocampus homogenates was carried out by 2D-gel electrophoresis with protein identification on matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (Bruker Daltonics, USA).
RESULTS: In total, 273 proteins were detected and 33 identified as significantly changed in IPC group when compared to control and IR group. Deregulated expression manifested particularly molecular chaperones, mainly high overexpression of stress inducible Heat Shock 70kDa Protein 1. Over twofold downregulation was observed in expression of Peroxiredoxin 5 and 6 linked to cellular redox state, and Isocitrate Dehydrogenase and Succinate Dehydrogenase. Upregulated were proteins involved in glutamine metabolism - Glutamine Synthetase and Glutamine Dehydrogenase, and proteins of energy metabolism ATPsynthase subunit β and

glycolytic α-enolase, γ-enolase and Glyceraldehyde-3P Dehydrogenase.
CONCLUSION: Proteomic analysis of preconditioned rat hippocampus showed modified regulation in different metabolic pathways and higher sensitivity to changes in overall redox state. Upregulation in proteins handling glutamate metabolism implies for utilization of alternative energy sources. Moreover, upregulation in enolase isoenzymes suggest connection to hypoxic tolerance and neuroprotection.

Disclosures: A. Tomascova: None. **Z. Tatarkova:** None. **D. Kalenska:** None. **B. Tóthová:** None. **J. Lehotsky:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.03/P6

Topic: C.08. Ischemia

Support: NIH F32 NS100245
NIH R01 NS076620

Title: Ischemic preconditioning induces cortical microglial proliferation and a transcriptomic program of cell cycle activation

Authors: *A. MCDONOUGH, S. NOOR, R. DODGE, III, J. S. STROSNIDER, J. SHEN, T. LE, J. R. WEINSTEIN
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Abstract: Stroke is the 5th leading cause of death in the United States and the leading cause of long-term disability. Progress in the development of effective therapies for acute stroke has been limited and centered on neuronal preservation despite extensive and robust data implicating glial cells, including microglia, in the pathophysiology of ischemic injury. Although microglial activation was once considered to be a strictly pro-inflammatory process, recent studies indicate that microglia can also have a protective function in stroke. Ischemic preconditioning (IPC) in the CNS is a brief period of ischemia that confers robust neuro- and axonal- protection against subsequent prolonged ischemic injury. Elucidating the mechanisms of IPC-mediated protection is widely considered a promising avenue for stroke research. Previously we characterized a robust interferon-stimulated gene signature as a hallmark response to IPC in acutely isolated cortical microglia. Here we report a distinct but equally striking finding from our microglial genomic profiling dataset: the transcriptomicresponse of cortical microglia to IPC is dominated by marked up-regulation of genes involved in cell cycle activation, DNA replication and cell proliferation. In the course of performing these experiments, we noted a significant increase in the number of microglia isolated from the preconditioned cortex. Here we demonstrate using

immunofluorescent microscopy and quantitative stereology that this observed increase is not an artifact of flow cytometry, but reflects *in situ* microglial responses to IPC. The response includes robust proliferation and marked morphological changes in the microglia, even in the absence of cortical infarction. Furthermore, the increase in microglia can be accounted for entirely by a population of cells expressing a proliferative marker (BrdU, Ki67). We also examined microglial proliferation after IPC within two transgenic mouse models: 1.) mice lacking type I interferon receptor (IFNAR1), which we and others have previously reported as necessary for IPC-mediated protection, and 2.) mice with haploinsufficiency for the CX3CL1 (fractalkine) receptor CX3CR1. Based on these studies, we conclude that IPC-induced microglial proliferation is independent of type I interferon signaling, but dependent on fractalkine signaling. Results from this work will refine our understanding of the mechanisms of IPC-mediated endogenous protection and guide our choice of cellular and molecular pathways to study in the development of future stroke therapies.

Disclosures: A. McDonough: None. **S. Noor:** None. **R. Dodge:** None. **J.S. Strosnider:** None. **J. Shen:** None. **T. Le:** None. **J.R. Weinstein:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.04/P7

Topic: C.08. Ischemia

Support: SfN-IBRO travel award

Title: Neuroprotective effects of oxidative preconditioning against apoptosis induced by H2O2 in differentiated neuroblastoma SH-SY5Y cells

Authors: *R. AKKI[1], R. SIRACUSA[2], R. MORABITO[2], A. REMIGANTE[2], M. CAMPOLO[2], M. ERRAMI[3], S. CUZZOCREA[2], A. MARINO[2]
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Abstract: Background: Oxidative stress plays a role in age-related pathologies such as neurodegenerative diseases, cancer and ischemic stroke. Generally, high levels of oxidative stress are associated with cell damage during ischemic insults. However, a slight rise of reactive oxygen species (ROS) levels can be protective developing a resistance against subsequent challenges in "preconditioning" cells. Therefore, the aim of the study is examine how differentiated neuronal–like SH-SY5Y cells may be adapted to a mild and transient H_2O_2-induced oxidative stress.

Methods: The neuroprotective effects of preconditioning (PC) with hydrogen peroxide against oxidative stress induced ischemic-like damage were examined in neuronal like differentiated SH-SY5Y cells. The Cells were pretreated with mild-concentration H_2O_2 (10 µM -50 µM) for either 6 or 24 hours and then treated with higher H_2O_2 concentrations (100 µM, 200 µM, and 300 µM) for 24 hours. Then, neuronal like differentiated SH-SY5Y cells were divided into 5 groups, as follows: 1) control group; 2) cells treated with 10 µM H_2O_2 followed by higher H_2O_2 concentration; 3) cells treated with 20 µM H_2O_2 followed by higher H_2O_2 concentration, 4) cells treated with 30 µM H_2O_2 followed by higher H_2O_2 concentration; 5) cells treated with 50 µM H_2O_2 followed by higher H_2O_2 concentration.
Results: Our findings demonstrated that mild concentration (10-50 µM H_2O_2) applied before damage (100 µM H_2O_2) could protect neuronal-like differentiated neurons against ischemic insult. Particularly, we observed that cell viability and cell size recovery were effective 24 hours after pretreatment with low concentration H_2O_2 (10-30 µM). Thus, expression of markers for anti-apoptotic as Bcl-2 protein and pro-apoptotic proteins (Bad, Bax, Bid, caspase-9, AIF and PARP-1) were examined.
Conclusions: we conclude that i) PC response to a mild and transient H_2O_2-induced oxidative stress is clearly detected in neuronal like differentiated SH-SY5Y and revealed that both cell viability and cell size improved recovery; ii) apoptotic and inflammatory pathways are involved in such response, which is worthy and interesting of further investigation**.**

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Poster

294. Ischemia I

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Program #/Poster #: 294.05/P8

Topic: C.08. Ischemia

Support: DGAPA-PAPIIT IN226617

Title: Proteomic profiling of exosomes derived from brain microvascular endothelial cells under hypoxia: Identifying molecular pathways of adaptive responses to ischemic stress

Authors: *A. N. CAMPERO-ROMERO[1,2], E. RÍOS-CASTRO[3], L. B. TOVAR-Y-ROMO[2]
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Abstract: Extensive data analyses of protein content have been recently conducted in many different populations of extracellular vesicles. Exosomes, formed in late endosomes and released to the extracellular milieu conveying chemical messages to distant targets, have uncovered complex systems of distant cell-to-cell communication. All cell types synthesize and release exosomes upon stress activation, and the characterization of their proteomic content might enable the identification of target signaling that would unveil systemic adaptive responses to stress. Under this premise, we set out to study the protein content of brain microvascular endothelial cells (BMEC)-derived exosomes following hypoxia. Brain microvascular endothelium plays a critical role in the modulation of adaptive responses to stroke, such as the modulation of blood-brain barrier and neuroinflammatory processes that involve crossing of blood-borne molecules and peripheral immune cells into the brain parenchyma, as well as blood flow and reperfusion after stroke. We cultured primary BMEC from adult rat brains and subjected them to hypoxia in an atmosphere of 100% N_2 for 6 h followed by recovery (~21% O_2) for 18 h. After this period, we collected conditioned media and isolated exosomes by differential ultracentrifugation. We also harvested exosomes released by BMEC cultured under normoxic conditions. We characterized the extracellular vesicles by shape and size with transmission electron microscopy and assessed the presence of typical exosome markers by western blot. We resolved exosome proteins by polyacrylamide gel electrophoresis and performed in-gel digestion with trypsin. The proteomic profiling was carried out by tandem mass spectrometry (MS/MS) with electrospray ionization followed by ion mobility separation. MS/MS spectra were deconvoluted and compared against reversed *Rattus norvegicus* databases with ProteinLynx Global SERVER. We obtained 262 high quality hits, among which several exosomal markers and BMEC-specific molecules involved in focal adhesion, prostaglandin synthesis and regulation, integrin signaling, and phagocytosis pulled. We identified 117 proteins not previously reported in other exosome proteomics studies, of which 29 were specific of cells subjected to hypoxia. Overrepresentation and pathway enrichment analyses of data from hypoxia and normoxia-derived exosome proteomes enabled us to identify proteins involved in adaptive responses to hypoxic stress. This exploratory study depicts for the first time the molecular profile of exosomes secreted by BMEC under stress relevant in brain pathologies such as stroke.
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Disclosures: A.N. Campero-Romero: None. **E. Ríos-Castro:** None. **L.B. Tovar-y-Romo:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

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Program #/Poster #: 294.06/P9

Topic: C.08. Ischemia

Support: 2R25GM060507

Title: Docosahexaenoic acid stimulates autophagy and rescues NGFDPC12 cells from hypoxia-induced cell death

Authors: *M. L. MONTERO, J.-W. LIU, M. A. DELEÓN
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Abstract: Docosahexaenoic acid stimulates autophagy and rescues NGFDPC12 cells from hypoxia-induced cell deathHypoxia is at the core of neuronal death during traumatic brain injury, spinal cord injury and stroke. We subjected nerve growth factor differentiated pheochromocytoma cell line 12 (NGFDPC12) to .5% [O_2] for 24 to 48hrs. The mRNA levels of the stress response protein HIF-1α went up 3.5, 5 and 6 fold of control at 18, 24 and 48hrs, respectively. Pro-apoptotic protein BNIP3 went up 2.5 and 3.5 fold of control at 18 and 24hrs, respectively. Hypoxia treatment also induced a 2.5 fold increase in ROS after 24hrs and that increase in ROS could be prevented with antioxidant MCI-186 at 50 and 100 μM concentration. In addition, hypoxia increased Annexin V conjugation 2.5 fold of control at 24hrs. Treatment with docosahexaenoic acid (DHA) or the autophagy promoter, rapamycin, during hypoxia increased cell viability and brought back the levels of Annexin V to control level. Interestingly, pre-treat cells with DHA for 24 hours before hypoxic insult also increased cell survival. We found that DHA increased the levels of conjugated LC3 at 24 hrs under hypoxic condition, suggesting that autophagy is involved in DHA-induced neuroprotection. Lastly, treating the cells with the lysosomotropic agent chloroquine during hypoxia eliminates the protective effect of DHA. We propose that DHA inhibits apoptosis, stimulates autophagy and protects NGFDPC12 cells from .5% [O_2] hypoxia.

Disclosures: M.L. Montero: None. **J. Liu:** None. **M.A. DeLeón:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.07/P10

Topic: C.08. Ischemia

Title: Spatial memory in zebrafish (Danio rerio) following cerebral hypoxia

Authors: *J. A. WINDELBORN, K. M. MARINO
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Abstract: With few reliable therapeutic approaches for cerebral ischemia, developing new laboratory models continues to be a pressing concern. Zebrafish (*Danio rerio*) have recently been utilized to model pathologies associated with cerebral hypoxia, and we aim to develop the model

to further understanding of the cellular and molecular mechanisms of memory impairment following cerebral hypoxia. First, a behavioral assay has been designed to test the effects of hypoxia on spatial memory. We take advantage of the species' preference to swim in shoals rather than alone, when given the choice. A T-maze has been developed in which fish are trained to associate one arm of the maze with shoaling. The effects of hypoxia (10 minutes at <1mg/L dissolved oxygen) on the formation and maintenance of spatial memory are tested by hypoxia exposure prior to or immediately following maze training, respectively. Brain tissues are extracted at the termination of each experiment, and damage is assessed by 2,3,5-Triphenyltetrazolium Chloride (TTC) absorbance.

Disclosures: J.A. Windelborn: None. **K.M. Marino:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

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Topic: C.08. Ischemia

Title: Attenuated response to hypoxia in hippocampal slices from mice lacking the glutamate antiporter, xCT

Authors: B. S. HEIT[1], A. CHU[1], *J. R. LARSON[2]
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Abstract: Loss of blood supply to brain tissue during ischemic stroke depletes neurons of energy (ATP), leading to failure to maintain membrane potentials and the excitotoxic release of glutamate. In intact neural networks, anoxic depolarization (AD) occurs rapidly and synchronously in large populations of neurons, due to the excitatory effects of released glutamate. Both the latency to AD and the duration of time spent in AD dictate the extent of ultimate cell death and represent the most reliable determinants of ensuing brain damage. One particularly vulnerable area to ischemic trauma is the hippocampus, insomuch that with any non-specific blood loss to the brain, the CA1 neurons are the first to experience cell death. Importantly, much of the "ischemic cascade" can be reproduced by transient deprivation of oxygen to *in vitro* hippocampal slices. xCT, glutamate antiporter, is identified as the primary source of extracellular glutamate in the brain during physiologic and pathologic conditions. This glial membrane-bound transport system serves as a source of cystine, which is intracellularly converted to cysteine - the rate-limiting substrate for glutathione synthesis. The high rate of oxygen consumption in the brain renders this antiporter vital to antioxidant defense, and its expression is rapidly upregulated during oxidative stress. However, the release of glutamate into the extracellular space, accompanying the uptake of cystine, could exacerbate ischemic

excitotoxicity. The present study compared mice lacking xCT (xCT-KO) with wild-type (WT) littermate control mice for response to hypoxic challenge in hippocampal slices *in vitro*. Slices prepared from eight-week old mice were tested for two measures of hypoxia sensitivity: (a) the time required to induce AD after total O_2 deprivation, and (b) the sensitivity of synaptic transmission to hypoxia ($30\%O_2/70\%N_2$). Slices from xCT-KO mice showed extended AD times and attenuated neuronal response suppression during hypoxia. These results suggest that loss of the antiporter affects hypoxia sensitivity due to (a) its contribution to extracellular glutamate levels, (b) the downstream effects of xCT-mediated glutamate release, or (c) an unknown consequence of its action.

Disclosures: B.S. Heit: None. **A. Chu:** None. **J.R. Larson:** None.

Poster

294. Ischemia I

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Topic: C.08. Ischemia

Support: RO1NS076715

Title: Dysregulation of mitochondrial quality control mechanisms during *in vitro* ischemia-reperfusion injury

Authors: *A. R. ANZELL[1], S. RAGHUNAYAKULA[2], J. M. WIDER[2], T. H. SANDERSON[3]
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Abstract: Ischemic brain injury caused by cardiac arrest or stroke continue to be leading causes of death and disability in the U.S. While the restoration or reperfusion of blood flow is essential to salvage ischemic tissue, reperfusion paradoxically exacerbates damage via the excessive production of reactive oxygen species (ROS) from mitochondria. Mitochondria are the key regulators of cell fate during ischemia-reperfusion (I/R) injury. They promote cell survival through the production of ATP that fuels cellular processes and, conversely, cell death through the production of ROS and the release of pro-apoptotic factors such as cytochrome C. Therefore, stringent quality control mechanisms are critical to ensure a healthy mitochondrial network. The role of mitophagy during I/R injury still remains to be elucidated and previous studies are confounded by the dynamic nature of this process. Therefore, we characterized mitophagic flux utilizing primary cortical neurons isolated from mitochondrial quality control (mito-QC) reporter transgenic mice (C57BL/6-Gt(ROSA)26Sortm1(CAG-mCherry/GFP)Ganl/J) in an *in vitro*oxygen-glucose deprivation (OGD) real-time imaging system. The reporter allele contains a CAG promoter and mCherry-GFP-mtFIS1 fusion protein inserted into the *Gt(ROSA)26Sor*locus

on chromosome 6. mCherry is stable in acidic pH (pKa 4.5) while GFP (pKa 5.9) is quenched in the acidic lysosomal environment, allowing identification of mitochondria inside autolysosomes. Simulation of I/R injury was achieved with a media-gas exchange system coupled to a Zeiss microscope with LED based fluorescent imaging for real-time imaging during OGD and reoxygenation.The combination of these two novel models allowed us to characterize mitophagic flux in primary cortical neurons with precise temporal resolution. These novel findings provide key evidence for the role of mitophagy in neuronal death following I/R injury as well as further insight into the basic mechanisms of mitochondrial dysfunction that may play a role in a variety of neurodegenerative disease.

Disclosures: A.R. Anzell: None. **S. Raghunayakula:** None. **J.M. Wider:** None. **T.H. Sanderson:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.10/P13

Topic: C.08. Ischemia

Support: VA BX000917

Title: NAD^+ precursor reverses ischemia-induced increase of mitochondrial fission protein P-Drp1 (S616) via a SIRT3 mediated mechanism

Authors: N. KLIMOVA[1], A. LONG[2], *T. KRISTIAN[1,2]
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Abstract: Global cerebral ischemia depletes brain tissue NAD^+, an essential cofactor for mitochondrial and cellular metabolism, leading to bioenergetics failure and cell death. The post-ischemic NAD^+ levels can be replenished by the administration of nicotinamide mononucleotide (NMN), which serves as a precursor for NAD^+ synthesis. Ischemic insult also leads to excessive fragmentation of mitochondria in vulnerable CA1 neurons. We have shown that NMN administration shows a dramatic protection against ischemic neurodegeneration. To assess the effect of NMN administration on ischemia-induced mitochondrial dynamics we used a transgenic mouse model with mitochondria targeted expression of neuron specific enhanced yellow fluorescent protein. The animals were subjected to transient forebrain ischemia and NMN was administered 30 minutes after the start of reperfusion at a dose of about 60 mg/kg. Alterations in mitochondrial fission and fusion were examined in post-ischemic animals treated with vehicle or NMN at 2, 4, and 24 hours of recovery. Fusion and fission protein levels were determined by western blots. NMN reversed the excessive mitochondrial fragmentation in CA1 neurons that was permanent in vehicle-treated ischemic groups. Thus, NMN administration

promoted normal mitochondrial morphology at 24 hours after the ischemic insult. Western blot analysis showed that NMN treatment reversed ischemia-induced increase of mitochondrial fission protein P-Drp1(S616). Similar results were also observed in non-ischemic naïve mice treated with NMN. Calcineurin, a calcium and calmodulin dependent phosphatase that dephosphorylates P-Drp1, did not contribute to the NMN mediated decrease in P-Drp1(S616) levels. This suggests that kinases, either CDK1 or PKCδ that phosphorylate Drp1 (S616), could be involved. As expected there was an increase in tissue NAD^+ levels following NMN administration that were associated with decrease in mitochondrial protein acetylation. Therefore, we examined the role of mitochondrial SIRT3 in NMN induced effect on mitochondrial dynamics by using SIRT3 null mice (SIRT3 KO). Interestingly, in SIRT3 KO animals the NMN-induced changes in P-Drp1 levels were attenuated. Our data thus suggest that maintaining normal mitochondrial morphology is essential for cell bioenergetics metabolism and survival. Furthermore, using NMN to target mechanisms of fission and fusion regulation could represent new therapeutic targets for neurobiological diseases.

Disclosures: N. Klimova: None. **A. Long:** None. **T. Kristian:** None.

Poster

294. Ischemia I

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Topic: C.08. Ischemia

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N.G. and Helen T. Hawkins Endowment

Title: Focal cerebral ischemia and reperfusion induces brain injury through alpha2delta-1-bound NMDA receptors

Authors: *Y. LUO, H. MA, J.-J. ZHOU, L. LI, S.-R. CHEN, J. ZHANG, L. CHEN, H.-L. PAN
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Abstract: Background and Purpose: Glutamate *N*-methyl-*D*-aspartate receptors (NMDARs) play a major role in the initiation of ischemic brain damage. However, NMDAR antagonists have no protective effects in stroke patients, possibly because they block physiological functions of NMDARs. α2δ-1 (encoded by *Cacna2d1*) is strongly expressed in many brain regions. We determined the contribution of α2δ-1 to NMDAR hyperactivity and brain injury induced by ischemia and reperfusion. **Methods**: Mice were subjected to 90 min of middle cerebral artery occlusion (MCAO) followed by 24 h of reperfusion. Neurological deficits, brain infarct volumes, and calpain/caspase-3 activity in brain tissues were measured. NMDAR activity of hippocampal

CA1 neurons was recorded in brain slices. **Results**: MCAO caused a significant increase in α2δ-1 protein levels in the cerebral cortex, hippocampus, and striatum. Coimmunoprecipitation showed that α2δ-1 physically interacted with NMDARs in the mouse brain tissue. Inhibiting α2δ-1 with gabapentin, uncoupling the α2δ-1-NMDAR interaction with an α2δ-1 C-terminus-interfering peptide, or genetically ablating *Cacna2d1* genetic ablation had no effect on basal NMDAR currents but strikingly abolished oxygen-glucose deprivation-induced NMDAR hyperactivity in hippocampal CA1 neurons. Systemic treatment with gabapentin or α2δ-1 C-terminus-interfering peptide or *Cacna2d1* ablation reduced MCAO-induced infarct volumes, neurological deficit scores, and calpain/caspase-3 activation in brain tissues. **Conclusions**: α2δ-1 is essential for brain ischemia-induced neuronal NMDAR hyperactivity, and α2δ-1-bound NMDARs mediate brain damage caused by cerebral ischemia. Targeting α2δ-1-bound NMDARs, without impairing physiological α2δ-1-free NMDARs, may be a promising strategy for treating ischemic stroke.

Disclosures: Y. Luo: None. **H. Ma:** None. **J. Zhou:** None. **L. Li:** None. **S. Chen:** None. **J. Zhang:** None. **L. Chen:** None. **H. Pan:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.12/P15

Topic: C.08. Ischemia

Support: NIH Grant 1R01NS096225-01A1
AHA Grant 17GRNT33660336
AHA Grant 17POST33660174

Title: Detrimental role of neuropeptide Y in cardiac arrest-induced cerebral ischemia

Authors: *R. H.-C. LEE[1], T.-H. HSIEH[1], A. DO COUTO E SILVA[2], H. POSSOIT[1], C. T. CITADIN[1], C. Y.-C. WU[1], J. T. NEUMANN[3], H. W. LIN[1]
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Abstract: Cardiopulmonary arrest (CA) is the leading cause of death and disability in the United States. Although multi-faceted treatment strategies against CA (i.e. rapid ambulatory responses and better automated external defibrillation training and awareness) have improved, the survival rate and prognosis following CA remain poor. Of utmost importance is CA-induced hypoperfusion (a decrease in cerebral blood flow, CBF) is essential for the progression of neuronal cell death and learning/memory deficits. Thus, identifying the unknown regulatory mechanisms that influence hypoperfusion will provide high therapeutic potential in the treatment

of CA. We previously found that enhanced sympathetic nervous system (SNS) activity is one of the major contributors to CA-induced hypoperfusion. It is important to note that neuropeptide Y (NPY, a 36-amino acid neuropeptide) is released upon SNS activation to induce a long-lasting and potent vasoconstriction (100-fold more potent than other sympathetic neurotransmitters, such as norepinephrine), as a result of reduced blood supply to the brain. We sought to inhibit NPY release from pre-synaptic sympathetic nerves via peptide YY $(PYY)_{3-36}$ (a pre-synaptic NPY2 receptor agonist) to study the role of NPY in CA-induced hypoperfusion and brain injury. A rat model of global cerebral ischemia (6 mins asphyxial cardiac arrest, ACA) was utilized. Results from intra-vital two-photon laser scanning microscopy and laser speckle contrast imaging indicate post-treatment with PYY_{3-36} at 120 μg/kg (56.87 ± 4.48%; $p<0.05$ evaluated by Student's t test) attenuated cortical hypoperfusion (-33.20 ± 2.65%) 24 hrs after ACA. Interestingly, post-treatment with PYY_{3-36} (40 μg/kg) inhibited neuronal cell death (via hematoxylin/eosin and fluoro-Jade C stain), while maintained synaptic transmission (via hippocampal slice recording) in the CA1 region of the hippocampus. Finally, we assessed cognitive/behavioral function (via Y-maze and novel object recognition test) to evaluate the rats' functional learning/memory after ACA. Rats post-treated with PYY_{3-36} (0.64 ± 0.02) presented with better neurological outcomes than untreated rats (0.48 ± 0.05) after ACA. In conclusion, NPY is detrimental to CA-induced brain injury. Attenuation of NPY release via PYY_{3-36} affords neuroprotection against CA-induced hypoperfusion, neuronal cell death, and neurological deficits.

Disclosures: R.H. Lee: None. **T. Hsieh:** None. **A. Do Couto E Silva:** None. **H. Possoit:** None. **C.T. Citadin:** None. **C.Y. Wu:** None. **J.T. Neumann:** None. **H.W. Lin:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.13/Q1

Topic: C.08. Ischemia

Title: Neuroprotective effect of intracranial chronic toxoplasma gondii infection in cerebral ischemia

Authors: *S. LEE[1], B.-K. JUNG[2], H. SONG[2], E. HEO[1], H. SEO[1], J.-Y. CHAI[2], G. LEE[3], J.-H. LEIGH[4], B.-M. OH[1]
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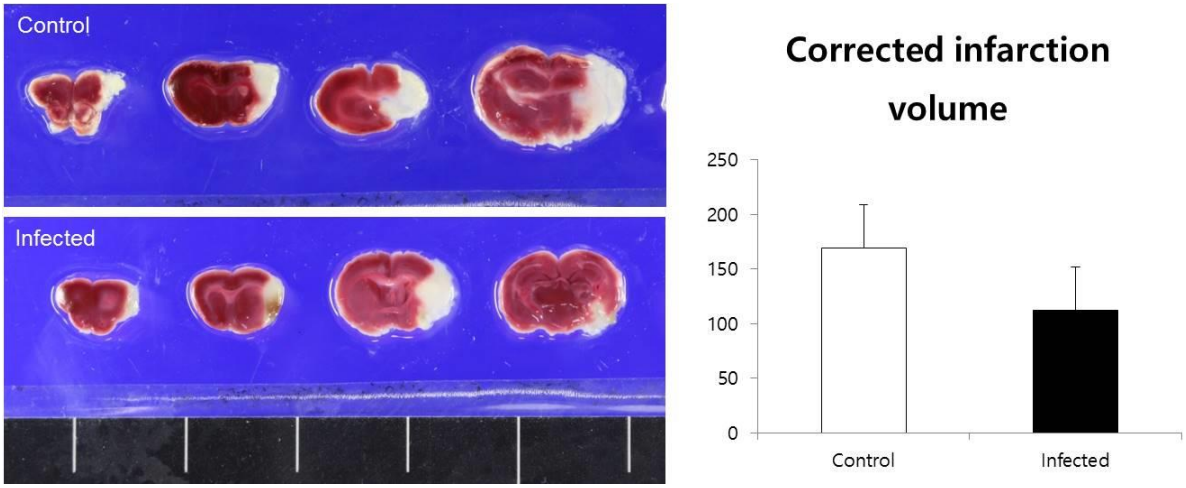
Abstract: Purpose *Toxoplasma gondii* (*T. gondii*) is an intracellular protozoan parasite spread all over the world and can invade various organs of the host body and forms tissue cysts in the

central nervous system. It is known that the *toxoplasma* tissue cyst, which is latent in the brain, interacts with brain cells in various ways. The purpose of this study is to investigate the neuroprotective effects of chronic *T. gondii* infections in cerebral ischemia and to explore its mechanism. **Methods** Eighteen ICR mice were used in the experimental group and the control group, respectively. Middle cerebral artery occlusion (MCAO) was used to induce cerebral ischemia and reperfusion was performed 90 minutes after occlusion. In the experimental group, *T. gondii* (ME49 strain) was injected through intraperitoneal route 4 weeks before the surgery. The neurobehavioral effects of cerebral ischemia were assessed by measurement of Garcia score and Rotaroad test on the 1st and 3rd day after surgery. After behavioral tests, mice were sacrificed and brains were harvested. The volume of brain ischemia was measured by Triphenyl tetrazolium chloride (TTC) staining. In addition, isolated brain tissues were analyzed the changing of genes expression to investigate the protective effects of *toxoplasma* chronic infection. **Results**
The survival rate of the mice was much higher in the infected group. (33% in control group, 61% in infected group) Corrected infarction volume was significantly reduced in infected group (control, n = 6, 168.8 ± 40.4; infected, n = 11, 112.5 ± 39.2, $P < 0.05$), and the neurobehavioral function of the infected group was significantly better than control group. We found that *T. gondii* chronic infection induces the HIF-1 and VEGF gene expression in the brain. **Conclusion** Chronic intracerebral infection of *T. gondii* causes neuroprotective effects in mouse cerebral ischemia and reduces the volume of cerebral infarction with better neurobehavioral function.



Disclosures: B. Jung: None. **H. Song:** None. **E. Heo:** None. **H. Seo:** None. **J. Chai:** None. **G. Lee:** None. **J. Leigh:** None. **B. Oh:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.14/Q2

Topic: C.08. Ischemia

Support: NMRC/STaR/0009/2012

Title: Contribution of cyclophilin A and CD147 receptor in brain ischemia

Authors: *Q. FANG[1], L. LEE[1], S. KANG[1], J. WONG[2], R. A. NOWAK[3], T. V. ARUMUGAM[1], E. H. KOO[4,2,1]
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Abstract: A recent study from Bell and colleagues (2012) proposed that the immunophilin, cyclophilin A (CypA), induces MMP-9 expression in pericytes in an ApoE dependent manner resulting in blood-brain barrier (BBB) leakage. Previous studies have also implicated CypA playing a role in cerebrovascular disease principally from the beneficial effects of cyclosporin A given in stroke models, which inhibits CypA mediated signalling pathways. To test whether the neuroprotection seen following cyclosporin treatment is due to inhibition of CypA, we tested the effects of unilateral middle cerebral artery occlusion (MCAO), a model of acute stroke, in CypA deficient mice. As compared to control littermate mice, there was a significant 75% reduction in infarct area associated with about 50% improvement in functional outcome in CypA knockout animals, thus showing that CypA is the likely substrate that mediates the beneficial effects of cyclosporin A treatment. We next asked whether CD147 (also known as *basigin* or EMMPRIN) the only established receptor for CypA, is involved in neuroprotection or in activating downstream effects to modulate BBB function given that CD147 is a known inducer of MMP expression. The precise distribution of CD147 expression in brain has not been described previously. By immunohistochemistry, we found that CD147 was widely expressed in brain, primarily in neurons and endothelial cells. In the former setting, CD147 was most abundant in both axons and dendrites but relatively sparse within neuronal cell bodies. Interestingly, in the hippocampus, there was a striking localization of CD147 to processes of CA1 and CA3 neurons and virtual absence of immunostaining in CA2 neurons. This differential distribution was confirmed using targeted deletion of CD147 in CA1 or CA3 neurons, respectively. In the latter setting, CD147 was primarily expressed in capillaries and a small subset of arteries but absent in most of the smaller arteries in brain. This heterogenous distribution of CD147 expression suggests that this receptor plays multifunctional roles in brain. Studies are underway to

determine the contribution of neuronal or endothelial CD147 in neuroprotection using targeted deletion of CD147 in neurons or endothelial cells.

Disclosures: Q. Fang: None. **L. Lee:** None. **S. Kang:** None. **J. Wong:** None. **R.A. Nowak:** None. **T.V. Arumugam:** None. **E.H. Koo:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.15/Q3

Topic: C.08. Ischemia

Support: King abdulaziz University

Title: Protective effects of melatonin in corpus callosum astrocytes during ischemia

Authors: *B. S. ALGHAMDI
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Abstract: Stroke is a leading cause of adult death and disability worldwide. Around 80% of all stroke cases are classed as ischemic stroke, which affects both gray and white matter brain regions. During ischemia, reactive oxygen species (ROS) are generated and initiate multiple damaging processes such as lipid peroxidation, DNA injury, mitochondrial dysfunction, blood-brain barrier (BBB) damage and brain edema. Melatonin is a potent antioxidant which can act as a direct oxygen species scavenger. Melatonin can also act at receptors (MT1 and MT2), which are expressed in the nervous system cells including astrocytes. Using live cell imaging of GFAP-GFP mice, the viability of astrocytes in the corpus callosum of adult brain sections was monitored during a standard 60 minutes period of modeled ischemia (oxygen-glucose deprivation: OGD). Addition of melatonin (10 µM) significantly reduced the level of astrocyte death during OGD from 71.94% ± 1.45 to 37.84% ± 1.9. This protective effect was blocked by luzindole (10µM), a nonselective melatonin receptor (MT1/MT2) antagonist, or PDOT (10µM), a selective MT2 melatonin receptor antagonist. Using a glial injury scoring system, ultrastructural studies confirmed the protective action of melatonin against acute ischaemic injury in the white matter glial cells.

Disclosures: B.S. Alghamdi: None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

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Program #/Poster #: 294.16/Q4

Topic: C.08. Ischemia

Support: NIH NS095192
NIH NS099531

Title: Deletion of FosDT an abundantly expressed lncRNA in vertebrates does not affect normal development, but improves post-ischemic functional outcome

Authors: *S. L. MEHTA, T. KIM, K. C. MORRIS-BLANCO, A. K. CHOKKALLA, S. BATHULA, R. VEMUGANTI
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Abstract: Long noncoding RNAs (lncRNAs) are a unique class of ncRNAs that are thought to control transcription and translation. We recently observed that that lncRNA called Fos downstream transcript (FosDT) transcribed from Fos locus is significantly induced in the brain following stroke (focal ischemia) in adult rats. We further showed that knockdown of FosDT promotes neuroprotection and better functional outcome following stroke. Mechanistically, FosDT scaffolds the transcription factor REST and its corepressors enabling REST-mediated suppression of neural genes. To understand its roles, we conducted further studies on FosDT expression and function. FosDT is observed to be abundantly expressed in both peripheral organs and brain with cerebral cortex showing the highest levels. FosDT expression is also developmentally regulated with adults showing higher expression than neonates. Its expression is highest in the cerebral cortex of adult as compared to the P7 stage. When FosDT was knocked-out in rats using CRISPR/Cas9, there were no developmental effects. FosDT knockout rats showed normal body weight and fertility compared to wildtype rats. However, when challenged with a focal cerebral ischemic insult, FosDT knockouts showed better survival and smaller infarcts than wild-type controls at 7 days of reperfusion. FosDT deletion also significantly reduced post-ischemic functional deficits and improved sensory-motor recovery as noticed with Rotarod, foot faults and adhesive removal tests. Thus, our results show that FosDT levels have to be maintained properly in the brain and its induction under pathological conditions like stroke promotes secondary brain damage. Targeting lncRNAs such as FosDT is a viable strategy to minimize post-stroke brain damage. Funded by NIH.

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Poster

294. Ischemia I

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Program #/Poster #: 294.17/Q5

Topic: C.08. Ischemia

Support: VEGA 1/0229/15
VEGA 1/0128/16
APVV-15-0107

Title: Hyperacetylation as a response to neurodegeneration process

Authors: *B. TÓTHOVÁ[1], M. KOVALSKÁ[2], D. KALENSKÁ[3], A. TOMAŠCOVÁ[3], E. HALAŠOVÁ[1], J. LEHOTSKÝ[3]
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Abstract: OBJECTIVES: Epigenetic regulation plays an important role in normal condition as in pathological situations of the organism. These epigenetic modifications are closely affected by the overall metabolic state of the cell, that is influenced by various exogenous and endogenous factors. One of such triggers is hyperhomocysteinemia (hHcy), referred to elevated plasma homocysteine (Hcy) level, a non-esential amino acid formed during the methionine cycle. Hcy can act via epigenetic pathways, predominantly by modifying the methylation potencial, thus affecting the acetylation process as well. Moreover, hHcy is considered as a risk factor and a target of preventive strategies for neurodegenerative diseases including cerebral stroke, during which occur considerable changes in epigenetic patterns. **MATERIAL AND METHODS:** Adult male Wistar rats were used in the study. They were randomly divided into control and hyperhomocysteinemic group and the latter was subjected to subcutaneous Hcy administration for 21 days at a dose 1.2 μmol Hcy/g of body weight per day. After this period, animals from both groups were further divided into control, ischemic and ischemia-reperfusion (IR) group, 4 animals/group. Global forebrain ischemia was induced for 15 min by standard 4-vessel occlusion, in the IR group it was followed by 72-hour reperfusion. To assess the extent of neuronal tissue damage, cresyl violet staining was used and the alterations in acetylation levels of histones H3 at lysine 9 and H4 at lysine 12 in the rat brain cortex were examined by fluorescent immunohistochemistry as well as by western blot. **RESULTS:** Cresyl violet staining revealed massive neural disintegration in the M1 *(primary motor cortex)* region as well as in the CA1 *(cornu ammonis)* area of hippocampus induced by IR. The neural tissue damage was significantly bigger in the groups with induced hHcy. Moreover, immunohistochemistry showed prominent changes in the acetylation of H3 (Lys9) and H4 (Lys12) in all experimental conditions with significant changes between the control and hHcy groups, especially in the levels of

acetylated H3 (Lys9). Similar results were observed by western blot analysis. **CONCLUSION:** Combination of hHcy and IR injury increases the extent of neuronal tissue damage. In the cortical region, these conditions manifest different histone acetylation patterns. Taken together, it seems that hyperacetylation have a preferred role in pathological processes such as neurodegeneration and should be considered in therapeutical strategies.

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Poster

294. Ischemia I

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Program #/Poster #: 294.18/Q6

Topic: C.08. Ischemia

Support: NIH Grant R21NS095192
NIH Grant R01NS099531
NIH Grant R01NS101960

Title: DNA hydroxymethylation of neuroprotective genes by Tet3 ameliorates ischemic brain injury

Authors: *K. MORRIS-BLANCO[1], M. J. BERTOGLIAT[1], T. KIM[2], R. VEMUGANTI[2]
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Abstract: Epigenetic factors are known to play a role in the pathophysiology of ischemic brain injury. The mammalian ten-eleven translocases (TET1-3) convert methyl groups in cytosine in DNA to hydroxymethylcytosine (5hmC) and this epigenetic modification is known to regulate transcription and thus neuronal function. We presently evaluated if TETs play a role in neuronal survival by enhancing 5hmC in neuroprotective genes following cerebral ischemia. Adult C57BL/6J male mice subjected to experimental stroke showed increased 5hmC and TET activity in the cortical penumbral tissue as early as 5 min to as late of at least 24h of reperfusion following stroke. TET3 mRNA expression, but not TET1 and TET2, showed induction from 6h to 24h after stroke. TET3 protein expressed preferentially in neuronal cells in the cortical penumbra following stroke. Knockdown of TET3 by intracerebral injection using siRNA blocked the post-stroke 5hmC and led to increased brain degeneration and mortality. TET3 knockdown also resulted in alterations in the expression of several genes that modulate autophagy, apoptosis, oxidative stress and DNA repair in the post-ischemic brain. Treatment of mice with a known TET inducer ascorbate increased TET activity and decreased post-stroke brain damage. We further show that ascorbate specifically acts via TET3 as TET3 knockdown

prevented ascorbate-induced 5hmC levels and neuroprotection after stroke. These results demonstrate that TET3 is a major regulator of DNA hydroxymethylation and provides endogenous neuroprotection after cerebral ischemia. Furthermore, ascorbate can promote neuroprotection after stroke by inducing TET3 and 5hmC in beneficial genes. Funded by NIH.

Disclosures: K. Morris-Blanco: None. **M.J. Bertogliat:** None. **T. Kim:** None. **R. Vemuganti:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.19/Q7

Topic: C.08. Ischemia

Support: DGAPA-PAPIIT IN226617

Title: DNA methylation and gene expression of astroglia before, during and after oxygen and glucose deprivation

Authors: *I. PONCE, L. B. TOVAR-Y-ROMO
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Abstract: Epigenetic mechanisms such as DNA methylation are well known regulators of genetic expression and they play key roles in the development of neurodegenerative diseases, mainly through a substantial transcriptional regulation of active and inactive promoters and by modifying transcription elongation and splicing in CpG islands located intra and inter-genically. It is also widely recognized that astrocytes, that are critical regulators of neuronal function, play a crucial role in neurovascular-related disorders like ischemic stroke. However, few studies have addressed at the molecular resolution the overall genetic and epigenetic changes of these complex phenomena, and in events like reperfusion damage that occurs after ischemic stroke, these processes are practically unknown. We performed RNA-seq and methylated DNA immunoprecipitation sequencing (MeDIP-seq) analyses of cultured human astrocytes-like cells derived from grade I non-tumorigenic glioblastoma subjected to oxygen and glucose deprivation (OGD), in order to establish a relationship between DNA methylation and gene expression under normoxia, OGD and recovery. We identified several genomic features including proximal and distal promoters whose methylation levels change not only during OGD but also after 8 h of recovery that showed statistically significant differences in both; high (house-keeping and ubiquitous genes) and low (cell lineage-specific genes) CG promoters. Moreover, DNA methylation remodeling was correlated with gene expression of several genes under OGD and recovery, and the organization of the transcriptome and methylome resulted different under normoxia, OGD and recovery. These results can help to elucidate the overall transformation of

cells in terms of transcription and DNA methylation in pathological occurrences involving ischemia and characterize the damage that occurs during reperfusion at the genomic scale that has been incompletely described until now. Supported by DGAPA-PAPIIT IN226617.

Disclosures: I. Ponce: None. **L.B. Tovar-y-Romo:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.20/Q8

Topic: C.08. Ischemia

Support: NIH Grant NS100803

Title: The DNA repair enzyme apurinic/apyrimidinic endonuclease-1 (APE1) improves oligodendrocytic survival following ischemic insults

Authors: J. CHEN[1], M. V. BREGY[1], K. ZHANG[1], *R. A. STETLER[2]
[1]Pittsburgh Inst. for Brain Disorders and Recovery, Neurol., [2]Neurol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Objective: Induction of oxidative DNA damage is a hallmark event following cerebral ischemic insults and has been identified to be predictive of subsequent cellular injury and adverse outcomes. We have previously demonstrated that induced global knockout of APE1 sensitizes the brain to cerebral ischemia. Although neurons have classically been the focus of oxidative stress-related injury following stroke, we wished to investigate whether oligodendrocytes are sensitive to changes in APE1 expression in the context of ischemic injury. **Methods:** Stroke was induced by 30 or 60 min transient middle cerebral artery occlusion (tMCAO, suture method) in adult male C56BL/6J mice with or without tamoxifen-induced global APE1 knockout. Viability was determined using TTC staining and MAP2 immunostaining. White matter tracts were visualized with MBP/smi32 or APC immunostaining co-labeled with TUNEL staining for apoptotic nuclei. Primary cultured oligodendrocytes (OL) were derived from oligodendrocyte percursor cells from P1 rat pups, differentiated in culture, and subjected to 90 min oxygen/glucose deprivation (OGD). Lentiviral vectors were constructed to overexpress APE1 or a non-phosphorylatable mutant (S163A), or shRNA targeted to APE1, and mature OLs were transduced 72 h prior to OGD. Toxicity was determined using the live/dead assay (calcein green/propidium iodide) and lactate dehydrogenase release. **Results:** Deletion of APE1 caused extensive loss of white matter tracts after mild ischemic injury (30 min MCAO) as well as significant increase in APC+/TUNEL+ cells in the corpus callosum/external capsule compared to wildtype ischemic brain. Similar to the animal model, knockdown of APE1 in cultured OL led to exacerbated toxicity following OGD. Viral verexpression of APE1

decreased OGD-induced OL cell death. Overexpression of the non-phosphorylatable APE1 mutant APE1-S163A further protected OL from OGD toxicity compared to mock transduction or transduction of APE1. **Conclusion:** The DNA repair enzyme APE1 functions in a protective manner in ischemic oligodendrocytes, and elimination of phosphorylation at S163 further improves the protective effects of APE1 against ischemic injury.

Disclosures: J. Chen: None. **M.V. Bregy:** None. **K. Zhang:** None. **R.A. Stetler:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.21/Q9

Topic: C.08. Ischemia

Support: R01NS085019

Title: Developmental transcription factors in post-stroke axonal sprouting

Authors: *C. A. SCHWEPPE, I. BAGGA, S. T. CARMICHAEL
Univ. of California Los Angeles, Los Angeles, CA

Abstract: Ischemic stroke produces a limited process of neural repair, characterized by axonal sprouting and cortical reorganization in the peri-infarct region. Previously, our lab has used transcriptional profiling of single sprouting neurons to identify their unique gene expression profile, a post-stroke sprouting neuron transcriptome. Within this transcriptome dataset are a number of transcription factors known to play a role in cortical development that are differentially regulated in sprouting neurons following stroke. Developmental transcription factors present an intriguing target for study due to their inherent ability to act as master regulators of genes responsible for neuronal growth. As such, a number of these differentially regulated developmental transcription factors have been investigated for their ability to regulate axonal sprouting following stroke. Transcription factor targets were initially screened for their ability to promote axonal outgrowth following lentiviral overexpression in primary cortical neurons obtained from P12 mice. Two genes, Ctip2 (BCL11B) and Hhex demonstrated an ability to promote neurite growth in culture. To test the ability of these targets to promote post-stroke axonal sprouting in vivo, adult Rosa26 Cre-reporter knock-in Ai14 mice received a focal stroke via photothrombosis in the forelimb motor cortex, followed by delivery of lentivirus expressing genes of interest and Cre reporter. Four weeks following injury, relative axonal sprouting was evaluated via tracing of tdTomato+ projections both the peri-infarct region and subcortical structures. The results of these studies begin to explore the role of development-associated transcription factors in neural regenerative processes in the adult cerebral cortex.

Disclosures: C.A. Schweppe: None. **I. Bagga:** None. **S.T. Carmichael:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.22/Q10

Topic: C.08. Ischemia

Support: NIH NRSA F31 NS073149
NIH RO1 NS081055
The Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Mechanistic gain-of-function and loss-of-function studies of Wnt7A in post-stroke neural repair

Authors: *H. ZHAO[1], T. LENGNING[2], A. BRUMM[1], S. T. CARMICHAEL[1]
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Abstract: Stroke is a leading cause of adult disability without treatments for long-term recovery. Stroke itself induces a wide-range of repair mechanisms, including the proliferation and long-distance migration of immature neurons (neuroblasts) from the subventricular zone (SVZ) to peri-infarct tissue, a process termed post-stroke neurogenesis. These neuroblasts localize to angiogenic blood vessels, forming a neurovascular niche in the peri-infarct zone. The reciprocal signaling between neuroblasts and endothelial cells has not been clearly characterized. Understanding these endogenous signaling systems may provide novel targets for pharmaceutical intervention to enhance functional recovery.
In genome-wide expression profiling studies, we identified Wnt7A as a candidate signaling gene that is down-regulated in stroke-responsive neuroblasts. Wnt7A stimulates neural stem cell proliferation and is important for neuronal differentiation and maturation in the hippocampus of adult mouse brains (Qu, et. al, 2013). However, its role in post-stroke neural repair is not well understood. In a set of gain- and loss-of-function studies, we show that Wnt7A regulates long term vessel growth, blood brain barrier formation, and neural progenitor cell maturation. In addition, we demonstrate these long-term effects are mediated by Wnt7A stimulation of vessel remodeling and neural progenitor cell migration from the subventricular zone in the acute period after stroke. Here, we provide assessment of Wnt7A-mediated tissue repair at subacute and chronic time points after stroke in the photothrombotic model in rodents.

Disclosures: H. Zhao: None. **T. Lengning:** None. **A. Brumm:** None. **S.T. Carmichael:** None.

Poster

294. Ischemia I

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Topic: C.08. Ischemia

Support: NIH grant NS104117

Title: Elovanoids are novel class of homeostatic lipid mediators that protect brain after experimental ischemic stroke

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Abstract: Ischemic stroke triggers a pattern of cellular and molecular disturbances that include lipid peroxidation and neuronal injury. Recently, we have uncovered and characterized a novel neuroprotective signaling mechanism, which involves the activation of the biosynthesis of a family of lipid mediators in the brain made from omega-3 very-long-chain polyunsaturated fatty acids, that we named Elovanoids (ELVs). This study evaluated ELVs, which are made of 32 to 34 carbon atoms in length (ELV-N32 and ELV-N34) in cerebral ischemia, and their potential mechanisms. Male Sprague-Dawley rats were subjected to 2 h of middle cerebral artery occlusion (MCAo). As sodium salts (Na) or methyl esters (Me), ELVs were dissolved in artificial CSF and administered into right lateral ventricle at 3 h after onset of stroke. There were five groups: ELV-N32-Na, ELV-N32-Me, ELV-N34-Na, ELV-N34-Me (5µg/50µl), and CSF (50µl). Neurological function was evaluated on days 1, 3, and 7 after MCAo. *Ex vivo* MRI and immunohistochemistry were conducted on day 7. All ELV treatments greatly improved neurologic scores in a sustained fashion up to the 7-day survival period. Ischemic core and penumbra volumes (computed from T2WI) were significantly reduced by all ELV treatments, and total lesion volumes were significantly reduced by ELV-N32-Na, ELV-N32-Me, ELV-N34-Na, and ELV-N34-Me compared to CSF-treated group (by 60%, 56%, 99%, and 91%, respectively). ELV-treated rats showed less infarction with an increased number of NeuN- and GFAP-positive cells as well as SMI-71-positive vessels in the cortex and less IgG staining in the cortex. ELV-mediated protection was extensive in the frontal-parietal cortex (tissue was salvaged by 57-96%), subcortex (73-75%), and total infarct volume, correction for brain swelling was dramatically reduced in all ELV-treated groups by 55-91%. Conclusion: We have shown that the administration of ELVs provides high-grade neurobehavioral recovery, decreases ischemic core and penumbra volumes, as well as attenuates cellular damage, blood vessel integrity, and BBB

disruption. These treatments might provide the basis for future therapeutics for patients suffering from ischemic stroke.

Disclosures: N.G. Bazan: None. **A. Obenaus:** None. **H. Menghani:** None. **S. Marcell:** None. **L. Khoutorova:** None. **N. Petasis:** None. **L. Belayev:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.24/Q12

Topic: C.08. Ischemia

Support: KBRI Grant 18-BR-01-04

Title: Role of Semaphorin 3E signaling in the developing brain vasculature and remodeling after ischemic stroke

Authors: *R. YU, D.-G. KIM, W.-J. OH
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Abstract: Most major axon guidance molecules have been shown to play a role in developing vascular network formation. As shown in the previous studies, secreted Semaphorin 3E (Sema3E), and its receptor Plexin-D1 pair which is one of the traditional axon guidance cues seems to have diverse roles in vascular topology in the periphery as well as retinal vasculature by regulating VEGF signaling. However, in spite of significant expression of Plexin-D1 in the angiogenic vessels, it remains still unclear whether the Sema3E-Plexin-D1 axis is implicated in the brain vasculature formation during development and remodeling process in the injured vessels. In this study, to address whether Sema3E-Plexin-D1 signaling is playing any roles in the developing brain vasculature, we performed 3D vascular network analysis using tissue clearing method and found that the vascular network of Plexin-D1 knockout exhibited a significant increase in the multiple parameters such as vascular length, branch, and density. Next, to elucidate whether the patterning role of Sema3E-Plexin-D1 axis during development can be recapitulated in the injured vessel remodeling process, we first analyzed their gene expressions in the stroke-induced brain. Interestingly, after ischemic injury by transient middle cerebral artery occlusion (tMCAO) method, Sema3e mRNA expression is markedly elevated in the penumbra of the ipsilateral cerebral hemisphere. Also, the brain was more severely damaged by ischemic stroke in the Sema3E knockout. Moreover, we observed that critical process involved in vascular remodelings such as tip cell sprouting and pericyte coverage was significantly less developed in the penumbra under ischemic condition. Taken together, these results demonstrate that Sema3E-Plexin-D1 signaling serves as a major player to establish proper brain vasculature during normal development as well as remodeling after vascular impairment such as stroke.

Disclosures: R. Yu: None. **D. Kim:** None. **W. Oh:** None.

Poster

294. Ischemia I

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Program #/Poster #: 294.25/Q13

Topic: C.08. Ischemia

Support: NIH R01 NS048216 (D.S)

Title: Astrocytic Na/H exchanger modulates Wnt/b-catenin signaling activation in cerebral vessels following ischemic stroke

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Abstract: Astrocytes play an important role in tissue repair following brain injury including ischemia or hypoxia and maintains the functional integrity of the blood-brain barrier. We have previously shown that in response to ischemia and hypoxia, reactive astrocytes stimulate Na^+/H^+ exchanger isoform 1 protein (NHE1) activity to counteract the acidic pHi. This leads to intracellular Na^+ overload, astrocytic swelling, and impaired glutamate uptake which exacerbates ischemic brain damage. In this study, we find that targeted deletion of *Nhe1* in astrocytes using *Gfap-Cre$^{ERT2+/-}$;Nhe1$^{f/f}$* mice (*Nhe1* KO) abolishes ischemic stroke-mediated astrogliosis, preserves blood-brain barrier (BBB) function, and reduces cerebral microvessel damage after transient middle cerebral artery occlusion (t-MCAO), a mouse model for ischemic stroke. RNA-sequencing transcriptome comparison of reactive astrocytes isolated from either control or *Nhe1* KO ischemic brains reveals that genes involved in nervous system development, ion transport, establishment of blood-brain barrier, and Wnt signaling are highly upregulated in *Nhe1* KO mice. In particular, the canonical Wnt signaling pathway is significantly upregulated with *Wnt7a* mRNA as the top upregulated gene in *Nhe1* KO astrocytes. This was accompanied by upregulation of several additional Wnt pathway genes (Wnt7b, Fzd9, Fzd10, Sox1, Sox21, and Ndp). Elevation of both Wnt 7a/b and β-catenin proteins are detected in microvessels of the ischemic peri-lesion areas in astrocytic *Nhe1* KO brains. Most importantly, *Nhe1* KO brains display intact tight junctions and increased expression of the tight junction protein occludin indicating that reactive astrocytes are involved in potential repair of the cerebral vessel through upregulation of canonical Wnt signaling. Taken together, our findings suggest that NHE1 functions as a modulator of Wnt expression in astrocytes to fine tune the levels of Wnt/β-catenin

signaling activity in cerebral endothelial cells to promote stabilization of the BBB function and tissue repair after ischemic stroke.

Disclosures: G. Begum: None. **X. Guan:** None. **S. Song:** None. **V. Pigott:** None. **H. Huang:** None. **M. Sun:** None. **D.B. Stolz:** None. **G.E. Shull:** None. **D. Agalliu:** None. **D. Sun:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.26/Q14

Topic: C.08. Ischemia

Support: Italian Ministry of Health, GR-2011-02350132

Title: Role of the glycoprotein Dickkopf3 as a novel central and peripheral modulator of blood pressure

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Abstract: Dickkopf3 (Dkk3) is a secreted glycoprotein member of the dickkopf protein family widely characterized as a pro-apoptotic and angiogenic factor in tumor development and involved in the pathophysiology of neurodegenerative disorders. A role of Dkk3 in molecular mechanisms of the blood pressure regulation is actually unknown. Remarkably, Dkk3 gene maps inside a WKY/SHR (Wistar Kyoto/Spontaneously hypertensive rat) chromosome 1 QTL (Quantitative Trait Locus) included between D1Mit3 and D1Rat57 markers and linked to the hypertensive phenotype. This observation raises the intriguing possibility that Dkk3 gene may be considered as a candidate gene for high blood pressure. We addressed this hypothesis by performing experiments of cerebral lentiviral Dkk3 hyperexpression in stroke-prone SHR rats (SHRsp), which develop high blood pressure and increased stroke occurrence after high-salt/low potassium diet (Japanese diet, JD). Dkk3 cerebral overexpression reduced blood pressure levels and led to a lower rate of cerebrovascular accidents in SHRsp rats. Coherently, by using Dkk3 knockout mice, we observed that the Dkk3 genetic deletion was associated to higher blood pressure levels under basal condition as compared to the wild-type mice. Furthermore, cerebral

lentiviral Dkk3 overexpression in Dkk3 knockout mice led to blood pressure levels similar to those observed in the wild-type mice. In both SHRsp rats and in Dkk3 knockout mice, the cerebral lentiviral Dkk3 overexpression led to a massive downregulation of the angiotensin receptor AT-1 and of the catalytic subunit of the NADPH oxidase, gp91phox, and to an increased phosphorylation of both extracellular signal-regulated kinase (ERK) and endothelial NO synthase (eNOS). Finally, vascular reactivity analysis performed on mesenteric vessels of Dkk3 knockout mice showed that the genetic deletion of Dkk3 led to endothelial dysfunction with a reduced eNOS phosphorylation. Moreover, incubation of mesenteric vessels with the human recombinant Dkk3 peptide rescued these alterations suggesting that the glycoprotein Dkk3 directly modulates vascular reactivity. Taken together, these data raise the hypothesis that Dkk3 may represent a novel molecule acting as a key component of peripheral and central control of blood pressure.

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Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.27/R1

Topic: C.08. Ischemia

Support: CIHR

Title: Amyloid β reduces pannexin-1 channel opening during ischemia through a novel mGluR1-mediated mechanism

Authors: *L. A. PALMER[1], A. K. J. BOYCE[2], A. W. LOHMAN[2], R. J. THOMPSON[2]
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Abstract: Alzheimer's disease (AD) is associated with over-production of the amyloid β (Aβ) protein. Genetic causes of AD account for ~5% of cases, indicating that there are unknown co-morbidities for the disease. Ischemic stroke has been identified as an important risk factor, and accounts for up to five-fold increase in risk of developing AD. Interestingly, hypoxia upregulates production of Aβ. The purpose for this is unknown, but was previously assumed to be a pathological consequence of ischemia. We hypothesized that Aβ may play a physiological role during hypoxia, such as modulating the anoxic depolarization (aDP). The aDP is a large inward current that occurs in response to excessive glutamate release, activating *N*-methyl-*D*-aspartate

receptors (NMDARs). Previously, our group has demonstrated activation of pannexin-1 (Panx1), a large, non-selective ion channel, downstream of NMDARs during hypoxia. Furthermore, mGluRs are known to regulate NMDARs, and may contribute to the aDP. Since NMDARs/mGluRs are a known target of Aβ, we hypothesized that Aβ would modify Panx1 opening during ischemia. Using whole-cell patch clamp electrophysiology in rat hippocampal slices, the aDP was assayed using low oxygen (~5 mmHg) artificial cerebral spinal fluid. Rat (r) and human (h) $Aβ_{1-42}$ were matured into a mixture of small to large oligomers. We report that low concentrations (pM to nM) of exogenous rAβ attenuated the aDP, and also blocked Panx1 opening on an NMDA overstimulation assay. Reducing endogenous Aβ levels using L-685,458 increased aDP severity. Human Aβ also had a protective effect on the aDP, and hippocampal slices from transgenic mice that overexpress hAβ oligomers had reduced aDP compared to those of wild-type littermates. Importantly, Aβ failed to block Panx1 currents directly in Panx1-expressing HEK cells. The apparent neuroprotective effect of Aβ on the aDP was reversed with co-application of mGluR1 antagonists, but not with an mGluR5 antagonist. Furthermore, the mGluR1 inverse agonist, Bay 367620 blocked the aDP in a similar manner to Aβ, and had no additive block with concurrent Aβ application, suggesting that Aβ may function as an mGluR1 inverse agonist. These data suggest a novel modulation of Panx1 opening by mGluR1, which is regulated by Aβ. Aβ production could be increased during hypoxia to reduce activation of Panx1, thereby attenuating the aDP and downstream cell death pathways.

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Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.28/R2

Topic: C.08. Ischemia

Title: Exosomes derived from human neural stem cells-stimulated by interferon gamma enhance cellular stress mechanisms and accelerate neurological recovery of cerebral ischemic rats

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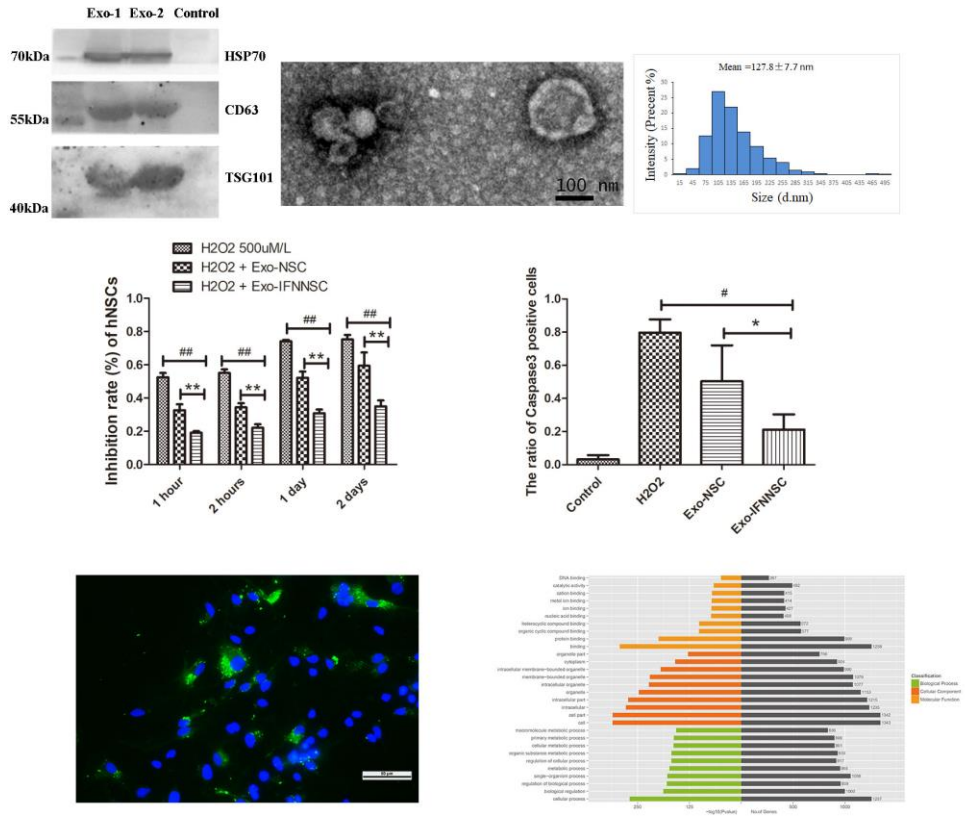
Abstract: Ischemic stroke recovery is associated with neural stem cells (NSCs) development and neurovascular unit reconstruction. Exosomes, as important intercellular players in cellular communication, mediate neuro-restorative events, however, their effects / mechanisms in the injured brain is unknown. The objective of this study is to determine the effect of human NSCs-derived exosomes on the repair of ischemic stroke, and whether interferon gamma (IFN-γ)

stimulating can enhance the functions of NSCs exosomes. This study finds that IFN-γ stimulating managed the abilities of human NSCs-derived exosomes (hNSCs-Exo), including alleviated the level of oxidative stress of NSCs following H2O2 stimulating, augmented the NSC survival, and promoted the neuronal differentiation of NSCs. Furthermore, in rats ischemic stroke model, IFN-γ-hNSCs-Exo further facilitated the neurological functional recovery (such as modified Neurological Severity Score, Rotarod test, etc.) compared to hNSCs-Exo group, enhanced nerve cell survival and promoted neovascularization (microvessel density, MVD). Importantly, exosomes can be internalized or endocytosed by cells, after labeled with PKH67, it showed that exosomes migrated to the infarct regions together with cells, as interestingly, many exosomes entry into the nucleus. Next generation sequencing (NGS) revealed significant enrichment of hsa-miR-3656 and hsa-miR-133a-3p in IFN-γ-hNSCs exosomes compared with hNSCs exosomes. The mechanisms or effects of exosomes was to deliver specific exosomal microRNAs to cells for increasing cell survival and proliferation. In summary, hNSCs-derived exosomes possess the ability of neural regeneration and modulate neurological functional recovery, and play more positive roles by stimulating with IFN-γ (IFN-γ-hNSCs Exo). Exosomes provide a novel and promising strategy in modulating disease treatment and tissue regeneration, avoiding the risk of teratomas associated with cells.



Disclosures: G. Zhang: None. **L. Chen:** None.

Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.29/R3

Topic: C.08. Ischemia

Support: NIH Grant K99NR013593
NIH Grant R01NS096091

Title: Liquefaction of the brain following stroke shares characteristics with atherosclerosis

Authors: *K. P. DOYLE[1,2,3], A. CHUNG[1], J. B. FRYE[1], J. C. ZBESKO[1], E. CONSTANTOPOULOS[4], M. HAYES[1], A. G. FIGUEROA[5], W. A. DAY[6], J. P. KONHILAS[4], B. S. MCKAY[5], T.-V. V. NGUYEN[1,2]
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Abstract: In response to ischemia, the brain degenerates by the process of liquefactive necrosis while the heart degenerates by coagulative necrosis. Liquefactive necrosis intensifies post-stroke injury, persists for months following a stroke and occurs for unknown reasons. Cholesterol is a central structural component of myelin. This means that in the aftermath of a brain injury the immune system must clear away substantially more cholesterol than in the aftermath of an injury to an alternative area of the body such as the heart following a myocardial infarction. Therefore, the goal of this research was to understand if the brain undergoes liquefactive necrosis following stroke due to cholesterol derived from myelin debris overwhelming the processing capability of phagocytic cells in the brain, leading to the overproduction of degradative enzymes. To that end, we used mouse models of myocardial infarction and ischemic stroke to compare the kinetics and characteristics of the inflammatory response to ischemia in the heart, a protein rich organ, to the inflammatory response to ischemia in the brain, a lipid rich organ. We then looked-for evidence of overlap in the molecular profile of the chronic inflammatory response to stroke and atherosclerosis. Finally, we tested if targeting pathways involved in the pathophysiology of atherosclerosis also modulate the damaging effects of liquefactive necrosis following stroke. We show that the brain takes substantially longer than the heart to heal from ischemia, and that intracellular and extracellular cholesterol crystals form within the infarct in the weeks following stroke. This is proceeded by the expression of many of the same proteolytic enzymes and pro-inflammatory cytokines associated with atherosclerosis. We then show that the expression of these proteolytic enzymes and pro-inflammatory cytokines is profoundly reduced in osteopontin (OPN) deficient mice, and that this is concordant with an accelerated recovery of motor function and a reduction in secondary neurodegeneration compared to wildtype mice. We anticipate these

findings to be a starting point for testing if treatments that target cholesterol overloading in microglia and macrophages are also useful for improving recovery in stroke patients. **Efforts to ensure scientific rigor:** Studies were performed in male wildtype and transgenic mice on the C57BL/6 background. Groups numbers were determined by power analysis and experimenters were blind to experimental condition. All antibodies, kits, and chemicals were obtained from established vendors that authenticate their reagents prior to shipment as part of a standard quality control procedure.

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Poster

294. Ischemia I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 294.30/R4

Topic: B.11. Glial Mechanisms

Support: NSFC81760280

Title: $CD11b^{+}$ cells in developing brain and it's phagocytotic function change in neonatal hypoxia and ischemia model

Authors: *F. LI, Y.-J. MIN, L. YAN, Q. WANG, F. WANG, H.-R. HUA, Y. YUAN, H.-Y. JIN, Y. YANG
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Abstract: Hypoxia ischemia brain damage (HIBD) is one of the major causes of mortality in neonatal diseases and leads to long-term behavior abnormalities. The pathogenesis of long term behavioral disorder after HIBD is still unclear. However, the current studies suggests that this is associated with active brain inflammation and synaptic dysfunction. Synapses, during the developmental period experienced "synaptic pruning", this is the brain with phagocytotic cells to remove the weak synapses, and thus ensure the advantages of synaptic full growth process. HIBD causes local inflammantory response and phagocytotic cells activation, which involves both resident microglia cell (MC) and infiltrating monocyte-derived macrophage (MDMs). Due to lack of specific discriminate cell makers, little is known about the functional differences between resident MC and MDMs following hypoxia and ischemia, especially their phagocytotic function change in the developing brain. Therefore, we used a HIBD model of P9-11d mouse pups to investigate the dynamic changes of these two populations in the brain and their roles in phagocytosis. Immunofluorescence was used to test the expression of protein NeuN, CD11b, LAMP1 after HIBD 1d and 3 d. The flow cytometry was applied to detect target proteins

expression in $CD11b^+$ cells. CD11b/CD45 were used to distinguish MDMs ($CD45^{high}/CD11b^+$) and inherent MC ($CD45^{low}/CD11b^+$). In addition, CD36, TLR2, LAMP1 were used to indicate the phagocytotic function of $CD11b^+$ cells in mice' brain cortex after HIBD 1 d and 3 d. Analyses by flow cytometry and immunocytochemistry found that number of $CD11b^+$ cells within the brain increased after 1-3d with the severe injury and the increased $CD11b^+$ cells were mainly MDMs. So the CD11b cannot be used alone as a marker for the inherent MC in the brain. Additionally, the inherent MC is still the major cell that plays phagocytosis in early period after HIBD in $CD11b^+$ cells.

Disclosures: F. Li: None. **Y. Min:** None. **L. Yan:** None. **Q. Wang:** None. **F. Wang:** None. **H. Hua:** None. **Y. Yuan:** None. **H. Jin:** None. **Y. Yang:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.01/R5

Topic: C.10. Brain Injury and Trauma

Support: R01HD083001-02

Title: Hypothermia ameliorates neurotoxicity of anesthesia in the neonatal brain

Authors: *C. IKONOMIDOU[1], G. KIRVASSILIS[2], H. WANG[4], J. HUFFMAN[4], S. L. WILLIAMS[4], S. CAPUANO III[3], K. R. BRUNNER[3], K. CROSNO[3], H. A. SIMMONS[3], K. K. NOGUCHI[5]
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Abstract: Sedative and anesthetic drugs can injure neurons and oligodendrocytes in the developing brain. They can cause widespread cell death, impair synaptic maturation and plasticity, inhibit neurogenesis in the brains of rodents and non-human primates (NHP) and trigger long term behavioral and cognitive deficits. Hypothermia (HT) is successfully applied in neonatal and pediatric medicine to minimize brain injury from perinatal asphyxia and during cardiac surgery. We investigated HT as a potential protective treatment of the developing primate brain against histological toxicity of the anesthetic sevoflurane in NHP infants. Neonatal rhesus monkeys underwent sevoflurane anesthesia over 5 hours. Body temperature was regulated to lie in the normothermic (>37^{o}C), mild hypothermic (mean 36.27^{o}C) and moderately hypothermic (<35^{o}C) range. Animals were euthanized and brains collected at 8 hrs and examined immunohistochemically (activated caspase 3) and stereologically to quantify apoptotic neuronal and glial death. Sevoflurane anesthesia was well tolerated with oxygen saturation, end tidal CO_2

and electrolytes remaining at optimal levels throughout the procedures. Brains displayed significant apoptosis in both the white and gray matter. Areas predominantly affected included the visual, frontoparietal, cingulate and retrosplenial cortex, the thalamus, globus pallidum and putamen. Approximately 50% of the dying cells were glia and 50% were neurons. Mild hypothermia (35-37^{o}C) conferred significant protection from apoptotic injury whereas moderate hypothermia (<35^{o}C) did not. Our findings indicate that exposure of the infant rhesus macaque to sevoflurane for 5 hours is sufficient to cause widespread apoptosis of neurons and oligodendrocytes and that mild hypothermia is cytoprotective in the neonatal primate brain.

Disclosures: C. Ikonomidou: None. **G. Kirvassilis:** None. **H. Wang:** None. **J. Huffman:** None. **S.L. Williams:** None. **S. Capuano III:** None. **K.R. Brunner:** None. **K. Crosno:** None. **H.A. Simmons:** None. **K.K. Noguchi:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.02/R6

Topic: C.10. Brain Injury and Trauma

Support: HD052664
HD083001
U54-HD087011
Frontiers in Anesthesia Research Award
P51-OD011092

Title: Noxious stimulation from surgery has no effect on anesthesia-induced apoptosis in the developing macaque brain

Authors: *J. N. HUFFMAN[1], S. WILLIAMS[2], S. LIU[3], K. LUCAS[3], L. D. MARTIN[4], G. A. DISSEN[6], K. SCHENNING[5], A. BRAMBRINK[7], K. K. NOGUCHI[8]
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Abstract: Exposure to either NMDA antagonists or $GABA_A$ agonists produces a massive neuroapoptotic response in numerous animal models and has caused great concern since these two drug classes include many commonly used sedatives, anesthetics, and anti-epileptic drugs. This has resulted in the FDA requiring labels on 11 commonly used drugs warning they may disrupt brain development in children under 3 years of age if exposure exceeds 3 hours or occurs

multiple times (estimated to include around 160,000 children a year in the United States alone). Since clinical studies have produced conflicting results, animal models have become critically important. The initial studies in rodents were met with healthy skepticism based on the limited translatability to humans and the inability to continuously monitor small neonatal rodents during anesthesia. To address these concerns, studies in nonhuman primates (NHPs) confirmed this toxicity still occurs even when anesthesia is accompanied with mechanical ventilation and vital signs are maintained within normal limits. However, a second criticism is that the pain from surgery may protect the developing brain from anesthesia induced apoptosis. Rodent studies examining this possibility have produced inconsistent results with some finding inflammatory pain with anesthesia increases apoptosis and others finding neuroprotection. However, these studies might be criticized since: 1) they used a rodent animal model, 2) the inflammatory pain administered may not accurately simulate surgery, and 3) vital signs were not monitored throughout anesthesia. In order to address these deficiencies, we examined whether anesthesia with surgery can still increase apoptosis in the neonatal NHP. To eliminate possible confounding variables, animals were mechanically ventilated and vital signs were monitored throughout surgery. Necrotizing enterocolitis is the most common condition of the newborn requiring surgical intervention. We therefore exposed neonatal NHPs to either no anesthesia, isoflurane anesthesia alone, or isoflurane anesthesia with surgical resection of the bowel and anastamosis prior to sacrifice for histological assessment for apoptosis. Results revealed that isoflurane anesthesia increased both oligodendrocyte and neuronal apoptosis that was not altered by surgical intervention even when vital signs, blood gasses, and metabolic values are maintained within normal limits. These results indicate that the noxious stimulation from surgery has no effect on the apoptotic effects of anesthesia.

Disclosures: J.N. Huffman: A. Employment/Salary (full or part-time):; University of Missouri-St. Louis. **S. Williams:** A. Employment/Salary (full or part-time):; Washington University St Louis. **S. Liu:** A. Employment/Salary (full or part-time):; Washington University St Louis. **K. Lucas:** A. Employment/Salary (full or part-time):; Washington University St Louis. **L.D. Martin:** A. Employment/Salary (full or part-time):; Oregon Health Sciences University. **G.A. Dissen:** A. Employment/Salary (full or part-time):; Oregon Health Sciences University. **K. Schenning:** A. Employment/Salary (full or part-time):; Oregon Health Sciences University. **A. Brambrink:** A. Employment/Salary (full or part-time):; Columbia University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Frontiers in Anesthesia Research Award 2012. **K.K. Noguchi:** A. Employment/Salary (full or part-time):; Washington University St Louis. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; RO1-HD052664, R01-HD083001, U54-HD087011.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.03/R7

Topic: C.10. Brain Injury and Trauma

Support: HD061963
DA031900

Title: DREADD-mediated activation of dopaminergic neurons ameliorates mild TBI-induced depression-like behavior in the adolescent female rat

Authors: *L. L. GIACOMETTI, D. LENGEL, R. A. ESPAÑA, R. RAGHUPATHI
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Abstract: Following mild TBI, girls report more emotional symptoms and take longer to recover from their symptoms than boys. Thirty five-day-old female rats were used to model mild TBI in the adolescent human. Rats were anesthetized and directly impacted on the skull using a 5mm metal tip just behind bregma over the midline suture (2mm depth, 5.5m/s velocity); sham-injured rats were anesthetized, but not injured. We have previously reported that female, but not male, adolescent rats subjected to this mild TBI exhibit depression-like behavior using the forced swim test (FST) at 5-6 weeks post-injury during the estrus phase of the estrous cycle. The dopaminergic system has been implicated in depression-like behavior and chronic alterations in dopaminergic neurotransmission, suggestive of a state of hypodopaminergia, have been reported following moderate-severe TBI. We hypothesized that a state of hypodopaminergia may contribute to depression-like behavior. Brain-injured tyrosine hydroxylase (TH)-Cre rats received bilateral ventral tegmental area (VTA) injections of the Cre-dependent Gq DREADD virus, pAAV-hSyn-DIO-hM3D(Gq)-mCherry, in order to activate dopaminergic neurons in the VTA or control virus, pAAV-hSyn-DIO-mCherry. Rats were tested 5 weeks later in the forced swim test 45 min following IP injection of clozapine-N-oxide (0.5mg/kg) or saline. CNO-injected, Gq-DREADD-expressing rats exhibited significantly lower immobility in FST than either saline-injected, Gq-DREADD-expressing rats or CNO-injected, control virus-expressing rats. We next hypothesized that the depression-like behavior occurred specifically in the estrus phase due to the surge in progesterone and estradiol occurring during proestrus as this has been shown to reduce dopamine D2 receptor density during estrus. Brain-injured rats were injected with the estrogen receptor antagonist, tamoxifen, and the progesterone receptor antagonist, mifepristone, during proestrus and tested in FST the following day during estrus. Tamoxifen and mifepristone administration during proestrus prevented the depression-like behavior in estrus. Administration of the dopamine D2-like receptor agonist, quinpirole (0.05, 0.1mg/kg), 1hr prior to testing in FST also ameliorated depression-like behavior during estrus in brain-injured rats.

Taken together, this data suggests that mild TBI-induced hypodopaminergia in combination with estrous phase-dependent changes in dopamine D2 receptor density may contribute to depression-like behavior in female rats.

Disclosures: L.L. Giacometti: None. **D. Lengel:** None. **R.A. España:** None. **R. Raghupathi:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.04/R8

Topic: C.10. Brain Injury and Trauma

Support: NICHD Grant HD061963
Merit Review grant from the Veterans Administration

Title: Sex-dependent cellular and cognitive deficits following traumatic brain injury in neonate rats are reversed by progesterone

Authors: *D. LENGEL[1], J. W. HUH[2], R. RAGHUPATHI[3]
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Abstract: Childhood traumatic brain injury (TBI) is associated with an increased risk for anxiety disorders, impaired cognitive function, and alterations in hypothalamic-pituitary-adrenal (HPA) axis function in adulthood. In order to investigate the long-term consequences of pediatric TBI on anxiety-related and cognitive function, 11-day-old male and female Sprague-Dawley rats were subjected to closed-head injury or sham surgery, and were evaluated for behavioral deficits in the novel object recognition (NOR) test, elevated plus maze (EPM), and forced swim test (FST), and for changes in neuronal excitability in the prefrontal cortex (PFC) 4 weeks following injury. Injured male rats showed a significant impairment in novel object recognition (NOR), which was associated with an increase in spontaneous excitatory post synaptic current (sEPSC) frequency and excitability in layer V Prelimbic area (PrL) pyramidal cells. In females, there was a deficit in NOR that did not reach statistical significance, but that was associated with an increase in sEPSC frequency in layer II/III PrL pyramidal cells and an increase in excitability in layer V PrL pyramidal cells. Treatment with progesterone following injury reversed NOR deficits and electrophysiological changes in both male and female injured rats. These deficits combined suggest that TBI may lead to increased dopamine release or increased D1 receptor activation in the PFC. Thus, progesterone may reduce cognitive and cellular deficits by modulating D1 receptor signaling in the PFC, presumably by inhibiting sigma-1 receptors. Male and Female injured animals also showed reduced anxiety in the elevated plus maze (EPM)

compared to sham animals. Further, female but not male injured rats had decreased immobility in the forced swim test (FST) specifically in the estrus and metestrus phases of the estrous cycle. The acquisition and retention of immobility in the FST are regulated by hippocampal glucocorticoid receptors (GRs), and are sensitive to changes in glucocorticoid levels. These data combined suggest that TBI may impair GR signaling, potentially to a greater degree in female rats, leading to altered anxiety-like behavior and stress-related adaptive behavior in the FST. Future experiments will focus on investigating the impact of pediatric TBI and sex differences on HPA axis function and GR expression associated with anxiety-related deficits, and on changes in DA transmission associated with cognitive and cellular deficits.

Disclosures: D. Lengel: None. **J.W. Huh:** None. **R. Raghupathi:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.05/R9

Topic: C.10. Brain Injury and Trauma

Support: New Jersey Commission on Brain Injury Research (NJBIR) - CBIR17PIL007
Seed funds from Rowan University

Title: Repetitive mild traumatic brain injury impairs performance in a rodent assay of cognitive flexibility

Authors: R. L. NAVARRA[1], C. P. KNAPP[1], *D. M. DEVILBISS[1], D. P. FOX[1], R. RAGHUPATHI[2], L. L. GIACOMETTI[2], S. B. FLORESCO[3], B. D. WATERHOUSE[1]
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Abstract: Mild traumatic brain injury (mTBI) occurs in almost 80% of the 3 million reported cases of TBI-related emergency department visits each year in the United States. The majority of mTBIs, sometimes classified as concussions, are due to sports-related activities and typically occur repeatedly over the course of an athlete's career. mTBI symptoms are generally classified as either somatic or neuropsychiatric/cognitive in nature and include impairments in prefrontal cortex mediated functions, including attention, memory, processing speed, reaction times, problem solving, and cognitive flexibility. To date, there remains a major gap in our understanding of the behavioral manifestations, underlying neurobiology, and treatment of mTBI. An even greater gap exists in our understanding of the consequences of repeated mTBI incidents. The goal of the present study was to examine the effects of repetitive mTBI within a rodent assay of cognitive flexibility. Rats were exposed to a series of three closed head injuries (controlled cortical impact model) within a week prior to performing an automated strategy

shifting task, which required rats to learn and shift strategies according to changing task demands. Rats initially acquired a visual cue strategy in which a light illuminated above one of two possible levers (left or right) indicated the correct response for reward. Twenty-four hours after initial acquisition, rats again performed the task using the visual cue strategy followed by a series of strategy shifting and reversal learning challenges. Repetitive mTBI reduced throughput scores, a performance index that blends accuracy and response speed, and increased reaction times within the task. Preliminary immuno-histological analyses of brain tissue from experimental animals revealed a reduction of noradrenergic fiber density in the anterior cingulate, medial prefrontal, and lateral orbitofrontal cortical regions of injured vs un-injured sham animals. These results indicate that performance and task efficiency in an operant test of cognitive flexibility are impaired after repetitive mTBI. As such, this model presents a useful approach for further investigating the behavioral deficits and potential treatment strategies for patients who have experienced multiple mTBI insults. Moreover, evidence of reduced noradrenergic function in prefrontal cortex provides a potential link between a neuromodulatory system normally associated with arousal, attention, and decision making and this model of repetitive head trauma-induced behavioral deficits.

Disclosures: R.L. Navarra: None. **C.P. Knapp:** None. **D.M. Devilbiss:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NexStep Biomarkers, LLC., Cerora, Inc.. **D.P. Fox:** None. **R. Raghupathi:** None. **L.L. Giacometti:** None. **S.B. Floresco:** None. **B.D. Waterhouse:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.06/R10

Topic: C.10. Brain Injury and Trauma

Title: Modeling the neural circuit of rodent lower urinary tract

Authors: *T. BANKS[1], V. GUNTU[2], M. GAHL[3], G. JONES[1], D. J. SCHULZ[4], S. S. NAIR[5]
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Abstract: We report results from an interdisciplinary study focused on an understudied but crucial aspect of how spinal cord injury (SCI) alters the properties and activity of uninjured neural networks focusing on the rodent lower urinary tract. Our hypothesis is that neurons are fundamentally altered when inputs are removed by injury. Understanding how and why these neurons and networks are altered by denervation as a result of injury is essential for studies aimed at restoring function. Computational models complement biological experiments very well

in such a study.The sympathetic pathway controls bladder filling and includes pre-ganglionic neurons in the spinal cord and post-ganglionic cells of the inferior mesenteric ganglion. Sacral parasympathetic outflow controls bladder voiding and includes the pre-ganglionic cells and the postganglionic neurons of pelvic ganglia. The urethral sphincter is innervated by motor neurons projecting through the pudendal nerve. While urine storage mechanisms are largely dependent on spinal reflex pathways, urine voiding is dependent on a rapid switch from filling to voiding mediated by descending Supraspinal inputs. Sensory information regarding bladder fullness is conveyed to the spinal cord through the pelvic and splanchnic nerves.We have developed biophysical models of the cells in all major ganglia using information from the literature and first-hand biological recordings pelvic ganglia neurons from Schulz Lab. Sensory afferents are modeled presently using a regression fit with filling rate. The model successfully reproduced the sympathetic storage reflex and guarding reflex. With the base model, we added spinal interneurons which makes the circuit more realistic and give us flexibility to explore how these spinal circuits complement normal functioning of LUT. On-going work focuses on simulating both normal as well as abnormal (e.g., detrusor-sphincter dyssynergia) functioning at neuronal and micro-circuit level. This improved model will then be modified for SCI studies by disconnecting the top down control and investigate mechanisms that might restore the reflexive arc.

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.07/R11

Topic: C.10. Brain Injury and Trauma

Support: Fellowship from the New Jersey Commission on Brain Injury Repair

Title: Repeated mild traumatic brain injury in a mouse model: The effect of BDNF genetic polymorphisms on recovery and personalized treatment approaches

Authors: *S. THAKKER-VARIA[1], S. L. TENG[2], A. O. GIRRATANA[2], C. ZHENG[2], J. ALDER[2]
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Abstract: Traumatic Brain Injury (TBI) is a serious and potentially life threatening clinical problem. Clinicians have long noticed that certain patients recover better after TBI, and identifying what makes some patients more susceptible is a vital step in understanding the

underlying mechanisms through which TBI causes its deleterious effects. Following TBI, a number of factors are regulated; among them are neurotrophic factors, such as brain derived neurotrophic factor (BDNF). Previous studies in our lab have shown that TBI results in the activation of proBDNF pathway while the mature BDNF pathway is downregulated, which may play a role in the poor recovery that is seen. In this study, we sought to determine the effect of specific single nucleotide polymorphisms (SNPs) on recovery after TBI, and to investigate the underlying mechanisms that may be a factor. We have investigated cellular and behavioral outcomes in genetically engineered mice with the BDNF Val66Met polymorphism following repeated, mild TBI (rmTBI) in a lateral fluid percussion model. We have found that Met carriers have a larger injury volume as assessed by MRI and increased levels of neurodegeneration, apoptosis, p-tau, microglia, and gliosis in the cortex compared to Val carriers at 1 and/or 21 dpi. We have done rotarod and balance beam testing to examine sensorimotor ability, and found that injured mice have worse motor function than sham mice, but that there are no differences in sensorimotor function across genotypes. We have done novel object recognition testing and Morris water maze to investigate learning and memory in this paradigm. In the novel object paradigm, we have found that Met carriers in general spend less time exploring the open field and the novel object, but that there is no difference in the preference index after our injury paradigm. In order to gain insight into the mechanism of action of the cellular differences that we have seen, we used western blot analysis to investigate the levels of pro and mature BDNF after injury across the genotypes at 1 and 21 dpi, and found Met carriers have more proBDNF and less mature BDNF than Val carriers. As a result, we have concluded that the Met allele is a risk allele after rmTBI and have begun rescue experiments in injured mice by targeting the altered BDNF pathway using an AAV vector that overexpresses BDNF.

Disclosures: S. Thakker-Varia: None. **S.L. Teng:** None. **A.O. Girratana:** None. **C. Zheng:** None. **J. Alder:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.08/R12

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R01NS067417
NIH Grant 5T32NS041218

Title: Hippocampal synaptic plasticity changes following exposure to high frequency head impacts (HF-HI)

Authors: *S. S. SLOLEY[1], B. S. MAIN[2], C. N. WINSTON[5], M. S. PARSADANIAN, 20057[2], J.-Y. WU[3], J. G. PARTRIDGE[6], S. VICINI[7], M. P. BURNS[4]

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Abstract: Mild traumatic brain injury, or concussion, accounts for over 70% of all cases of TBI reported each year. Sustaining multiple concussions is associated with the development of long lasting cognitive and memory impairments. The severity of these impairments increases longitudinally, and in an injury frequency-dependent manner. Chronic traumatic encephalopathy (CTE), a slowly developing tauopathy, has been associated with the development of these impairments; however, it is unknown if the cognitive deficits associated with CTE can occur prior to the deposition of tau and death of neuronal cells. We therefore sought to identify any tau-independent mechanisms associated with deficit development following exposure to high frequency concussive impacts. To perform these studies, our group has developed an experimental model of high frequency head impacts (HF-HI) in which mice receive 5 hits a day for 6 days (30 hits total). Immunohistochemical analyses revealed that HF-HI did not cause cell death or inflammation. Golgi staining for dendritic spines indicated that there was no excitatory synapse loss detectable compared to sham mice. Despite the normal synapse number, behavioral testing at one month post injury showed that HF-HI results in deficits in the acquisition and probe phases of the Morris water maze, as well as a reduction of spontaneous alterations in the T-Maze, suggesting impaired learning and memory. Given the development of these deficits in the absence of structural or synaptic loss, we hypothesized that HF-HI was eliciting synaptic adaptations to confer neuroprotection at the cost of normal physiological function. To examine this, we first tested the effect of HF-HI on hippocampal synaptic plasticity using the long-term potentiation (LTP) paradigm and extracellular field recordings. Input/output curves for HF-HI mice were identical to sham mice, indicating that the Schaffer collateral pathway remained undamaged after HF-HI - however there were significant impairments in LTP. Whole cell patch clamp electrophysiology done on individual CA1 pyramidal neurons after HF-HI reveal differences in intrinsic membrane properties, excitability, and NMDA receptor contributions to excitatory post synaptic currents after HF-HI, reinforcing the hypothesis that synaptic adaptations alter function following HF-HI. These changes in synaptic transmission also provide a mechanism for altered plasticity. We have concluded that exposure to a high frequency of concussive and sub concussive head impacts causes synaptic adaptations to promote cellular survival that ultimately hinder plasticity and neurotransmission.

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.09/R13

Topic: C.10. Brain Injury and Trauma

Support: NIH R01NS099596

Title: Chondroitin-sulfate glycosaminoglycan (CS-GAG) matrix implants mediate chronic neuroprotection after severe traumatic brain injury

Authors: *R. C. MOHANKUMAR, N. BALAJI, M. BETANCUR, H. D. MASON, G. SIMCHICK, M. LOGUN, C. LENEAR, Q. ZHAO, P. HOLMES, L. KARUMBAIAH
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Abstract: Severe traumatic brain injuries (TBIs) are a major cause of death and disability in the United States and account for around 30% of injury-related deaths. Severe TBIs are commonly caused by penetrating or blunt force injuries to the brain. Individuals who sustain these injuries, encounter significant loss of brain tissue, which directly contributes to the debilitating long-term disabilities and sensorimotor and cognitive dysfunction in this population. Current standard-of-care is limited to the acute administration of anti-inflammatory drugs followed by aggressive rehabilitation upon patient stabilization. There are currently no tissue-replacement or regenerative therapies for severe TBI. We hypothesized that a hydrogel-based brain tissue mimicking implant containing sulfated chondroitin sulfate glycosaminoglycans (CS-GAGs) native to the brain extracellular matrix (ECM) will bind and retain neurotrophic factors, enhance paracrine signaling of infiltrating neural stem cells (NSCs), and provide physical support to facilitate tissue repair after a severe TBI. Adult male Sprague-Dawley rats (2 months old) were subjected to a controlled cortical impact injury, which produced a severe TBI in the frontoparietal cortex of the brain. Sham control rats received a craniotomy but did not receive a TBI. Animals assigned to the CS-GAG treatment group received 20 µl of CS-GAG hydrogel intraparenchymally at the site of injury. The brains were harvested 20-weeks post-injury/sham treatment, sectioned and stained for neuron, astrocyte, oligodendrocyte, NSCs, growth factors, and vascularization specific markers. Administration of CS-GAG matrices significantly reduced the extent of glial scar when compared to TBI only controls ($p<0.05$). CS-GAG matrix treated animals also demonstrated a significant increase in the number of proliferating NSCs (Ki67, Sox1) and biomarkers for vascularization (Collagen, RECA) at the site of injury when compared to TBI-only controls ($p<0.05$). These results provide evidence suggesting that CS-GAG matrix implants can reduce inflammation and promote NSC mediated repair and recovery from severe TBI. **Supported by NIH R01NS099596-01 to LK.**

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.10/R14

Topic: C.10. Brain Injury and Trauma

Support: U54NS100064
R01NSo33310

Title: Developing potential quantitative tractography biomarkers of epileptogenesis following experimental traumatic brain injury

Authors: *R. P. CABEEN[1], D. DUNCAN[1], A. BRAIMAH[1], R. IMMONEN[2], X. NDODE-EKANE[2], O. GRÖHN[2], D. WRIGHT[3], I. ALI[3], R. BRADY[3], S. SHULTZ[3], N. JONES[3], P. CASILLAS-ESPINOSA[3], C. SANTANA-GOMEZ[4], R. STABA[4], N. HARRIS[5], G. SMITH[5], A. PITKANEN[2], T. J. O'BRIEN[3], J. ENGEL, Jr.[4], A. W. TOGA[1]
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Abstract: Objectives:
Some traumatic brain injury (TBI) cases subsequently develop epilepsy, and research on antiepileptogenic therapies is hampered by a lack of biomarkers for identifying high risk individuals. This work develops techniques for identifying potential quantitative magnetic resonance imaging (MRI) biomarkers of epileptogenesis in a rodent model following experimentally-induced TBI. We examine tractography imaging metrics of brain connectivity and white matter microstructure.
Methods:
The Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) is an international, multicenter Center without Walls (CWOW), and the animal imaging component of the study has collected in vivo MRI across three sites. Rats were separated into sham and experimentally-induced TBI groups, anesthetized, and imaged in Bruker scanners at high-field strength (one at 4.7T and two at 7T). The MRI protocol included 3D-multiecho GRE for T2* and magnetization transfer ratio (MTR) mapping and a 3D-EPI sequence for diffusion MRI with 42 gradients at a b-value of 2800 s/mm2. Multi-fiber deterministic tractography was performed using the Quantitative Imaging Toolkit with masks drawn to select the fibers from the internal capsule, corpus callosum, fimbria fornix, and perforant pathway. The following bundle metrics were analyzed: track density, volume, length, and averages of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, MTR, and T2*.

Results:
Our results demonstrate the feasibility of extracting quantitative tractograhy metrics across subjects, which may be used for detecting structural brain alterations related to epileptogenesis. We also show the improved anatomical accuracy of tractography with multi-fiber tracking in the study's data and the value of deriving metrics through multimodal analysis.
Conclusions:
This work demonstrates the potential value of combining tractography models with other MRI modalities to develop biomarkers of epileptogenesis in our continuing work. This is in part due to the added structural information provided by diffusion MRI in delineating relevant white matter pathways, which can then be combined with other discriminative quantitative MRI parameters identified by previous studies. Future work will combine these findings with epilepsy parameters and biospecimens collected as part of EpiBioS4Rx and potentially translate them to human imaging to facilitate the discovery of novel antiepileptogenic therapies.
This research was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number U54NS100064.

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.11/R15

Topic: C.10. Brain Injury and Trauma

Title: Assessing cognitive correlates of cellular regeneration after brain injury in adult zebrafish

Authors: *K. SKAGGS
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Abstract: Zebrafish (*Danio rerio)* have become a popular vertebrate model organism for analyzing disorders of the nervous system because, unlike mammals, they have the ability to regenerate neurons following brain injury or degenerative neuronal loss. In the past, experiments have focused on scientific inquiry concerning the genomic and cellular mechanism of neuronal regeneration following brain injury. More recently, studies using learning and memory tasks have provided evidence that zebrafish can also be useful models for investigating cognitive function. The purpose of these experiments was to extend previous cellular work by examining the effect of neuronal loss and regeneration on behavior. We examined several established tasks

to determine their sensitivity of neuronal loss and recovery following telencephalic injury in adult zebrafish. The tasks selected use natural behaviors, such as shoaling and scototaxis, that assessed anxiety, learning, and memory: light-dark preference (LDT), associative learning (AL), and latent learning (LL). Groups of adult zebrafish (equal numbers of males and females) were randomly assigned to task, condition within the task (if appropriate) and injury condition. Results indicated that LDT and AL, but not LL, were potentially sensitive to the effects of injury on behavior and recovery. Modifications to test conditions, such as extended habituation to the test apparatus, were employed to minimize inter- and intra-individual variability in behavior on all tasks both before and after injury.

Disclosures: K. Skaggs: None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.12/R16

Topic: C.10. Brain Injury and Trauma

Title: Chronic neurocognitive sequelae of tbi & ptsd: An animal model

Authors: *A. FESHARAKI
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Abstract: There an increasing level of awareness of the long term neurocognitive impact of mild traumatic brain injury (mTBI), both in the civilian population, as well as the veterans. The individuals with brain injury are more susceptible to developing chronic neurodegenerative disorders, such as chronic traumatic encephalopathy (CTE), which was initially diagnosed in the domain of contact sports, such as boxing. The characteristic of CTE is comprised of neurofibrillary tangles (NFTs), pre-tangles, dot-like and thread-like neurites within the neocortex, depth of sulci, and proximal blood vessels. The animal model that we are proposing to study using C57BL/6 mice, utilizes the synergism of mTBI and chronic stress, and will be used as a simulation of the real life CTE. This will in turn will create a robust model for functional deficits of chronic traumatic encephalopathy (CTE). As per our preliminary data, the combination of CVS and CHI creates induces tauopathy, as early as one week after receiving injury, as well as significant neurocognitive deficits, as measured by performance in memory paradigms, such as Morris Water Maze task, novel object recognition test, and passive avoidance test.

Disclosures:

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.13/R17

Topic: C.10. Brain Injury and Trauma

Title: Exploring the effects of age in a fruit fly model of traumatic brain injury

Authors: *A. M. BRISENO, L. S. VILLALPANDO, A. D. TROFIMOVA, W. HARDEMAN, C. BARCENAS, R. E. HARTMAN
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Abstract: Traumatic brain injury (TBI) is one of the leading causes of neurological deficits and death worldwide, and over 1.7 million individuals suffer a TBI each year in the United States. Sustaining a TBI can result in immediate and long-term behavioral, physical, and cognitive deficits, and older adults are at a higher risk for death following a TBI. Our laboratory has previously characterized the neuropathological and behavioral consequences of varying degrees of TBI in both mice and rats of varying ages. To develop a high-throughput platform upon which to test the effects of therapeutic interventions, we have started to assess behavior and physiological parameters in Drosophila melanogaster (the fruit fly) using the High Impact Trauma (HIT) device- a model of fly closed-head TBI described by Katzenberger et al. (2015). Briefly, the procedure involves placing flies into a plastic tube that is mounted via a spring to a table. The tube is lifted against the force of the spring and allowed to slam back into the table, causing the flies in the tube to accelerate toward the inner surface of the tube at high velocity. Adult, wild-type Drosophila were purchased as a culture, bred, and raised through metamorphosed adult fly. At various ages, groups of Drosophila received TBI via the HIT device (or a “sham” procedure for controls), followed 24 hours later by motor performance testing using the Rapid Iterative Negative Geotaxis (RING) assay. The data demonstrate a significant age-related decline in motor function, and preliminary results suggest that TBI exacerbated the decline. This model of TBI in flies thus corroborates clinical observations of aging humans, providing a viable, high-throughput model of aging and its interaction with TBI that may be used in future studies to assess therapeutic interventions.

Disclosures: A.M. Briseno: None. **L.S. Villalpando:** None. **A.D. Trofimova:** None. **W. Hardeman:** None. **C. Barcenas:** None. **R.E. Hartman:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.14/R18

Topic: C.10. Brain Injury and Trauma

Support: SIP-IPN 20170579

Title: Noradrenergic and motor assessment in an experimental model of cerebellar injury iron-induced

Authors: N. CHÁVEZ-GARCÍA[1,3], G. GARCÍA-DÍAZ[4], R. GONZÁLEZ-PIÑA[5], L. E. RAMOS-LANGUREN[6], *J. LOMELI[2]
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Abstract: Disabilities resulting from cerebellar damage in humans, ranging from motor to cognitive disorders, produced both by traumatic brain injury as for hereditary diseases. This study aimed to identify the motor sequelae after cerebellar injury produced by ferric sulfate administration in adult rats and to know the noradrenergic status in the hippocampus, pons and cerebellum during functional recovery. Because rats have a spontaneous recovery of the levels of noradrenaline (NA) as well as the motor sequelae after cortical brain injury and considering that the cortex has anatomical relations with the cerebellum through the pontine relay, we have the hypothesis is that the cerebellar injury the same effects can be happen. Rats were subjected to surgery, one group received saline infusion in the cerebellum and the other group ferric sulfate. Motor activity was recorded using the paradigm of the balance beam for 10 days, the rats from the saline group and from the iron group were sacrificed by decapitation to obtain the cerebellum, pons and hippocampus. The NA was measured by a chromatograph (HPLC) coupled to an electrochemical detector. The data obtained from the behavioral assessment were analyzed and compared using the Mann Whitney test, the concentrations of NA were analyzed by the Student's t test for independent groups. The animals were improving their motor skills days after receiving the injury. NA levels in the cerebellum, pons and right hippocampus showed a nonsignificant increase, however, the left hippocampus did have a significant increase. This study suggest that the NA is affected in a similar way that is observed in cortical lesions during functional recovery.

Disclosures: N. Chávez-García: None. **G. García-Díaz:** None. **R. González-Piña:** None. **L.E. Ramos-Languren:** None. **J. Lomeli:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.15/S1

Topic: C.10. Brain Injury and Trauma

Support: NIH NICHD R37HD059288

Title: Pattern separation deficits and enhanced dentate gyrus activity following mild traumatic brain injury

Authors: *R. T. SOMACH[1], S. SAMUEL[2], H. METHENY[2], A. S. COHEN[2]
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Abstract: Cognitive deficits are one of the most common outcomes after mild Traumatic Brain Injury (mTBI). Patients have symptoms of attentional deficits, difficulties in cognitive planning and memory impairments. An important component of many of these symptoms is pattern separation, which is the ability to discriminate between similar information for better cognitive processing. The dentate gyrus (DG) of the hippocampus has been shown to be particularly involved with pattern separation. The hippocampus is also especially vulnerable to mTBI. After injury, shifts in neural excitability are seen throughout the hippocampus in DG, CA1 and CA3. The purpose of this study was to examine the behavioral changes in pattern separation after injury and examine shifts in neural excitability that would correspond with these behavioral changes. Using the lateral fluid percussion injury (LFPI) model, mice were injured and trained with a modified spatial object learning task to test pattern separation. Injured animals showed a deficit in the ability to recognize objects as compared to sham animals. In addition, hippocampal slices were taken from these animals within 2 weeks following the behavioral tasks. Post-synaptic field potentials and paired pulse ratio were measured extracellularly in these hippocampal slices. Recordings were taken by stimulating either the Lateral Perforant Pathway or the Medial Perforant Pathway and recording in DG, or by stimulating the Schaffer Collaterals and recording in CA1. Injured animals were found to have an increase in excitability in the Medial Perforant Pathway of DG as compared to sham animals.

Disclosures: R.T. Somach: None. **S. Samuel:** None. **H. Metheny:** None. **A.S. Cohen:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.16/S2

Topic: C.10. Brain Injury and Trauma

Support: HD069620, HD069620-S1, NS060005, NS084967, NS099674

Title: Chronic stress exposure provided during adolescence confers protective effects on experimental traumatic brain injury acquired as an adult

Authors: *P. BARRA DE LA TREMBLAYE, J. L. WELLCOME, K. M. WILEY, I. H. BLEIMEISTER, M. S. HELKOWSKI, J. P. CHENG, C. O. BONDI, A. E. KLINE
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Abstract: Early-life stress experiments have been developed to model early adverse events in humans. However, the long-term consequences of early-life adversities on adult behavioral outcomes after traumatic brain injury (TBI) have not been examined. Hence, we propose to focus on early-life stress specifically in adolescence, a time of dynamic developmental changes, to examine the long-term effects on adult emotional and cognitive behavior post TBI. On postnatal days (PND) 30-60, adolescent male Sprague-Dawley rats were exposed to 4 weeks of chronic unpredictable stress (CUS). After an additional 4 weeks of resting (PND 60-90), the rats were anesthetized and receive either a controlled cortical impact of moderate severity (2.8 mm tissue deformation at 4m/s) or sham injury. The rats were assessed for anxiety-like behavior in the open field test (OFT), and learning and memory in the novel object recognition (NOR) and Morris water maze (MWM). CUS exposure in adolescence lead to better outcomes relative to non-CUS TBI controls as evidenced by increased time exploring the open field and more focus on the novel task ($p < 0.05$). The CUS rats also performed significantly better in the spatial learning task relatively to the non-CUS controls ($p < 0.05$). Despite the CUS rats performing better on each task relative to the non-CUS controls, they were still significantly impaired on all tests relative to the uninjured sham controls ($p < 0.05$). These preliminary data suggest that moderate chronic unpredictable stress provided during adolescence may provide a protective effect against TBI acquired during adulthood and/or induce adaptive behavioral responses after TBI. These speculations as well as potential mechanisms for the effects are currently being investigated.

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.17/S3

Topic: C.10. Brain Injury and Trauma

Support: NIH grants HD069620, HD069620-S1, NS060005, NS084967

Title: Amantadine confers significant motor and cognitive benefits after experimental brain trauma

Authors: A. OKIGBO, B. ROYES, I. H. BLEIMEISTER, J. P. CHENG, D. M. BROOKS, C. O. BONDI, *A. E. KLINE
Phys Med. & Rehab, Psych, Safar Ctr. Resuscitation Res., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Introduction: Traumatic brain injury (TBI) is a pervasive health care issue affecting 10 million individuals worldwide each year. Approximately 1.7 million reside in the United States. Currently, treatments are limited and therefore various pharmacotherapies have been, and continue to be, evaluated. The ability of amantadine (AMT), a dopamine$_2$ receptor agonist, to attenuate the behavioral and histological deficits that manifest following a traumatic brain injury (TBI) was assessed in rats using three doses to determine the dose with greatest efficacy. Hypothesis: AMT will produce increased motor and cognitive benefits over vehicle-treated controls. Methods: Isoflurane anesthetized adult male rats received either a controlled cortical impact (CCI) of moderate severity (2.8 mm tissue deformation at 4m/s) or sham injury, and then were randomly assigned to receive AMT (10, 20, and 40 mg/kg) or saline vehicle (VEH, 1 mL/kg). Treatments began 24h after injury and were administered intraperitoneally once daily for 19 days. Motor function was assessed on post-operative days 1-5 using beam-balance and beam-walk protocols. Spatial learning and memory was assessed on post-operative days 14-19 using a Morris water maze task with corresponding probe and visible trials. The behavioral data were analyzed by a repeated measures ANOVA followed by a Newman-Keuls post-hoc test to determine group differences. Results: There was no statistical difference between the AMT and VEH-treated sham groups so the data were pooled. The 20 mg/kg dose of AMT enhanced both motor and cognitive performance relative to the other doses and vehicle-treated TBI groups ($p < 0.05$). Conclusion: the data suggest that 20 mg/kg is optimal for improving motor function and spatial learning and memory in this model of TBI. Significance: These results suggest that AMT may be a viable pharmacotherapy for clinical TBI. Future studies should evaluate potential mechanisms for the AMT-induced benefits, but a likely candidate may be restoration of dopaminergic neurotransmission.

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.18/S4

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS095950
NIH Grant NS099683
Univ Pittsburgh Rehabilitation Institute

Title: The effect of experimental brain trauma on sustained attention and behavioral flexibility in rats

Authors: T. J. CRAINE, L. A. KUTASH, D. A. O'NEIL, A. IOUCHMANOV, J. P. CHENG, A. E. KLINE, *C. O. BONDI
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Abstract: Impaired attention is central to the cognitive deficits associated with long-term sequelae for many traumatic brain injury (TBI) survivors. Considering that cognitive deficits are often assessed in the clinic using multi-domain neuropsychological cognitive battery tests, we employed, for the first time, a multimodal approach to determine higher-order attentional capabilities after moderate TBI. We used two frontal cortex-dependent 'attentional tasks', namely the operant 3-choice serial reaction time task (3-CSRT) and the digging attentional set-shifting (dAST) paradigms. We hypothesized that rats subjected to TBI will exhibit attentional deficits on both higher-order cognitive tests. The 3-CSRT, a modified version of the five-choice serial reaction time task, which was designed as an analogue of the human continuous performance test, requires the animal to orient toward and divide attention between three nose poke holes in an operant chamber, in which brief (300 ms) cues are randomly presented, to obtain a sucrose pellet reward. Upon reaching baseline of greater than 70% accuracy, which takes approximately 2 months using incrementally-decreasing cue durations, adult male Sprague-Dawley rats were subjected to a controlled cortical impact (2.8 mm cortical tissue deformation depth at 4 m/sec) or sham injury over the parietal cortex in the right hemisphere. After two weeks of recovery, they were re-tested on 3-CSRT for ten days and then trained and tested on dAST, which involves a series of increasingly difficult stages, including simple and compound discriminations, stimulus reversals, and intra/extradimensional set-shifts, at approximately 28-29 days post-surgery. Preliminary results suggest that rats subjected to parietal TBI display reduced percent accuracy, as well as increased omissions and premature responses (a possible indication of reduced vigilance) when re-tested post-surgery on 3-CSRT compared to Sham rats and to their own pre-insult baseline. Ongoing analyses include post-surgery reaction times, dAST performance (total trials, total errors, and set-loss errors), as well as within-subject correlations

between attention test modalities. The experimental approach to assess complex attention capabilities post-TBI via multimodal testing is clinically-relevant and may provide reliable avenues towards developing therapeutic targets.

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.19/S5

Topic: C.10. Brain Injury and Trauma

Support: NIH R21 NS099683
Univ Pitt Rehab Institute

Title: Multimodal assessment of executive function and behavioral flexibility after frontal brain trauma: Beneficial effects of milnacipran

Authors: *L. KUTASH, T. J. CRAINE, D. A. O'NEIL, J. P. CHENG, A. E. KLINE, C. O. BONDI
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Abstract: This study aims to investigate complex cognitive deficits after experimental TBI in rats subjected to a clinically relevant frontal lobe injury, and the beneficial effects of chronic milnacipran treatment, a dual serotonin-norepinephrine reuptake inhibitor. We hypothesized that rats will display cognitive deficits in both the operant and digging versions of the attentional set-shifting task, and that chronic milnacipran treatment will attenuate these deficits. To maintain a parallel with the clinic where patients are given multi-domain cognitive test batteries, we employed a multimodal approach to determine executive function after moderate frontal lobe TBI, by using two prefrontal cortex-dependent attentional set-shifting tasks, the operant (oAST) and digging (dAST) paradigms, as analogs of the clinical Wisconsin Card Sorting Test. The oAST requires rats to perform flexible switches between perceptual dimension rules “light” and “side” to obtain a sucrose pellet reinforcer. The dAST involves a series of increasingly difficult discriminative tasks, including simple and compound discriminations, stimulus reversals, and intra/extradimensional shifts. Dependent measures for tasks include number of trials to reach criterion (TTC), as well as total, perseverative, and set-loss errors. Adult male Sprague-Dawley rats reached oAST baseline in approximately three weeks (TTC within 10% variability of previous three days) and then were subjected to a controlled cortical impact (2.4 mm cortical deformation depth at a speed of 4 m/sec) or sham injury over the prefrontal cortex in the right hemisphere. During surgery, they also received intraperitoneal implantation of osmotic

minipumps containing milnacipran (30 mg/kg/day) or vehicle. After ten days of recovery, they were re-tested on oAST for ten days and then trained/tested on dAST, at approximately 26 days post-surgery. Preliminary results suggest that injured rats require higher numbers of total trials to complete oAST post-surgery compared to Sham and to their own pre-insult baseline, while also displaying higher numbers of total and perseverative errors (n=5/group). These alterations are largely remediated by chronic milnacipran treatment. Statistical analyses will employ repeated-measures ANOVA followed by Newman-Keuls post hoc for individual test days when appropriate. In summary, milnacipran appears to be a potential therapeutic option for managing higher-order cognitive deficits following TBI. A scatter plot correlation for individual rats' performance on both tests indicates the dAST and oAST are concurrently valid and sensitive to TBI-induced cognitive disturbances.

Disclosures: T.J. Craine: None. **D.A. O'Neil:** None. **J.P. Cheng:** None. **A.E. Kline:** None. **C.O. Bondi:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.20/S6

Topic: C.10. Brain Injury and Trauma

Support: Univ of Pittsburgh Rehabilitation Institute

Title: Alterations in motivational behavior and executive function in adolescent rats following pediatric traumatic brain injury

Authors: *K. GROBENGIESER, N. PATEL, T. J. CRAINE, D. A. O'NEIL, L. A. KUTASH, J. P. CHENG, A. E. KLINE, C. O. BONDI
Physical Med. and Rehabil., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Traumatic brain injuries (TBIs) affect 2.5 million individuals in the United States each year, ranging from mild concussions to severe trauma or death. With 500,000 yearly emergency room visits being attributed to childhood-acquired brain trauma (under 14 years of age), patients endure long-lasting cognitive impairments, as well as psychopathological consequences. When head trauma occurs during a critical period of neuronal development and maturation characterized by increased educational and environmental demands, survivors of childhood TBI display reduced learning rates, delays in making age-appropriate developmental gains, as well as behavioral and emotional disturbances. The overarching aim of this proposal was to assess clinically-relevant motivational and cognitive-behavioral dimensions in adolescent rats who received a TBI as pediatrics, by using an instrumental learning task and an attentional set-shifting test (AST). We hypothesized that rats subjected to TBI will display task-dependent

impairments in motivated behavior and executive function. We employed a multimodal approach to determine instrumental learning and cognitive flexibility capabilities after moderate parietal lobe (2.2 mm tissue deformation depth at 4 m/sec) or sham controlled cortical impact injury to the right hemisphere in pediatric Sprague-Dawley rats (PND 17). After ten days of recovery, they were trained on a fixed-ratio schedule of 1 for 12 consecutive days in operant chambers fitted with three nose-poke holes and a food trough, by learning to poke for sucrose pellet reinforcement in the center hole when illuminated. Each session lasted 100 trials or 30 min, whichever occurred first. Outcome measures included the number of total trials completed, task-irrelevant pokes (left or right nose-poke holes), and latency for pellet retrieval following instrumental nose-poking. Rats were then trained/tested on AST at PND 42-43, which involves a series of increasingly difficult stages, including simple and compound discriminations, stimulus reversals, and intra/extradimensional set-shifts. Dependent measures included the number of trials to reach criterion, as well as total and perseverative errors. While testing is currently ongoing, upcoming statistical analyses will employ repeated-measures ANOVA followed by Newman-Keuls post hoc for individual test days when appropriate. These findings will advance our understanding of long-term higher-order cognitive and motivational deficits in adolescent survivors of childhood brain trauma.

Disclosures: K. Grobengieser: None. **N. Patel:** None. **T.J. Craine:** None. **D.A. O'Neil:** None. **L.A. Kutash:** None. **J.P. Cheng:** None. **A.E. Kline:** None. **C.O. Bondi:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.21/S7

Topic: C.10. Brain Injury and Trauma

Support: Sigma Xi Research Honor Society

Title: An investigation of zinc supplementation in a mouse model of repetitive mild traumatic brain injury

Authors: *C. L. NEELY[1], C. M. HERNANDEZ[1], G. M. GRANT[2], T. H. SHAW[1], J. M. FLINN[1]
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Abstract: Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative tauopathy caused by repetitive mild traumatic brain injury (rmTBI). The condition is characterized by tau hyperphosphorylation in the cortex and limbic structures, disordered memory, and impaired executive functioning. One target for possible intervention is zinc (Zn), a tightly regulated trace biometal found throughout the brain. Brain injury causes an immediate

increase in Zn release followed by a Zn deficiency in the synapse, worsening secondary injury cascades beyond levels caused by initial Zn release. Prophylactic dietary Zn supplementation increased neuronal proliferation and improved behavioral outcomes following a single severe TBI (Cope et al, 2012; Cope et al., 2016); however, other research has suggested that supplemental Zn can exacerbate TBI-related neuropathology such as tau aggregation (Huang et al., 2014). Given the conflicting evidence, this project sought to explore whether Zn possessed the same prophylactic properties in a mouse model of rmTBI to represent the same injury that leads to CTE. Approximately 100 four-week-old male and female C57BL/6J mice consumed either standard lab water or 10 parts per million Zn-supplemented water for eight weeks prior to injury. At 12 weeks of age, mice underwent either 5 sham procedures or 5 closed-head injuries spaced apart by 48 hours using a Leica ImpactOne device (V = 5m/sec; dwell time = 200ms; impact depth = 1mm; impact tip diameter = 5mm). Mice completed a battery of behavioral tests that measured anxiety and locomotion, wellbeing, and spatial memory. Preliminary data collapsed across sex showed no effect of Zn supplementation or TBI on open field or burrowing behavior. In the elevated zero maze, injured mice consuming lab water had a reduced number of head dips compared to their sham counterparts. Both sham and injured mice consuming Zn water had a lower number of head dips compared to injured and sham mice consuming lab water; however, injured mice consuming Zn water had a modest increase in the number of head dips. Injured mice on lab water had the lowest number of total entries; in contrast, injured mice consuming Zn water had the highest number of total entries compared to the other groups. Injured animals showed slower latencies to reach the hidden platform in Morris Water Maze. Histology and western blotting will assess free Zn levels, gross morphological damage, and changes in protein expression associated with CTE-like pathology. Results will further develop evidence for Zn as a potential target for those who are at higher risk for brain injury.

Disclosures: C.L. Neely: None. **C.M. Hernandez:** None. **G.M. Grant:** None. **T.H. Shaw:** None. **J.M. Flinn:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.22/S8

Topic: C.10. Brain Injury and Trauma

Title: Interaction of chronic variable stress and intranasal zinc treatment following traumatic brain injury

Authors: *E. N. DOHERTY[1], W. R. KOCHEN[2], J. M. FLINN[3]
[1]Psychology, George Mason Univ., Springfield, VA; [2]George Mason Univ., Woodbridge, VA; [3]Psychology, George Mason Univ., Fairfax, VA

Abstract: Mild traumatic brain injury (mTBI) is the most common traumatic brain injury (TBI) affecting soldiers. mTBIs can produce long-term cognitive and behavioral deficits, which tend to be exacerbated by the high stress experienced by soldiers. The role of zinc (Zn) in TBI has been noted for its effect on memory, as Zn may be a neuroprotective agent following injury. This study seeks to examine the interaction between stress and TBI with intranasal Zn therapeutics. Approximately 64 six-week old C57BL/6J mice were subjected to two varied stressors each day for a period of seven days before undergoing burrowing and nesting behavioral tests. The mice then underwent another seven days of chronic variable stress that was accompanied by mTBI and intranasal zinc therapy every 48 hours, for a total of four mTBI hits. A subset of mice will be used for an analysis of acute protein changes via western blots (e.g., GFAP, vasopressin, BDNF) and alterations in ionic Zn concentration using Zinpyr-1. The remaining mice were subjected to a second battery of behavioral tests that assessed longitudinal deviations in activities of daily living (i.e., burrowing and nesting) as well as circadian rhythm. Preliminary pilot data indicates that Zn significantly interacts with stress and brain injury when assessed for activities of daily living (i.e., burrowing). As stress level increased, the difference in ability to perform burrowing increased between mice with and without Zn treatment. These findings suggest Zn treatment can have a therapeutic effect following mTBI and chronic variable stress. As hypothesized, stress was found to exacerbate the deficits seen in mTBIs when not provided with Zn treatment. This study may provide a greater understanding on the nature of how stress exacerbates the effects of TBI and how therapeutic Zn may affect biochemical and behavioral deficits.

Disclosures: E.N. Doherty: None. **W.R. Kochen:** None. **J.M. Flinn:** None.

Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.23/S9

Topic: C.10. Brain Injury and Trauma

Title: The behavioral and biochemical effects of social isolation following repetitive mild traumatic brain injury (rmTBI)

Authors: *K. M. CRAVEN, W. R. KOCHEN, C. M. HERNANDEZ, N. T. COSCHIGANO, E. Q. MURDOCH, J. M. FLINN
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Abstract: Traumatic brain injury (TBI) is a pervasive problem affecting millions worldwide. Mild TBIs (mTBI) constitute the majority of cases. These injuries affect athletes and soldiers, and are also very common in young adults. Individuals from ages 0-25 have an approximate 30% prevalence of TBI due to falls, contact sports, and accidents. Many young adults sustain additional injuries after the first TBI. They are at an increased risk of having anxiety, depression,

and attention disturbances. This experiment examined whether social isolation exacerbates the effect of repetitive mTBIs (rmTBI) on young adult mice. Mice sustained a closed-head mTBI once every day for five days starting at 8 weeks old. Half of the mice were socially isolated until the end of the experiment by placing them in a home cage by themselves. Mice subjected to rmTBI demonstrated significantly fewer platform crosses compared to sham mice during probe trials in Morris Water Maze (MWM) one week following the last TBI. Latency to find the platform in MWM was significantly longer for rmTBI mice compared to shams 7 weeks following the last TBI. There was no effect of social isolation in MWM. However, socially isolated mice had significantly fewer open arm entries in the elevated zero maze compared to socially housed mice after being isolated for 8 weeks, but not after only 2 weeks, indicating increases in anxiety over time. There was no effect of rmTBI on anxiety. Brain tissue will be assessed for differences in expression of BDNF and inflammatory markers, including GSK3, IL-1ß, and TNF-alpha.

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Poster

295. Brain Injury and Trauma: Animal Models of Brain Injury: Physiology and Behavior I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 295.24/S10

Topic: C.10. Brain Injury and Trauma

Title: Intranasal therapeutic zinc following traumatic brain injury with chronic stress

Authors: *W. R. KOCHEN, E. N. DOHERTY, C. CUNNIFF, L. BRADSHAW, M. WIENER, E. Q. MURDOCH, R. H. LIPSKY, J. M. FLINN
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Abstract: Traumatic Brain Injuries (TBI) are a leading cause of morbidity and mortality across ages. Most TBIs are mild TBIs (mTBI) which are identified by minor loss of consciousness (if any) and no fracturing of the skull. Accumulating evidence indicates that the effects of stress alter the pathology seen following TBI. This is especially relevant in military populations, where post-traumatic stress disorder (PTSD) and chronic stress are hallmark problems seen in soldiers returning from combat. Zinc (Zn) supplementation prior to TBI has been shown to mitigate the damage seen following injury. This experiment examined the efficacy of acute intranasal Zn therapy following repetitive mild TBI in both stressed and unstressed mice. Mice received chronic variable stress for one week which was followed by behavioral testing. Immediately following behavioral testing, mice endured a second week of stress during which four mild TBIs were administered with a 48-hour inter-injury interval. Following each injury, mice received either intranasal Zn or vehicle. The same behavioral tests were then conducted following the

final day of injury. Western Blots were performed for proBDNF, mature BDNF, doublecortin, TrkB, and phosphoTrkB. Results following the first week of stress show stressed mice spent significantly less time in the open areas of the elevated zero maze as well as spent more time helpless in forced swim. Furthermore, Burrowing and Nesting abilities were significantly compromised by stress. A significant interaction effect of stress and TBI was noted with TBI reducing the deficits caused by stress in Elevated Zero and Forced Swim. Intranasal Zn therapy caused significant therapeutic effects, reducing the deficits caused by TBI + Stress in Elevated Zero, Forced Swim, Burrowing and Nesting behaviors. Intranasal Zn therapy caused an increase in doublecortin levels as well as a significant alteration in the ratio of proBDNF to mature BDNF with mice who received intranasal zinc having a higher fraction of mature BDNF. These results indicate that Zn may be a strong candidate for use in an acute therapeutic intervention following TBI.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.01/S11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Foundation
The Leona M. and Harry B. Helmsley Charitable Trust
University of Louisville Hospital
Christopher and Dana Reeve Foundation
Medtronic, PLC

Title: Spinal cord epidural stimulation and recovery of cardiovascular function in individuals with chronic cervical spinal cord injury

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Abstract: Persons with cervical spinal cord injury (SCI) experience persistent and orthostatic hypotension that markedly diminishes their overall quality of life and increases risk of developing and dying from cardiovascular disease. We have found previously that spinal cord epidural stimulation (scES) can acutely increase blood pressure in four individuals with chronic, cervical SCI (Harkema, 2018). We decided to investigate long-term effects of scES in four

individuals with chronic, severe cervical SCI. Prior to intervention, individuals experienced persistent hypotension with bouts of orthostatic hypotension and autonomic dysreflexia. Implanted over the lumbosacral spinal cord was a Medtronic, RestoreAdvanced 16 Electrode Array. Stimulation properties, including electrode polarity, frequency, voltage, and pulse width, were selected to increase systolic blood pressure to between 105-120 mmHg (CV-scES). Cardiovascular response to a sit-up test was assessed before and after 89 ± 13 sessions of daily, two-hour CV-scES. Main outcome measures included beat-to-beat blood pressure and heart rate, heart rate variability, and baroreflex sensitivity and effectiveness during orthostatic stress. After training, orthostatic hypotension resolved in all four chronic cervical, motor-complete SCI participants. Prior to the CV-scES intervention, mean systolic blood pressure significantly decreased from supine to sit (104 ± 3 to 90 ± 6 mmHg, $p = .001$). This drop did not occur with stimulation (116 ± 4 to 117 ± 6 mmHg, $p = .18$) nor after 89 ± 13 sessions of CV-scES intervention without stimulation (106 ± 3 to 107 ± 6 mmHg, $p= .53$). Improved blood pressure response to orthostatic hypotension was associated with significant increases to heart rate variability (SD1: $p = .003$; SD2: $p = .003$) and baroreflex effectiveness ($p = .002$) and sensitivity ($p = .002$) pre-intervention with stimulation. Likewise, post-intervention without stimulation, significant increases to heart rate variability (SD1: $p = .009$; SD2: $p = .01$), baroreflex effectiveness ($p < .02$) and sensitivity ($p = .002$), and correlation between systolic blood pressure and heart rate ($p < .004$) were observed. CV-scES results in immediate normalization of cardiovascular and autonomic regulation during orthostatic stress that, with training, persists even without stimulation. CV-scES has the potential to be a viable therapeutic option to manage cardiovascular dysregulation in individuals with chronic SCI.

SJ Harkema, S Wang, CA Angeli, Y Chen, MB oakye, B Ugiliweneza, GA Hirsch. **Normalization of Blood Pressure With Spinal Cord Epidural Stimulation After Severe Spinal Cord Injury**. *Frontiers in Human Neuroscience*, 2018

Disclosures: B. Ditterline: None. **S. Wang:** None. **C. Ferreira:** None. **B. Ugiliweneza:** None. **C.A. Angeli:** None. **Y. Chen:** None. **A.V. Ovechkin:** None. **M. Boakye:** None. **S.J. Harkema:** None. **G. Hirsch:** None.

Poster

296. Spinal Cord Injury II

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Program #/Poster #: 296.02/S12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Grainger Foundation
Regenerative Medicine Minnesota
Jack Jablonski Bel13ve in Miracles Foundation
Mayo Clinic Graduate School of Biomedical Sciences

Mayo Clinic Center for Regenerative Medicine
Mayo Clinic Rehabilitation Medicine Research Center
Mayo Clinic Transform the Practice

Title: Refinement of lumbosacral epidural electrical stimulation enhances performance of stand and step functions after motor complete paraplegia

Authors: *P. GRAHN[1], M. L. GILL[2], J. S. CALVERT[2], M. B. LINDE[2], I. LAVROV[3], D. VEITH[2], L. BECK[2], J. STROMMEN[2], D. SAYENKO[4], M. VAN STRAATEN[2], A. THORESON[2], C. LOPEZ[2], Y. P. GERASIMENKO[6], V. EDGERTON[5], K. H. LEE[2], K. ZHAO[2]
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Abstract: To date, there is no cure for spinal cord injury (SCI), leading to permanent disruption of ascending and descending spinal pathways across the injury site and impairment of neural circuitry below the injury site. Epidural electrical stimulation (EES) has been shown to enable motor function in a small cohort of humans with chronic SCI-induced paralysis. In subjects diagnosed with motor complete paraplegia, EES of the lumbosacral spinal cord was initially shown to drive tonic and rhythmic motor activity in the legs in a stimulation setting-specific manner. More recently, EES facilitated intentional control of joint-specific muscles and independent standing after months of training with EES. Initially, we set out to replicate outcomes reported from an initial clinical trial at the University of Louisville that demonstrated EES enabled intentional control of leg movements while subjects were lying down and static standing while subjects used their arms on support bars to maintain posture and balance. We previously reported successful replication of these results and also reported that EES enabled intentional control over rhythmic, step-like motor activity when the subject's legs were freely suspended. From these observations, we set out to determine if continued refinement of EES settings during motor rehabilitation with a focus on improving stand and step function would lead to greater independence and improved performance during motor activities such as standing and stepping. Here, we report that continued refinement of EES settings with rehabilitation improved step and stand functions both on a treadmill and over ground.

Disclosures: P. Grahn: None. **M.L. Gill:** None. **J.S. Calvert:** None. **M.B. Linde:** None. **I. Lavrov:** None. **D. Veith:** None. **L. Beck:** None. **J. Strommen:** None. **D. Sayenko:** None. **M. Van Straaten:** None. **A. Thoreson:** None. **C. Lopez:** None. **Y.P. Gerasimenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies. **V. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovery Technologies. **K.H. Lee:** None. **K. Zhao:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

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Program #/Poster #: 296.03/S13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Jack Jablonski Bel13ve in Miracles Foundation
Craig H. Neilsen Foundation
Mayo Clinic Center for Regenerative Medicine
Mayo Clinic Graduate School of Biomedical Sciences
Mayo Clinic Transform the Practice
Minnesota Government Office of Higher Education – SCI/TBI Grant
Regenerative Medicine Minnesota

Title: Characterization of epidural electrical stimulation evoked motor responses during stepping in humans with complete spinal cord injury

Authors: *J. S. CALVERT[1], P. GRAHN[2], M. GILL[3], I. LAVROV[4], M. LINDE[3], M. VAN STRAATEN[3], J. STROMMEN[3], L. BECK[3], A. THORESON[3], C. LOPEZ[3], D. VEITH[3], D. SAYENKO[5], Y. P. GERASIMENKO[7], V. EDGERTON[6], K. ZHAO[3], K. LEE[2]
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Abstract: Epidural Electrical Stimulation (EES) of the lumbosacral spinal cord has shown promise in enabling motor function following spinal cord injury (SCI) in both animal and clinical experiments. Modulation of evoked responses during hind-limb stepping in rat models of SCI have been characterized as the animal regains motor function and during the progression of the step cycle. However, EES-evoked responses during walking with EES in individuals with chronic SCI have yet to be investigated. Here, we report characteristics of human leg muscle evoked responses during EES-enabled stepping and while supine. Two males diagnosed with functionally complete paraplegia due to SCI (American Spinal Injury Association Injury Scale A) were implanted with a 16-contact electrode array (Specify 5-6-5, Medtronic, Fridley, MN) placed over the dorsal epidural surface of the lumbosacral spinal cord (T11-L1 vertebral levels). Following three weeks of recovery, EES was optimized to enable standing, intentional control while supine and side-lying, and intentional control of stepping on a treadmill. Skin surface electromyography (EMG) was collected from proximal and distal flexor and extensor muscles of the leg. EES-evoked motor responses were analyzed during motor activities to characterize spinal network facilitation by EES. Sensorimotor networks were facilitated by EES to produce motor responses that varied in thresholds, amplitudes, and latencies with respect to each muscle,

EES voltage intensity, and step cycle phase. EES-evoked motor responses were comprised of monosynaptic components, defined within EES literature as early response (ER) components that are associated with EES-activation of motor axons, middle response (MR) components that are thought to be of monosynaptic origin, and late response (LR) polysynaptic components. Specific electrode configurations resulted in rhythmic, bursting EMG activity both in supine and EES-enabled stepping activities. These results demonstrate that human spinal networks can be transformed, even years after injury, to reach physiologic states that generate coordinated and robust spinal motor outputs to generate intentional stepping on a treadmill and over ground.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.04/S14

Topic: C.11. Spinal Cord Injury and Plasticity

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Mayo Clinic Graduate School of Biomedical Sciences
Mayo Clinic Center for Regenerative Medicine
Mayo Clinic Rehabilitation Medicine Research Center
Mayo Clinic Transform the Practice

Title: Lumbosacral neuromodulation with task specific motor training enables independent performance of dynamic motor functions following clinically complete sci

Authors: *M. GILL[1], P. GRAHN[2], J. S. CALVERT[3], M. LINDE[3], I. LAVROV[4], D. VEITH[3], L. BECK[3], J. STROMMEN[3], D. SAYENKO[5], M. VAN STRAATEN[3], A. THORESON[3], C. LOPEZ[3], Y. P. GERASIMENKO[7], V. EDGERTON[6], K. H. LEE[3], K. ZHAO[3]
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Abstract: Previously, clinical reports have shown that epidural electrical stimulation (EES) of the lumbosacral spinal cord enabled standing and step-like leg movements in humans with complete lower extremity paralysis due to spinal cord injury (SCI). In addition, investigations

using rodent models with SCI have shown that locomotor training of multiple tasks such as forward and backward stepping on a treadmill improved performance of stepping by dynamically engaging multiple spinal sensorimotor networks. We applied multi task specific motor training with the presence of EES in training sessions that focus on maximizing subject independence of multiple tasks such as standing and stepping. A 16-contact electrode array (Specify 5-6-5, Medtronic, Fridley, MN) was placed over the dorsal epidural surface of the spinal cord at the lumbosacral (T11-L1 vertebral region) level. Following 3 weeks of recovery, task specific training was performed with EES for 113 sessions over 43 weeks. Tasks specific training included step and stand training during each session emphasizing adaptability of EES enabled activity. Training variables, including different stepping speeds and body weight support (BWS), were adapted regularly. Dynamic stand and step training performed with EES resulted in ability to both stand and step with maximum independence with optimal EES-task specific parameters. EES parameter optimization allowed subject control over motor activity based on intention to stand or step. EES alone did not facilitate spinal networks activating motor output of specific activity below the injury without patient intent. These outcomes suggest that repetitive, multi-task specific motor training within each session enhanced the organization of EES-facilitated spinal networks to achieve an adaptable state of functionality.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Center for Sensorimotor Neural Engineering (CSNE), a National Science Foundation Engineering Research Center (EEC-1028725)
Washington State Spinal Cord Injury Consortium (WASCIC)
Christopher and Dana Reeve Foundation (CDRF) International Consortium on Spinal Cord Injury Repair

Title: Restoring upper extremity function using concurrent transcutaneous cervical spinal cord stimulation and task-specific training in chronic spinal cord injury

Authors: *F. INANICI[1,6,7], S. SAMEJIMA[1,2,6,7], P. GAD[8], R. EDGERTON[8], C. P. HOFSTETTER[3,6,7], C. T. MORITZ[1,4,5,6,7]
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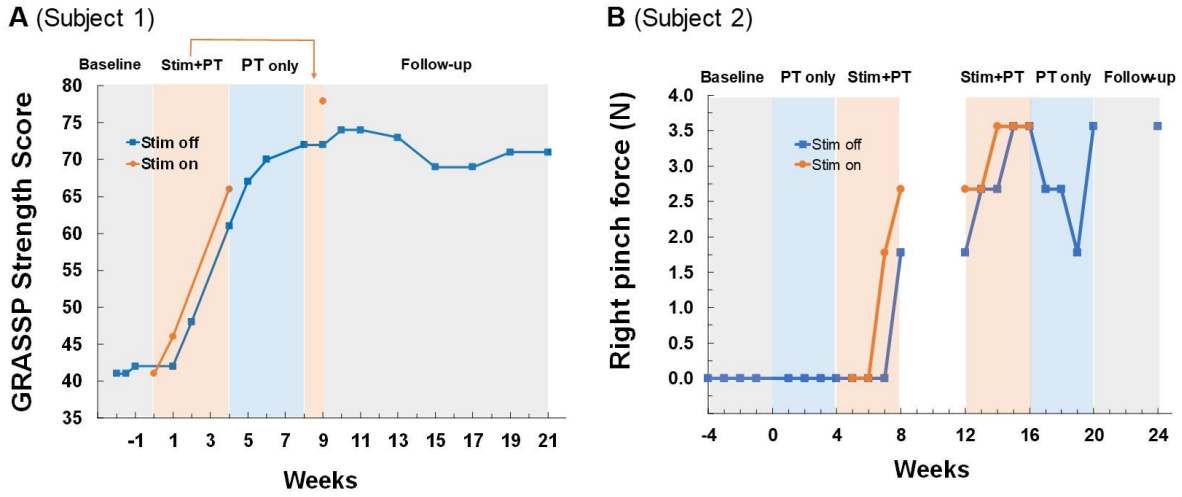
Abstract: There is growing evidence that electrical stimulation of spinal networks facilitates volitional motor control and induces neuroplasticity after spinal cord injury (SCI). Transcutaneous electrical spinal cord stimulation is a non-invasive strategy for neuromodulation of spinal circuitry. The present study was designed to (1) test the effect of concurrent transcutaneous cervical spinal cord stimulation and task-specific training on restoration of upper extremity function, and (2) quantify the sustained benefits to hand and arm function that persist beyond the period of spinal stimulation. A randomized two-arm cross-over design was used for subjects with chronic (>1 year) SCI. Intervention arms included (A) physical therapy (PT) only or (B) stimulation + PT (AB or BA). For electrical stimulation, we used biphasic, rectangular, 1 ms pulses at a frequency of 30 Hz, filled with a carrier frequency of 10 kHz, which permitted high stimulation intensities to be delivered to the cervical spinal cord through the skin without discomfort. Outcome measurements included the Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP) test, pinch strength measurements and International Society for Neurologic Classification of Spinal Cord Injury (ISNCSCI) assessment. All measures are performed during baseline, interventions and follow-up periods. Following four weeks of combined stimulation and PT, all of the outcome measurements improved remarkably in our first participant (C-3 AIS D). After stimulation + PT, strength sub-score of the GRASSP test increased 37 points (Fig 1A) and ISNCSCI upper extremity motor score improved 10 points. In our second subject (C-5, AIS B), pinch force was restored despite complete paralysis of the hands during baseline and physical therapy only intervention (Fig 1.B). Our results show that non-invasive electrical spinal cord stimulation conferred both immediate and sustained benefit, and restored functional use of the hands after SCI.



Disclosures: F. Inanici: None. **S. Samejima:** None. **P. Gad:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

funds); NeuroRecovery Technologies. **R. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **C.P. Hofstetter:** None. **C.T. Moritz:** None.

Poster

296. Spinal Cord Injury II

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Program #/Poster #: 296.06/S16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ONF-RHI grant 2016-RHI-PREV-1019
CIHR

Title: Inter-limb synchronization in standing balance in individuals with chronic incomplete spinal cord injury

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Abstract: ***Introduction*** Incomplete spinal cord injury (iSCI) compromises the neurologic structures and pathways that influence balance control and coordination, resulting in balance instability and an increased risk for falls. Individuals with iSCI have greater postural sway and increased dependency on vision. Though net measures of balance identify overall balance control, it lacks specificity on individual limb contributions. Inter-limb synchronization is a sensitive measure of individual limb contributions to balance control in healthy individuals and other clinical populations. The purpose of this study is to characterize inter-limb synchronization during quiet standing in individuals with iSCI relative to able-bodied controls (AB). ***Methods*** Standing balance was collected from 11 individuals with motor iSCI and 12 age- and sex-matched AB. With each foot on adjacent force plates, force data was sampled at 2000 Hz. Participants stood for 120 second in a standardized position in eyes open and eyes closed conditions. Net centre of pressure root mean square (COP RMS), and the cross-correlation coefficient at zero phase ($R_{xy}(0)$) of the left and right foot COP (i.e. inter-limb synchronization) in the anteroposterior (AP) and mediolateral (ML) directions were calculated, as was the weight-bearing force ratio (WBfratio) of the limb with the lowest vertical force. Independent 2×2 ANOVAs (Condition × Group) were conducted on net AP and ML COP RMS, $R_{xy}(0)$, and WBfratio. ***Results*** A significant interaction effect for AP COP RMS ($F_{1,21}$=9.06, p=0.007, partial η^2 = .30) showed greater AP sway in individuals with iSCI as a change of condition. A significant Condition effect ($F_{1,21}$=6.64, p=0.018, partial η^2 = .24) and Group effect ($F_{1,2}$=26.7, p<0.001, partial η^2 = .56) was found for ML COP RMS with greater ML sway in eyes closed in individuals with iSCI. A significant Group effect was found for AP $R_{xy}(0)$ ($F_{1,21}$=4.97, p=0.037,

partial η^2 = .19) and ML $R_{xy}(0)$ ($F_{1,21}$=7.34, p=0.013, partial η^2 = .26) with reduced inter-limb synchrony in individuals with iSCI. No Group effects were found for WBfratio (p=0.068). ***Conclusions*** Individuals with iSCI showed reduced inter-limb synchrony, which may contribute to increased postural sway.

	iSCI	**AB**
Sample size	11 (8M/3F)	12 (7M/5F)
Age	57.7 (±14.5)	57.8 (±12.9)
Time since injury (months)	168.8 (12 – 1370)	---
AP COP RMS (mm)		
EO	6.36 (±2.41)	6.48 (±3.04)
EC	8.98 (±2.92)	5.97 (±2.00)
ML COP RMS (mm)		
EO	5.41 (±4.43)	2.15 (±0.98)
EC	9.73 (±10.28)	2.57 (±1.02)
AP $R_{xy}(0)$		
EO	0.67 (±0.24)	0.85 (±0.08)
EC	0.72 (±0.17)	0.82 (±0.15)
ML $R_{xy}(0)$		
EO	-0.18 (±0.50)	-0.63 (±0.28)
EC	-0.43 (±0.37)	-0.68 (±0.22)
WBfratio		
EO	0.44 (±0.08)	0.48 (±0.02)
EC	0.43 (±0.05)	0.47 (±0.02)

EO=eyes open, EC=eyes closed

Disclosures: O.D. Habib Perez: None. **J. Lee:** None. **K. Masani:** None. **K.E. Musselman:** None.

Poster

296. Spinal Cord Injury II

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.07/S17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Guggenheim Fellowship

Title: Extraction and selective activation of muscle synergies through spinal stimulation for SCI

Authors: *R. CHENG, J. W. BURDICK
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Abstract: Epidural spinal stimulation (ESS) has been shown to enable recovery of motor control in patients with clinically complete spinal cord injury (SCI). It is hypothesized that this results from activation of postural and locomotor circuitry in the spinal cord, but the physiological mechanisms are still unknown. In this study, we extracted muscle synergies for standing in a complete SCI patient under ESS using a novel factorization algorithm, and compared them to muscle synergies in healthy subjects in order to better understand the physiological mechanisms enabling motor control under ESS.

Muscle synergies represent the coordinated recruitment of a group of muscles co-activated by a specific neural activation signal. Standard muscle synergy extraction algorithms (e.g. NNMF, PCA) fail when applied to SCI patients under ESS, because they do not compensate for the physiological delays of an electrically stimulated neural signal to reach different muscles (e.g. a signal takes longer to reach a thigh versus calf muscle). These delays are prevalent in SCI patients under ESS, since an activating signal with fixed frequency is externally induced at a specific area of the spinal cord. Therefore, we utilize a new algorithm -- regularized ShiftNMF -- that accounts for these delays when extracting muscle synergies. We find that muscle synergies extracted by this algorithm are significantly better at reconstructing EMG activity, they are much more reliable when cross-validated on other sections of the EMG, and their resulting features are more physiologically meaningful.

Using this algorithm, we examine muscle synergies for standing from SCI patients under different spinal stimulation conditions, and also compare them to muscle synergies in healthy subjects. We find that (1) SCI patients exhibit fewer muscle synergies than healthy subjects, (2) when stimulated with a fixed stimulation pattern during standing, the patient's muscle activity is composed of only a single muscle synergy, and (3) ESS with certain stimulation conditions (interleaving of multiple stimulation patterns) can activate an additional, distinct muscle synergy that greatly enhances patient standing quality. We provide evidence suggesting that muscle synergies are encoded in the human spinal cord, remain intact but possibly dormant after SCI, and are critical to quiet standing. The results allow us to hypothesize that an important physiological mechanism enabling motor control under ESS is the activation of muscle synergies in the spinal cord.

Disclosures: R. Cheng: None. **J.W. Burdick:** None.

Poster

296. Spinal Cord Injury II

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS16446 to JHK
NIH Grant NS067017 to QHX
Craig Neilsen Foundation to JLR

Title: Corticocuneate pathways are altered after dorsal column injury in New World monkeys

Authors: *C.-C. LIAO, H. X. QI, J. L. REED, H.-S. JEOUNG, J. H. KAAS
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Abstract: Dorsal column lesions (DCLs) in the cervical spinal cord deprive the cuneate nucleus (Cu) of its major tactile inputs, which immediately inactivate the hand regions in the contralateral somatosensory cortex and impair dexterous hand use. However, substantial neural reactivation and behavior restoration occur over an extended period of time. Since the cortical projections to Cu are part of a feedback loop that may be subject to modulation after loss of transmissions from the peripheral afferents to Cu, we examine whether the corticocuneate pathway is altered after injuries and contributes to the functional recovery over time. 11 adult New World monkeys (5 *Saimiri boliviensis, 3 Saimiri sciureus* & 3 *Aotus nancymaae*; 8 females & 3 males) were used. In 3 normal monkeys, a retrograde tracer, cholera toxin subunit B (CTB), was injected into the hand representation in Cu to label the cortical neurons. In 8 monkeys, unilateral DCLs were made at the C4-C5 level. CTB was injected into the Cu ipsilateral to the DCL in monkeys with 2 weeks (n=3) and 7-10 months (n=5) of DCLs. We mapped the hand regions in the contralateral areas 3b and 1 by electrophysiological recordings, and plotted the labeled neurons in both cortical hemispheres without the knowledge of lesion conditions. Our results revealed that: 1) in normal monkeys, the labeled neurons were extensively distributed in the contralateral cortex, predominately in the hand regions of somatosensory areas 3b, 3a, 1/ 2, parietal ventral (PV), secondary somatosensory cortex (S2), and primary motor cortex (M1). Fewer labeled neurons were located in the premotor cortex (PMC), supplementary motor cortex (SMA), cingulate areas, and cortex in the lateral sulcus. 2) After short recovery times from extensive DCLs, the hand neurons in contralateral areas 3b and 1 remained unresponsive or responded weakly to touch on the hand. The numbers of labeled neurons in the area 3b hand region were considerably reduced compared to the normal monkeys, although other corticocuneate connections remained intact. 3) After long recovery times, the affected somatosensory cortex responded from weakly to strongly to touch on the hand, and sometimes on the face and forelimb. Remarkably, somatotopically more extensive distributions of labeled neurons were found in the contralateral cortex. In addition, many labeled neurons were found in the hand region, with some in the forelimb region in area 3b. 4) The labeled neurons were also present in the ipsilateral cortex after Cu injections, but to a lesser extent. The results demonstrate the existence of a dynamic regulation of effective corticocuneate connections as a result of DCLs.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.09/T1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: California Institute for Regenerative Medicine (CIRM) (RT3-07616)
Dr Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF)

Title: Human stem cell-derived replacement of motor neurons after conus medullaris/cauda equina injury in rhesus macaques

Authors: *N. P. BISCOLA[1], J. H. NIETO[1], R. DATTA[3], M. C. CONDRO[3], D. MOORE[2], N. ZHANG[1], M. OHLSSON[5], K. L. CHRISTE[6], B. G. NOVITCH[7,8], H. I. KORNBLUM[8,9,10], L. A. HAVTON[4,7,8]
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Abstract: In traumatic injuries to the sacral spinal cord and in different neurodegenerative conditions, motor neurons may undergo degeneration and death. In these tools and technologies set of studies, we have investigated the feasibility of using human embryonic stem cell-derived motor neurons, as a potential replacement of degenerating spinal cord neurons in a non-human primate model of conus medullaris/cauda equina forms of spinal cord injury to restore motor functions. Approximately 250,000 cells (n=2) or 65,000 cells (n=2) were delivered in a single injection into the L5 spinal cord segment of female rhesus macaques subjected to an L6-S3 ventral root avulsion (VRA) injury and replantation of the L6 and L7 ventral roots into the spinal cord. All subjects were immunosuppressed using anti-thymocyte globulin as induction therapy and a combination of tacrolimus, prednisone, and anti-CD40 for maintenance therapy. Spinal cord tissues were harvested at 24 hours after surgery (n=1) or 2 months post-surgery (n=3). Morphological studies identified the injection site and survival of the injected human cells in the ventral horn of the L5 segment in all animals. Studies at 2 months post-surgery showed accumulations of large numbers of transplanted cells in sheets or clusters in both the grey and white matter of the spinal cords. Human identity was confirmed by STEM121 and TRA-1-85

immunostaining. Transplanted cells frequently formed rosettes of neural progenitors expressing SOX2, and NESTIN. Subsets of the transplanted human cells also showed labeling for OLIG2, a marker of motor neuron and oligodendrocyte progenitors, but not astrocytic or microglial markers such as GFAP and IBA1. A neuronal phenotype was also observed among subsets of the human cells which formed elongated axonal structures in the grey and white matter tracts that were positive for both STEM121 and Beta-III-Tubulin. While a small subset of transplanted cells showed Ki-67 labeling, no tumor formation was detected. Ultrastructural studies confirmed integration of human cells in the primate spinal cord using pre-embedding immuno-gold labeling for STEM121 and displayed a cytoplasmic staining pattern. Functionally, the subjects at 2 months post-surgery (n=3) showed a VRA-induced left leg weakness but preserved ability to use the affected limb for climbing, balancing, sitting on perch bar, and stepping. The subjects also showed independence in bladder and bowel control. Overall the immunosuppression protocol was successful with human cell survival and differentiation to neurons and glia progenitors.

Disclosures: N.P. Biscola: None. **J.H. Nieto:** None. **R. Datta:** None. **M.C. Condro:** None. **D. Moore:** None. **N. Zhang:** None. **M. Ohlsson:** None. **K.L. Christe:** None. **B.G. Novitch:** None. **H.I. Kornblum:** None. **L.A. Havton:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.10/T2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS09103104

Title: Cutaneous mechanoreceptor distributions in the hand change following cervical spinal cord injury in the macaque monkey

Authors: *M. CROWLEY, A. LILAK, J. AHLOY-DALLAIRE, C. DARIAN-SMITH
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Abstract: Meissner's corpuscles (MCs) are cutaneous mechanoreceptors found in glabrous skin that are sensitive to light touch and vibration. They are concentrated in the fingertip pads of macaque monkeys and humans, and in concert with other receptors, provide important sensory feedback during the execution of fine sensorimotor tasks such as object manipulation and grip control. Following cervical spinal cord injuries that block primary afferent input from these receptors, hand use can be severely impaired. However, over weeks to months, there is a significant recovery of digit and hand function. While most research has focused on the reorganization of central neural pathways underlying this process, little is known about the role of peripheral receptors in restoring sensory input during the post-injury recovery period. In this

study we begin to address this question by analyzing the distribution of MCs in the hand following selective injury. We first asked what the normal pattern of MCs is in the distal pads of all five digits in the macaque, which has a similar hand structure to humans and a fully opposable thumb. We then asked what happens to these MCs in animals that received either a dorsal column lesion (DCL; n=2) or a combined dorsal root/dorsal column lesion (DRL/DCL; n=4), 4-5 months earlier. In all of our lesioned monkeys, the lesion removed cutaneous input from the first three digits of one hand. In contrast to earlier reports, our findings in normal hands indicate that MCs are more densely populated in the thumb and index finger than in digits 3-5. This presumably corresponds to the greater dependence of these opposing digits in fine volitional tasks (e.g. grooming or foraging). In addition, in both groups of lesioned monkeys, the density of MCs in the first three digits was considerably less on the injured side compared to the same digits on the contralateral unimpaired hand. Our findings highlight the close functional relationship between MCs and precision grip, and demonstrate that MCs undergo a quantitative change following central and peripheral lesions, suggesting their implicit involvement in the recovery process. A deeper understanding of the changes to these mechanoreceptors following injury will help to elucidate how they are involved in restoring functional integrity of the hand.

Disclosures: M. Crowley: None. **A. Lilak:** None. **J. Ahloy-Dallaire:** None. **C. Darian-Smith:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.11/T3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Strategic Research Program for Brain Sciences from AMED

Title: Enhanced therapeutic effect of repetitive transcranial magnetic stimulation combined with anti-RGMa antibody treatment in a monkey model of spinal cord injury

Authors: *H. YAMANAKA[1], Y. TAKATA[1], H. NAKAGAWA[1], T. YAMASHITA[2], M. TAKADA[1]
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) has widely been used not only for basic research (e.g., investigating brain functions), but also for clinical application (e.g., relieving pain). On the other hand, it has recently been reported that treatment with antibody against repulsive guidance molecule-a (RGMa) ameliorates impairments in motor functions after spinal cord injury (SCI) in rodents and nonhuman primates. Here we analyzed the possible effect

of rTMS in combination with anti-RGMa antibody treatment on functional recovery after SCI in macaque monkeys. To prepare a monkey model of SCI, large hemi-transection lesions were made at the border between the C6 and the C7 segment of the spinal cord, as described elsewhere (Nakagawa et al., Cerebral Cortex, 2018). Simultaneously, the anti-RGMa antibody was delivered around the lesioned site over about four weeks via an osmotic infusion pump (see Nakagawa et al., Cerebral Cortex, 2018). The rTMS trials in the primary motor cortex (especially its forelimb region) started four to five weeks after the SCI surgery and lasted approximately 10 weeks. Behavioral assessments of forelimb movements were performed by means of the Brinkman board test and a reaching/grasping task. The rTMS sessions were carried out more than three times a week and, thereafter, behavioral changes were assessed on the same day. We found that compared with a control monkey group with the antibody treatment only, an experimental monkey group who underwent a combination of the antibody treatment and later rTMS execution exhibited an abrupt recovery from motor impairments. The present results indicate that rTMS combined with anti-RGMa antibody treatment provides an enhanced therapeutic effect in a monkey model of SCI.

Disclosures: H. Yamanaka: None. **Y. Takata:** None. **H. Nakagawa:** None. **T. Yamashita:** None. **M. Takada:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.12/T4

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Reactivation of spinal locomotor circuits by non-task-specific training after a complete spinal cord injury in adult cats

Authors: *J. HARNIE, A. DOELMAN, E. DE VETTE, E. DESROCHERS, J. AUDET, J. ALIZADEH, N. GAUDREAULT, A. FRIGON
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Abstract: After complete spinal cord injury (SCI), adult cats recover hindlimb locomotion after a few weeks of treadmill training. This recovery is due to the presence of a spinal locomotor central pattern generator (CPG) and its reactivation by sensory feedback from the moving legs. One of the central tenets of motor rehabilitation is that training must be task specific. However, as the locomotor CPG is present at birth, we hypothesized that task-specific training is not required to restore locomotion after complete SCI. To test this hypothesis, we investigated whether providing non-task-specific training in the form of rhythmic manual stimulation of the triceps surae muscles restored hindlimb locomotion after complete SCI in cats. Eight adult cats (>10 months, 4 females and 4 males) were divided into two groups and implanted with

electrodes to chronically record muscle activity (EMG, electromyography). After collecting data in the intact state, we transected the spinal cord at thoracic levels. Group 1 received rhythmic manual stimulation of the triceps surae muscles (0.33 Hz, 10 min per leg, 5 times a week for 5 weeks) while Group 2 received no treatment. We collected hindlimb EMG during manual stimulation in Group 1 and weekly-evaluated standing and locomotion on a treadmill at 0.4 m/s in both groups for six weeks after SCI, at which point we tested locomotion at different treadmill speeds. Cats in both groups recovered full body weight support during standing one week after SCI. Six weeks after SCI, although both groups performed full weight bearing hindlimb locomotion from 0.1 to 0.8 m/s, we observed some group differences. In Group 2, two cats could not perform consistent proper digitigrade paw placement while two other cats required perineal stimulation to facilitate hindlimb locomotion. In Group 1, EMG activity evoked by rhythmic manual stimulation became more structured and locomotor-like over the six-week period. With manual stimulation, we first observed ipsilateral flexor-extensor alternation and tonic contraction of contralateral muscles followed by contralateral flexor-extensor alternation and left-right alternation. The results indicate that the recovery of hindlimb locomotion after complete SCI does not require task-specific training and is partly spontaneous, consistent with the hypothesis that the spinal cord produces locomotion as its default pattern.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.13/T5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: New York State Department of Health (NYSDOH) Spinal Cord Injury Research Board (SCIRB) DOH01

Title: Simultaneous versus delayed pairing of rehabilitation and electrical stimulation: Functional recovery and axon outgrowth in rats after chronic unilateral corticospinal injury

Authors: *T. T. BETHEA[1], J. SANTOS[1], H. PARK[1], J. BOLGER[1], A. SINDHURAKAR[1], T.-C. WEN[1], J. B. CARMEL[1,2]
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Abstract: Electrical stimulation of motor cortex and motor training each drive structural and functional changes. It is unknown how these two very different forms of activity should be combined. We have previously demonstrated that motor cortex electrical stimulation of the

uninjured hemisphere after unilateral corticospinal tract injury promotes axon outgrowth to the impaired side of the spinal cord and recovery of forelimb function. The Schwab laboratory demonstrated that a plasticity treatment is most effective if given two weeks before motor training, rather than simultaneously. We hypothesized that motor cortex electrical stimulation given two weeks before forelimb training would promote greater functional recovery and more targeted axon sprouting than giving stimulation and training simultaneously. Adult Sprague-Dawley female rats were trained to proficiency on the knob supination task, which is highly impaired after corticospinal injury. They then received a cut lesion of the corticospinal tract that controlled the reaching paw. Six weeks later, electrodes were implanted over motor cortex, and used to deliver the electrical stimulation that we previously found to be effective (6 hours daily for 10 days). Rats were pseudorandomized by impairment to receive simultaneous rehabilitation (30 minutes after stimulation) or rehabilitation given 2 weeks later. Control groups included injury only, stimulation only, and rehabilitation only rats. Knob supination was measured weekly from the time of CST injury to 4 weeks after the last intervention. Across groups, the largest effects on recovery were observed in the weeks after training on the supination task. Rats that received simultaneous stimulation and training improved more quickly to the same degree as rats with stimulation and delayed training. To understand how training and stimulation alters CST connectivity, we have anterogradely labeled the intact half of the corticospinal tract and quantified axon length and distribution within the cervical spinal cord spinal cord. Anatomical analyses are ongoing, however early results show no difference in axon length in animals that received rehabilitation 2 weeks after electrical stimulation, compared to the animals where rehabilitation occurs 30 minutes after stimulation. Regional analysis quantifying sprouting axon distribution will also be analyzed. Stimulation has a larger effect on axon outgrowth than rehabilitation.

Disclosures: T.T. Bethea: None. **J. Santos:** None. **H. Park:** None. **J. Bolger:** None. **A. Sindhurakar:** None. **T. Wen:** None. **J.B. Carmel:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.14/T6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Minnesota State Office for Higher Education Spinal Cord Injury
Traumatic Brain Injury Research Grant Program (FP00093993)

Title: Orientation-selective spinal cord stimulation

Authors: *C. A. CUELLAR[1], L. J. LEHTO[3], M. BALTIN[4], A. C. PLIEGO[5], S. MANGIA[3], S. MICHAELI[3], I. A. LAVROV[2,4]

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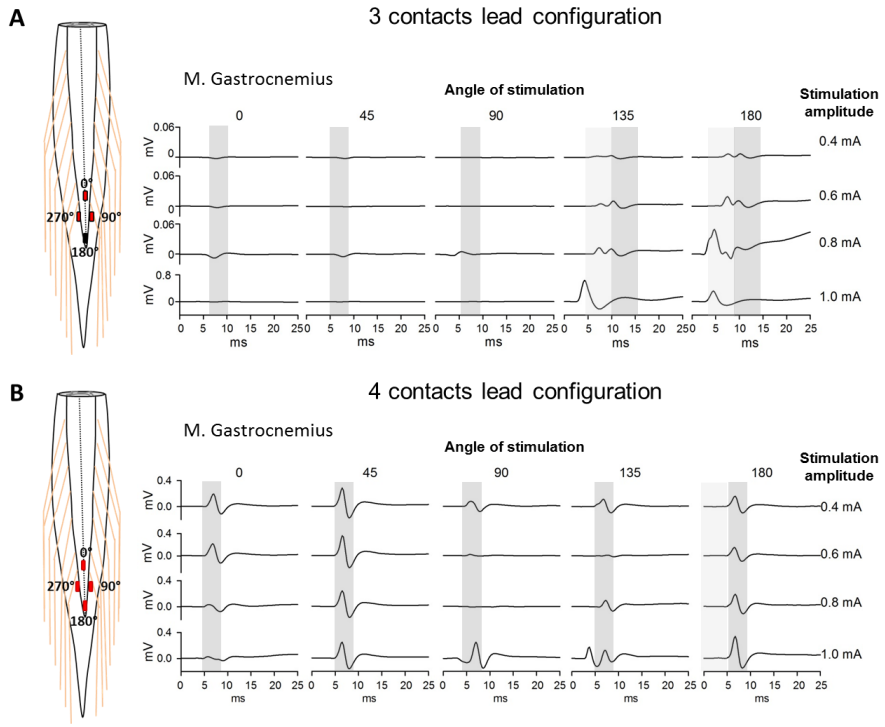
Abstract: Electrical epidural stimulation (EES) is used to treat chronic pain and spasticity. In clinical trials, it has been shown that EES enables motor function and improves autonomic function following spinal cord injury (SCI). Further development of EES including spatially-selective stimulation in order to provide a specific activation of neural elements is desired. In this study, Orientation-Selective Spinal Cord Stimulation (OS-ES) was delivered through a custom-built four-electrode array placed at S1 spinal segment. Sprague-Dawley rats (*n*=6, male, 325-350 gr) were anesthetized using urethane (1500 mg/kg IP). Electrode array was inserted and slid caudally through a partial laminectomy between Th13-L1. A laminectomy at L2 allowed verification of electrode array positioning. OS-ES was delivered every 45° by means of variable sets of biphasic pulses with chosen amplitudes (Lehto et al., 2017) to 3 or 4 contacts lead configurations using a multichannel stimulator. Rostral electrode on the midline of the spinal cord was defined as 0°. Electrical field was rotated in a clock- and anti-clock wise until completion of 180°. OS-ES was applied at 0.5 Hz in a range of 0.2-1.0 mA. Needle electrodes were inserted bilaterally in flexor and extensor hind limb muscles to record Motor Evoked Potentials (MEPs). From the stimulation pulse, latencies and amplitudes were determined for early (1-3 ms) and middle (>5 ms) responses detected using custom-made MatLab scripts. Our results show that amplitudes and thresholds of MEPs significantly vary depending on the angle of stimulation. In a 3 contacts lead configuration, higher amplitudes were observed when stimulation was delivered at 135° and 180° (Fig.1 A). On the other hand, in a 4 contacts lead configuration, similar amplitudes occurred at 0°-45° and 135°-180°, producing a symmetrical pattern of amplitudes (Fig. 1B). Interestingly, in both 3 and 4 contacts lead configuration, lower MEPs amplitudes were observed at 90°. Our results suggest that OS-ES with multi-contact electrode array can further optimize activation of the spinal cord motor circuits.



Disclosures: C.A. Cuellar: None. **L.J. Lehto:** None. **M. Baltin:** None. **A.C. Pliego:** None. **S. Mangia:** None. **S. Michaeli:** None. **I.A. Lavrov:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.15/T7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: AIIMS
ICMR

Title: Low intensity electromagnetic field exposure on neuronal connectivity and survival in spinal cord injured rats: A potential non-invasive therapy

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Abstract: Extremely low intensity magnetic (EMF) field has been shown to improve locomotion and general body condition after spinal cord injury (SCI). The aim of the present study was to

observe the effect of EMF on secondary damage and neuronal connectivity. EMF (17.96μT) exposure was given 2h/day for 5 weeks in 25mm contusion rat model of SCI. Basso, Beattie and Bresnahan (BBB) locomotor scoring was used to assess motor behavior, motor (MEP) and somatosensory evoked potentials (SSEP) and retrograde tracing were done to evaluate neuronal connectivity and survival respectively. The extent of lesion due to secondary damage was calculated by cresyl violet staining. A significant (P=0.000) improvement was observed in BBB score in EMF exposed group as compared to SCI after 5 weeks of contusion injury. A significant (P=0.01) increase in the threshold of MEP and SSEP was observed after SCI, which attenuated significantly (P=0.001) in the EMF group. Amplitudes of MEP and SSEP decreased significantly (P=0.001) after SCI as compared to sham, but showed a significant (P=0.001) increase after 5 weeks of EMF exposure. Retrograde tracing with fast blue showed a significant (P=0.001) increase in the number of surviving neurons, rostral and caudal (2cm) to the lesion site after EMF exposure. Further, extent of lesion and volume decreased significantly (P=0.005) after MF exposure as compared to SCI group. The results of the present study provide experimental evidence for the therapeutic potential in EMF spinal cord injured patients.

Disclosures: S. Jain: None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.16/T8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Paralyzed Veterans of America Research Foundation #3068
NIH/NINDS R37 NS030853
T32 Neurological and Rehabilitation Sciences Training Program

Title: Effects of a contusive spinal cord injury on spinal motor neuron activity, corticospinal coupling and conduction time in rats

Authors: *S. B. FROST[1,4], J. A. BORRELL[6], D. KRIZSAN-AGBAS[2], R. J. NUDO[3,5]
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Abstract: The purpose of this study was to determine the effects of a contusive spinal cord injury (SCI) on spinal motor neuron activity, corticospinal coupling, and conduction time in hindlimb spinal cord (SC) of the rat. Experiments were carried out in adult, male, Sprague Dawley rats using commercial neurophysiological recording equipment. Rats were randomly assigned to either a Healthy or SCI group. SCI rats were given a 175 kDyn contusion injury of

the SC at the T8 vertebrae. Four weeks after SCI, fine wire electromyographic (EMG) electrodes were implanted into 4 muscles of the right hindlimb under ketamine/xylazine anesthesia. A craniectomy was performed over the left hindlimb motor cortex (HLA), and a laminectomy was performed on the T13-L1 vertebrae. Intracortical (ICMS) and intraspinal microstimulation were used to determine the location of specific hindlimb movements evoked by stimulation. Similarly evoked movement sites in HLA and the ventral horn of the lumbar SC were identified and paired for further neurophysiological assessment. In SCI rats, the location of HLA was determined by the known location from previous mapping in healthy rats. At paired sites, a single shank, 16-channel, stimulating microelectrode was lowered into layer V of the HLA, and a similar recording microelectrode was lowered to a depth of ~2.27 mm in the hindlimb SC, spanning multiple laminae of the cord. ICMS was used to test corticospinal coupling by delivering a test stimulus in HLA, and evoked spikes were recorded from the SC and EMG from muscles for 5 min at each cortical/spinal site chosen for pairing. Evoked spikes were recorded, sorted, and displayed in post-stimulus spike histograms with 1-ms bins. In healthy rats, spike histograms showed ICMS-evoked spiking activity at two short latency epochs 7-8 ms (S1) and 10-12 ms (S2), and also at longer latencies. The longer latency responses followed a Gaussian distribution, ~20-60 ms, and were thus separated into three long-latency epochs: the first long-latency response (L1), peak response, and second long-latency response (L2) of the Gaussian distribution. The latency of the ICMS-evoked EMG responses, 25-27 ms, typically occurred between the L1 and peak. Short latency responses were evident in all layers of the SC while the longer latency responses were more evident in the intermediate layers. Within the SCI rats, one or both short latency responses were typically eliminated, the long-latency responses were disrupted or eliminated, and EMG responses were never evoked. The results from this study give insight into the effects of a contusive SCI on the neuronal activity, corticospinal coupling, and conduction time in the hindlimb SC of the rat.

Disclosures: S.B. Frost: None. **J.A. Borrell:** None. **D. Krizsan-Agbas:** None. **R.J. Nudo:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.17/T9

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Locomotor function evaluation of adult rats with complete and chronic spinal cord transection, after transplantation of bone marrow stromal cells, pre-degenerated peripheral nerve and chondroitinase ABC

Authors: *J. J. RIVERA OSORIO[1], E. GARCIA-VENCES[2], S. M. SÁNCHEZ-TORRES[3], I. GRIJALVA-OTERO[3], V. BUZOIANU-ANGUIANO[3]
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Abstract: The recovery of motor function is one of the main aims of regeneration protocols in the treatment of traumatic spinal cord injury (TSCI), so evaluation is an important step to determine the therapeutic efficacy of the regenerative protocols. Among the most used methods of motor evaluation, we found the motor assessment Basso, Beattie & Bresnahan scale (BBB), an open field test that allows us to observe motor recovery in contusion models. Other methods commonly used to observe recovery are the kinematic analysis, inclined plane test, as well as electrophysiological tests, among many others. This project aims to evaluate the recovery of motor locomotion in a transection model, after transplantation of pre-degenerated peripheral nerve (NPP), bone marrow stromal cells (BMSCs), and the chondroitinase enzyme ABC (ChABC). 70 female Fisher 344 rats with complete section at T9 level were used and divided into 5 groups (Control = 14 animals with TSCI, Group 1 = 14 animals with NPP, Group 2 = 14 animals with BMSCs, Group 3 = 14 animals with NPP + BMSCs and Group 4 = 14 animals with NPP + BMSCs + ChABC). A modified BBB scale and a cinematic motion analysis were used to observe the functional recovery after three months. The modified BBB analysis showed that the combined and non-combined treatment groups had a significant difference with a $p<0.0001$ compared with the control. Also, the combined and non-combined treatments showed a significant difference between them with a $p<0.005$, after the fifth week of treatment. The kinematic analysis of the gait cycle showed greater mobility in the extremities of the hip and knee, in the groups with combined treatment compared with non-combined treatment. We found that the combined-treatment (NPP + BMSCs, and NPP + BMSCs + ChABC) promote a higher functional regeneration of the hind limbs, improving the degree of coordination and mobility of the extremities involved in the walking cycle. In contrast, functional regeneration was also observed in the groups with non-combined treatment (BMSCs, and NPP), but in a lesser grade of mobility in comparison with the join-treatments groups.

Disclosures: J.J. Rivera Osorio: None. **E. Garcia-Vences:** None. **S.M. Sánchez-Torres:** None. **I. Grijalva-Otero:** None. **V. Buzoianu-Anguiano:** None.

Poster

296. Spinal Cord Injury II

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.18/T10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Paralyzed Veterans of America Research Foundation #3068
NIH/NINDS R37 NS030853
T32 Neurological and Rehabilitation Sciences Training Program

Title: Optimal spike-stimulus delay for increasing synaptic efficacy in descending motor pathways using an activity dependent stimulation paradigm in an acute, anesthetized rat model of spinal cord injury

Authors: *J. A. BORRELL[1,5], D. KRIZSAN-AGBAS[2], R. J. NUDO[3,4], S. B. FROST[3,4]
[2]Molec. & Integrat. Physiol., [3]Physical Med. and Rehabil., [4]Landon Ctr. On Aging, [1]Univ. of Kansas Med. Ctr., Kansas City, KS; [5]Bioengineering, Univ. of Kansas, Lawrence, KS

Abstract: The purpose of this study was to determine the optimal spike-stimulus delay for increasing synaptic efficacy in descending motor pathways using an activity dependent stimulation (ADS) paradigm in an acute, anesthetized rat model of spinal cord injury (SCI). Experiments were carried out in adult, male, Sprague Dawley rats with T8 contusion injury. Under ketamine/xylazine anesthesia, fine wire electromyographic (EMG) electrodes were implanted into 4 muscles of right hindlimb. After exposure of the left hindlimb motor cortex (HLA), laminectomy of the T13-L1 vertebrae, and removal of the dura matter, intracranial (ICMS) and intraspinal microstimulation (ISMS) were used to determine the location of evoked hip movements. One pair of sites evoking hip movements were chosen for each experimental procedure. For ADS conditioning, a single shank, 16-channel, Neuronexus recording microelectrode was used to detect neuronal spikes in HLA that were used to trigger ISMS in the spinal cord (SC) grey matter. SCI rats were randomly selected for one of four different parameters of cortical spike-triggered ISMS stimulus delays (10 ms or 25 ms time delay) and number of stimulus pulses used (1 pulse or 3 pulse square-wave stimulation). ADS sessions were conducted in three 1-hour conditioning bouts for a total of 3 hours. Synaptic efficacy was measured by number of ICMS-evoked spikes in the matched site in the lumbar SC in one 5 minute pre-ADS period and three 5 min test periods following each 1 hour ADS conditioning bout. During the testing periods, recording and stimulating microelectrodes were switched and ICMS was applied to the HLA while evoked-spikes were simultaneously recorded from the hindlimb SC for 5 min. Evoked spikes were recorded, sorted, and displayed in post-stimulus spike histograms with 1-ms bins. Post-stimulus spike histograms and EMG recordings were characterized using stimulus triggered averaging techniques. The results showed that after 3 hours of ADS conditioning using a 10 ms time delay and one stimulation pulse, ICMS-evoked spiking activity was significantly increased within the ventral horn at 10 ms post-onset ICMS. ADS conditioning using a 25 ms time delay and one or three stimulation pulses resulted in significant increases in ICMS-evoked spiking activity within the dorsal/intermediate layers of the spinal gray matter at 10 ms post-onset ICMS after 2 hours of ADS and continued to increase after 3 hours of ADS conditioning. EMG responses were never evoked pre-ADS nor was EMG activity increased after 3 hours of ADS. These results show that bouts of ADS conditioning can increase synaptic efficacy in intact descending motor pathways after SCI.

Disclosures: J.A. Borrell: None. **D. Krizsan-Agbas:** None. **R.J. Nudo:** None. **S.B. Frost:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.19/T11

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Nogo receptor antagonist LOTUS promotes axonal regeneration and inhibition of neuronal apoptosis after clinically relevant contusive spinal cord injury in adult mice

Authors: *S. ITO[1], N. NAGOSHI[2], O. TSUJI[2], K. KOJIMA[2], S. SHIBATA[2], M. SHINOZAKI[2], K. TAKEI[3], M. NAKAMURA[2], H. OKANO[2]
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Abstract: [Introduction] Natural recovery following spinal cord injury (SCI) is extremely limited in mammalian adults. One of the major reasons is the inhibition of axonal regeneration due to Nogo receptor-1 (NgR1) signaling. The ligands of NgR1, such as Nogo, MAG, OMgp, BLyS and CSPG cause collapsing of growth cone and inhibition of neurite outgrowth following SCI. Lateral olfactory tract usher substance (LOTUS), a NgR1 antagonist, binds to NgR1 and inhibits these five ligands, resulting in the decreased collapse of growth cones and inhibition of neurite outgrowth. The purpose of this study is to determine the therapeutic efficacy of LOTUS using clinically relevant contusive SCI model. [Method] Contusive SCI was induced at the Th10 level in LOTUS overexpressed mice (LOTUS group; n=20) and wild-type mice (control group; n=16). Hindlimb motor function was evaluated weekly for six weeks using BMS scores; and the DigiGait analysis was performed on the sixth week post-injury. On this sixth week, biotinylated dextran amine was injected into the primary motor cortex to trace corticospinal tract (CST), or Fluoro-Gold was injected into the lumbar enlargement to trace reticulospinal tract. Two weeks later, electrophysiological analysis using motor evoked potential was conducted. After the mice were sacrificed, histological analyses were examined. Additionally, histological analyses at 7 and 14 days post-injury were also performed. [Result] Tracing analyses showed that CST fibers increased significantly at the rostral to the lesion in the LOTUS group compared to the control group, but not at the caudal sites of the lesion in the two groups. On the other hand, reticular nucleus neurons increased significantly. Histological analyses showed the increase of the NF-H, 5-HT and p-GAP43 positive fibers at the caudal sites. As for 5-HT positive raphespinal tract, a significant increase was seen in the LOTUS group 14 days after SCI and continued to increase up to 56 days. Furthermore, cleaved caspase-3 staining revealed that LOTUS suppressed cellular apoptosis during the acute phase. Significant improvements in BMS scores was seen in the LOTUS group at one week following SCI and thereafter. DigiGait analysis also revealed significantly longer stride length and narrower stance angle in the LOTUS group. Electrophysiological analysis revealed significantly shorter latency and larger amplitude in the

LOTUS group. [Conclusions] LOTUS overexpression showed beneficial effects for functional recovery in clinically relevant contusive SCI model through promoting neuroprotection and axonal regeneration. The administration of LOTUS in the treatment of SCI could be a promising strategy.

Disclosures: S. Ito: None. **N. Nagoshi:** None. **O. Tsuji:** None. **K. Kojima:** None. **S. Shibata:** None. **M. Shinozaki:** None. **K. Takei:** None. **M. Nakamura:** None. **H. Okano:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.20/T12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR MOP-142288
FRQ-S

Title: Locomotor recovery in the rat after spinal hemisection is impeded by contralesional motor cortex inactivation

Authors: *A. R. BROWN[1,3], M. MARTINEZ[1,3,2]
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Abstract: Locomotor recovery can occur after incomplete spinal cord injury (SCI) where supraspinal structures and spinal circuits remain partially connected through residual descending pathways. The motor cortex is crucial for the voluntary control of movement and can reorganize after injury to promote recovery. The role of the hindlimb motor cortex in supporting locomotor recovery after SCI, however, is poorly understood. After a lateral hemisection of the thoracic spinal cord in the rat, hindlimb movements can no longer be evoked from stimulation of the de-efferented contralesional motor cortex, yet a combined hemisection and cortical trauma impedes recovery of the affected hindlimb. We tested here whether residual activity in the de-efferented contralesional motor cortex after thoracic hemisection impacts hindlimb locomotor recovery. Female Long-Evans rats were subjected to combined hemisection (T8 level) and cannula implantation targeting the contralesional hindlimb motor cortex. Cortical inactivation was achieved with continuous infusion of muscimol (GABA-A agonist, 10mM, 0.11 µL/hr) delivered via osmotic mini-pumps from the time of injury (n = 9). Rats with cortical saline infusion served as a SCI control group (n = 8). Hindlimb recovery was assessed in an open field, on a horizontal ladder, and on a treadmill during both quadrupedal and bipedal locomotion prior to and for 3 weeks after SCI. Inactivation of the contralesional motor cortex after SCI significantly impeded

recovery of the affected hindlimb in all behavioural tasks. During the first week after SCI, cortical inactivation disrupted voluntary control of the affected hindlimb that was maintained to some degree in SCI control rats. In particular, SCI rats with cortical inactivation showed increased foot-faults of the affected hindlimb during ladder walking compared to SCI control rats. During quadrupedal treadmill locomotion, cortical inactivation induced significant increases in toe drag along with decreases in step height and velocity during swing of the affected hindlimb. Coordination between hindlimbs and between fore- and hindlimbs was also more severely affected under cortical inactivation. During bipedal locomotion where the forelimbs were placed on a platform, the hindlimb locomotor pattern was significantly more disrupted in SCI rats with cortical inactivation, suggesting that cortical activity plays a role in the ability to regain an organized stepping pattern after SCI. Present results suggest that residual activity in the de-efferented contralesional motor cortex during the initial stage after SCI plays a prominent role in the recovery of hindlimb locomotor function.

Disclosures: A.R. Brown: None. **M. Martinez:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.21/T13

Topic: C.11. Spinal Cord Injury and Plasticity

Title: CORM-2 loaded solid lipid nanoparticle enhances anti-allodynic effect of CORM-2 via sustained carbon monoxide delivery

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Abstract: Neuropathic pain is devastating sequelae of neurotrauma. It’s already has been proven that carbon monoxide releasing molecule-2 (CORM-2) attenuates mechanical allodynia. This study compares the anti-allodynic effects of CORM-2 loaded solid lipid nanoparticles (CORM-2-SLNs) with CORM-2 solution (CORM-2-S). CORM-2-SLNs were prepared by nanotemplate engineering technique with slight modifications and physicochemical properties were evaluated. Chronic constriction injury (CCI) was performed to induce peripheral neuropthic pain in Sprague-Dawley rats. Rats were administered with CORM-2-SLNs (10 mg/kg/day I.P) and CORM-2 solution (10 mg/kg/day I.P) for one week. Animals were evaluated for neuropathic pain response before the day and 1, 3, 7 and 14 day after surgery. On days 7 and 14 after surgery, rats were sacrificed and tissues were collected. PCR and western blotting analysis were performed to assess heme-oxygenase (HO-1/HO-2) and other inflammatory mediators (TNF-α, iNOS/nNOS, IBA-1 and GFAP) expression in L4-L6 spinal cord and dorsal root ganglion (DRG)

at 7 day and 14 day after surgery. Allodynia was significantly reduced by CORM-2-SLNs compared to CORM-2-S. TNF-α, iNOS/nNOS, IBA-1 and GFAP expression were pronouncedly decreased by CORM-2-SLNs in comparison to CORM-2-S. HO-1 was significantly increased. However, HO-2 was decreased. Hence, the results demonstrated that CORM-2-SLNs have significant effect in reducing neuropathic pain as compared to CORM-2 Solution.

Disclosures: J. Kyung: None. **I. Han:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.22/T14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Foundation
NIH Grant NS091723
NIH Grant NS 104422

Title: Pain input after a spinal cord injury increases tissue loss and impairs long-term recovery: A comparison of male and female rats

Authors: R. BAINE[1], M. M. STRAIN-MALAMAKAL[2], Y. J. HUANG[1], J. A. REYNOLDS[1], M. HENWOOD[1], J. DAVIS[1], G. N. FAUSS[1], P. BEAN[1], A. NORRIS[1], T. JOHNSTON[1], C. COX[1], *J. W. GRAU[1]
[1]Texas A&M Univ., College Station, TX; [2]United States Army Inst. of Surgical Res., San Antonio, TX

Abstract: Spinal cord injuries (SCI) are often the result of traumatic accidents resulting in polytrauma. Pain input from associated injuries has been shown to impair locomotor recovery, increase hemorrhage, and expand the lesion site. Our laboratory has studied this effect using male rats. However, with the increasing number of females sustaining injury to the spinal cord, it is important to determine whether females are at risk of developing similar detrimental effects in response to pain input. Research has shown that females show greater tissue preservation and better locomotor recovery following SCI. Given these data, we examined the effect of sex on SCI recovery in two different pain models. Male and female rats were given a moderate contusion at T12. Groups receiving noxious input were treated 24 hours later. In the first experiment, animals received either six minutes of uncontrollable intermittent electrical stimulation to the tail or none at all. In the second experiment, animals received an intradermal injection of the peripheral irritant, capsaicin (3%), or vehicle to the hindpaw. After both treatments, blood pressure and BBB locomotor scores were evaluated at 0, 1, 2, and 3 hours. Animals were then sacrificed and a one-centimeter section of spinal tissue centered on the lesion

site was collected. Protein extracts obtained from the spinal tissue were analyzed for signs of hemorrhage using spectrophotometry. In the shocked condition, all animals receiving electrical stimulation showed impaired locomotor function and increased hemorrhage. Additionally, females showed more hemorrhage than their weight-matched controls. Conversely, only females showed a negative effect with administration of capsaicin, both in locomotor function and hemorrhage. Finally, we assessed the effect of capsaicin and shock treatment on long-term recovery. Rats were treated as described above and behavioral recovery was monitored for 28 days. Shock, but not capsaicin treatment impaired locomotor recovery, suggesting that the effect of pain input on secondary injury is variably affected by sex.

Disclosures: R. Baine: None. **M.M. Strain-Malamakal:** None. **Y.J. Huang:** None. **J.A. Reynolds:** None. **M. Henwood:** A. Employment/Salary (full or part-time):; Texas A&M University. **J. Davis:** None. **G.N. Fauss:** None. **P. Bean:** None. **A. Norris:** None. **T. Johnston:** None. **C. Cox:** None. **J.W. Grau:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.23/T15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS091723
NIH Grant NS104422

Title: Pain induced hemorrhage after spinal cord injury is blocked by pentobarbital and lidocaine anesthesia

Authors: *J. DAVIS[1], M. M. STRAIN[3], M. K. HENWOOD[2], R. BAINE[1], G. N. LEAL[2], T. JOHNSTON[1], J. W. GRAU[1]
[1]Psychology, Texas A&M Univ., College Station, TX; [2]Inst. for Neurosci., Texas A&M Univ., Bryan, TX; [3]Battlefield Pain Res., Inst. of Surgical Res., Fort Sam Houston, TX

Abstract: We have shown that nociceptive stimulation after a contusion injury increases tissue loss and impairs long-term recovery. We recently showed that the local application of an anesthetic (lidocaine; Turtle et al., 2017, J Neurotrauma, 34, 1200 1208), but not systemic morphine, has a protective effect that counters the adverse effect of nociceptive stimulation. Other work suggests that this local effect depends, in part, on communication with rostral (brain-dependent) neural systems. Supporting this, nociceptive stimulation has no effect on tissue sparing in rats that received a rostral spinal transection after a contusion injury (Reynolds et al., 2017). Given these findings, the present study examines the effect of CNS depressant pentobarbital, on the adverse effects of nociceptive input. In a subsequent experiment, we

assessed the effect of a pharmacological transection induced by applying lidocaine rostral to injury. Rats received a contusion injury at T12 and, 24 hrs later, were given an anesthetic dose of pentobarbital (30 mg/Kg). Animals then received 6 min of intermittent tailshock or nothing. Three hours after shock, rats were sacrificed and one cm of tissue was collected enveloping the injury site. The extent of hemorrhage was assessed by measuring the absorbance of light at 420nm and Western blotting for hemoglobin. In the second experiment, animals received a T12 contusion injury and 24 hrs later lidocaine (3.75mg/kg) was slowly infused rostral to the injury site (at T2-4). Rats were then given intermittent tailshock or nothing and tissue was collected three hours later. In both experiments, nociceptive stimulation increased the extent of hemorrhage in vehicle treated (awake) rats. This effect was attenuated by pentobarbital anesthesia and rostral lidocaine. Further work is exploring the circumstances under which these treatments attenuate hemorrhage.

Disclosures: J. Davis: None. **M.M. Strain:** None. **M.K. Henwood:** None. **R. Baine:** None. **G.N. Leal:** None. **T. Johnston:** None. **J.W. Grau:** None.

Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.24/T16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Nielson Foundation
NIH (NS091723 and NS104422 to JWG)

Title: Pain after SCI expands the area of hemorrhage: Evaluating the spread of secondary injury and the effect of injury severity

Authors: *M. K. BRUMLEY, J. REYNOLDS, J. A. DAVIS, G. FAUSS, J. D. TURTLE, A. NORRIS, P. BEAN, J. GRAU
Neurosci., Texas A&M Univ., Bryan, TX

Abstract: Recovery after spinal cord injury (SCI) is often complicated by additional tissue damage sustained at the time of injury. Previously, we have shown that peripheral noxious input after SCI produces a deficit in locomotor recovery, increases tissue loss, and increases indices of neuropathic pain (J Neurotrauma, 21, 1795). Recent findings suggest that noxious stimulation undermines long-term recovery because it leads to a break down in the blood spinal cord barrier and an expansion in the area of hemorrhage. Interestingly, the development of this effect depends upon spared fibers; if the spinal cord is transected rostral to the contusion injury, noxious stimulation does not induce hemorrhage. Here we evaluated the rostro-caudal extent of the hemorrhage and how the development of this effect varies with injury severity. We hypothesized

that the effect of pain input would be most evident after moderate SCI (12.5 mm drop; MASCIS device). To evaluate the relative effect of stimulation rostral/caudal to injury, adult male Sprague-Dawley rats received a contusion at T12 and a day later were exposed to intermittent shock for 6 minutes or an equivalent period of restraint. Three hours later, we collected a 1-cm section of tissue encompassing the injury site as well as 1-cm sections rostral and caudal to injury. We also collected a 1-cm section of cervical spinal cord tissue. Tissue was analyzed with western blotting for hemoglobin and cytokine content. In a second experiment, we varied injury severity (0, 6.25, 12.5, or 25 mm drop) and applied nociceptive stimulation, or nothing, 24 hours later. A 3-cm section of the spinal cord was collected 3 hours later and sectioned longitudinally. In animals that received a moderate injury, we found that pain input increased the infiltration of red blood cells in the (1 cm) region of injury. While nociceptive stimulation increased cytokine expression rostral and caudal to injury, it did not induce a significant increase in hemorrhage. Further work is being conducted to evaluate whether stimulation affects blood spinal cord barrier permeability outside the area of injury and how this effect interacts with the locus of injury.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.25/T17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: This work was supported by The Jerry Johnston Andrew Spinal Cord Research Award provided by TIRR Mission Connect.

Title: Reduction of allodynia following SCI using antioxidant nanoparticles

Authors: *J. J. HERRERA[1], K. H. BOCKHORST[1], L. NILEWSKI[2], W. SIKKEMA[2], J. M. TOUR[2]
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Abstract: Traumatic spinal cord injury (SCI) is devastating injury that results in motor neuron dysfunction and death at and below the lesion level. SCI patients not only live with the paralysis but as many as 80% of patients develop clinically significant neuropathic pain described as burning, stabbing, and/or electrical in sensation. We speculate that a one of the key underlying mechanism contributing to both issues is systemic inflammation. Both motor and sensory dysfunction is a combination of early necrotic as well as delayed progressive cell death processes, collectively referred to as secondary injury. Oxidative stress which is the results of

excess production of reactive oxygen species (ROS) and inflammation are widely considered hallmarks of the secondary injury cascade initiated after SCI. ROS are crucial contributors to a range of normal physiologic cell signaling such as energy production/regulation and contributors to our immune response to invading pathogens.
As our understanding of oxidative stress involvement in various human diseases increases, studies involving antioxidants have shown some benefit in disease treatment. The need for efficient antioxidants has led to the development of nanoparticle antioxidants. Antioxidant carbon nanoparticles can scavenge ROS with far higher efficacy than dietary and endogenous antioxidants. These nanoparticles are fabricated with poly (ethylene glycolation) on hydrophilic carbon clusters (PEG-HCC). Our study demonstrated that when antioxidant nanoparticles are administered intravenously following a moderate to severe spinal cord contusion there is a significant reduction in lesion volume determine by ex vivo MRI imaging when compared to saline treated animals ($p=0.0282$). This was also verified using luxol fast blue staining for white matter sparring. Our study also demonstrated that there was a significant improvement in the BBB locomotor scores. In addition there was attenuation in the development of neuropathic pain in the PEG-HCC treated group compared to saline treated. Together this data indicated that antioxidant nanoparticle treatment improved functional recovery after injury and attenuated the development of neuropathic pain.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.26/T18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Foundation (NS091723)
NIH Grant (NS104422)

Title: Noxious stimulation after spinal cord injury (SCI) induces a brain-dependent increase in hemorrhage

Authors: *G. N. LEAL[1], M. M. STRAIN[2], Y. J. HUANG[1], J. A. REYNOLDS[1], J. A. DAVIS[1], M. K. HENWOOD[1], C. R. WEST[3], J. W. GRAU[1]
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Abstract: Traumas that lead to spinal cord injury (SCI) frequently induce additional tissue damage (polytrauma) that provides a source of noxious input. Research has shown that pain (nociceptive) input after SCI can enhance tissue loss and undermine long-term recovery (Grau, 2004, J Neurotrauma, 21, 1795). This process can be modeled in rats by applying noxious electrical stimulation, or the irritant capsaicin, caudal to injury. Recent work suggests that nociceptive stimulation impairs long-term recovery because it expands the area of hemorrhage at the site of injury. The present study explores the role of brain systems and nociception-induced hypertension on hemorrhage expansion. Male Sprague-Dawley rats received a contusion injury at T12. Eighteen hrs later, half of the animals experienced a complete spinal transection at T2 to block brain-spinal cord communication. After 6 hours of recovery, half of the rats in each group were given intermittent electrical stimulation to the tail or a subcutaneous injection of capsaicin to one hindpaw. Blood pressure (BP) was monitored at discrete time points and tissue was collected for further examination. We found that shock administered to the tail resulted in an increase in BP. Tissue assays evaluating the extent of red blood cell infiltration at the site of injury showed that nociceptive stimulation increased hemorrhage. Spinal transection blocked both the increase in BP and hemorrhage. Capsaicin too increased hemorrhage and this effect was blocked by a spinal transection. Capsaicin did not, however, induce a significant increase in blood pressure. These results suggest that the adverse effect of pain input on tissue sparing depends upon brain systems. Further work is being conducted to determine whether nociception-induced hemorrhage is linked to alterations in blood pressure.

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Poster

296. Spinal Cord Injury II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 296.27/U1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: FAPESP

Title: Neuroprotective and immunomodulatory effects of dimethyl-fumarate after ventral root avulsion

Authors: *P. R. KEMPE[1,2], A. L. OLIVEIRA[2]
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Abstract: Spinal cord injury causes critical loss of motor and sensory function. Ventral root avulsion (VRA) is an experimental approach in which there is an abrupt separation of the ventral

(motor) roots from the surface of the spinal cord. This rupture, at the interface between the peripheral and the central nervous system (CNS), interrupts the contact between the motoneuron and the target muscle fibers. As a result, most of the axotomized motoneurons degenerate between the second and third week after avulsion. This is worsened by a significant loss of synapses and increased glial reaction, triggering a chronic inflammatory state. Therefore, the use of neuroprotective and immunomodulatory drugs can improve a regenerative response. Dimethyl-fumarate (DMF) is an FDA approved drug for psoriases and multiple sclerosis, and we hypothesize that it could support motoneurons after VRA. DMF promotes gene transcription of anti-oxidant and detoxifying enzymes, leading to cytotoxic protection and reestablishment of cellular homeostasis. Also, it modulates different types of cells of the immune system, reducing pro-inflammatory cytokines and local inflammation. Moreover, DMF was able to preserve myelin, axons and neurons in different experimental models of degeneration of the CNS. Accordingly, adult female Lewis rats subjected to VRA of L4 to L6 roots were daily treated with DMF (0, 7.5, 15, 30 and 45 mg/kg, gavage) for 4 weeks. The results involved analysis of neuronal survival by Nissl staining, glial reactivity by immunohistochemistry (anti-GFAP for astrocytes and anti-Iba-1 for microglia) and synapse preservation (anti-VGLUT1 and GAD65). Our results indicate that treatment with DMF at the dose of 15mg/kg is neuroprotective since it preserves 70% of motoneurons when compared to the vehicle group, in which approximately 20% of neurons survived. Furthermore, we observed a significant decrease of astrogliosis, and microglial reaction in DMF treated rats. Such parameters were combined with synapse preservation at the microenvironment of the motoneurons. Altogether, our results indicate that DMF has neuroprotective and immunomodulatory effects, which result in enhanced motoneuron survival following proximal lesion.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.01/U2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life Foundation
International Spinal Research Trust
The Bryon Riesch Foundation
NINDS RO1-NS083983-01

Title: Combined pro-regenerative strategies and targeted rehabilitation to improve behavioral outcomes after spinal cord injury

Authors: *D. B. NOWAK, E. T. EASTWOOD, N. JAYAPRAKASH, M. G. BLACKMORE
Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Regeneration of injured axons following spinal cord injury is critical to restore lost motor function. A low cell-intrinsic capacity for regeneration and hostile extrinsic factors at the injury site both act to limit axon regeneration. To overcome these twin barriers, we have combined overexpression of a pro-regenerative transcription factor called KLF6 in injured neurons with grafts of stem cells into spinal injuries. This combined treatment enables corticospinal tract (CST) regeneration through sites of spinal injury. Furthermore, combined optogenetics and electrophysiology showed that the regenerating axons form functional synaptic connections with host neurons below the injury. Despite the growth and synaptogenesis, however, behavioral gains were minimal. Here we test the hypothesis that elevating neural activity, in the context of stimulated CST regeneration, will improve behavioral outcomes after spinal injury. To do so we have developed a system of combined electrical stimulation, limb constraint, and post-injury rehabilitation in the form of forced irregular wheel running. In initial experiments, adult mice received midline cervical (C4-C5) 1mm deep wire-knife transections followed by casting of the uninjured limb for 4 weeks. Casted animals were placed on an elevated grate for one hour each day, forcing targeted placement of affected forelimbs. After cast removal, animals were exposed daily to forced locomotion on a wheel with irregularly spaced rungs every day for 8 weeks. The combined casting and rehabilitation significantly improved forelimb function on the horizontal ladder task. In our ongoing experiments this behavioral activity is supplemented by sub-threshold, extra-dural electrical stimulation of the motor cortex. By combining pro-regenerative treatments with optimized rehabilitative paradigms, we aim to improve behavioral outcomes after spinal injury.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.02/U3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS, NIH R01 NS081112
NIH, P01 NS 055976 Project 2
Craig H. Neilsen #338432

Title: Daily acute intermittent hypercapnia training to improve respiratory plasticity following spinal cord injury

Authors: *M. RANDELMAN, L. V. ZHOLUDEVA, V. M. SPRUANCE, T. BEZDUDNAYA, T. HORMIGO, H. MURALIDHARAN, M.-P. COTE, L. QIANG, M. A. LANE
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Abstract: Cervical level spinal cord injury (SCI) frequently leads to severe respiratory dysfunction due to damage of the spinal phrenic motor system which controls the diaphragm - the primary muscle for respiration. While some spontaneous functional plasticity does occur following cervical SCI, the extent is limited and diaphragm paresis persists. The goal of this research was to determine if respiratory plasticity and diaphragm recovery could be therapeutically enhanced using a novel respiratory training strategy: daily acute intermittent hypercapnia (dAIHc). We hypothesized that increasing respiratory activity with dAIHc will stimulate phrenic neuroplasticity and induce diaphragm recovery following a moderate mid-cervical contusion injury in the adult rat. Anatomical plasticity following injury and treatment was investigated using transynaptic tracing and immunohistochemistry. Pseudorabies virus (PRV) was used to retrogradely, transneuronally trace the spinal phrenic circuitry ipsilateral to injury and assess integration of premotor spinal interneurons with phrenic motorneurons. Immunohistochemistry and western blot analysis were performed to assess changes in serotonin (5-HT) and BDNF expression rostral and caudal to injury. Functional plasticity and respiratory recovery following dAIHc training was assessed with terminal diaphragm electromyography (dEMG). Hypercapnia trained animals showed an increased BDNF expression within the medulla, and greater density of serotonergic axons within the spinal cord when compared with untreated and air control animals. It was also found that 2 weeks of dAIHc training resulted in a greater recruitment of interneurons into ipsilateral phrenic circuitry when compared to untreated and air controls. Diaphragm EMG of the dAIHc trained animals resulted in modest improvement of the ipsilateral and contralateral diaphragm inspiratory amplitude as well as response to respiratory challenge. These results therefore suggest that dAIHc is able to promote plasticity within the phrenic network following cervical SCI.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.03/U4

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life (WfL)

Christopher and Dana Reeve Foundation
Forschungskredit "Candoc" of University of Zurich

Title: Timing and stimulation parameters of therapeutic deep brain stimulation of the mesencephalic locomotor region in rats

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Abstract: Functionally or anatomically incomplete spinal cord injury (SCI), characterized by sparing of some fibers and parts of tracts still connecting the brain with the spinal cord caudal to the lesion, affects millions of people worldwide. Loss of motor control and locomotion is common, with limited potential for functional recovery.
A small group of neurons in the pedunculopontine and cuneiform nuclei of the midbrain tegmentum, the mesencephalic locomotor region (MLR), is well known to initiate and control locomotion in vertebrates. Results of experiments recently conducted in our lab in rats with large but incomplete SCI showed that electrical deep brain stimulation (DBS) of the MLR was able to re-establish a high degree of locomotion in animals with functional deficits resembling those observed in severe ASIA C patients (Bachmann et al., 2013).
In order to consider DBS of the MLR as a potential treatment for incomplete spinal cord injury in humans, an evaluation of whether DBS facilitates the re-establishment of physiological movement patterns under voluntary movement control is necessary.
Electrodes were stereotactically implanted into the MLR of intact and spinal cord injured rats. The lesioned rats underwent kinematic analysis under stimulation at different post-injury timepoints. No reaction to the stimulation was obtained up to 7 days after the injury. Reactions started by 2 weeks and were fully developed at 4 weeks after the spinal cord injury. These results suggest that the spontaneously occurring sprouting and rearrangements of spared bulbo-spinal fibers could be required for the MLR impulses to reach functionally appropriate targets in the lumbar spinal cord. To assess the higher brain control over MLR stimulated locomotion, rats were confronted with e.g. place preference choices. Low and medium DBS stimulation strength allowed rats to fully respond to the sensory-motor tasks. At higher stimulation levels, full control over the stimulated locomotion was lost. Ongoing experiments will provide important additional information for a clinical trial in severe ASIA B and C SCI patients.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.04/U5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation
European Research Council (ERC) advanced grant (Nogorise)
Christopher and Dana Reeve Foundation
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Title: Anti-Nogo-A antibodies for treating and understanding neurogenic lower urinary tract dysfunction after spinal cord injury

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Abstract: Lower urinary tract dysfunction arises in a majority of people with spinal cord injury. The most common manifestation is detrusor sphincter dyssynergia (DSD), defined as bladder detrusor contraction with concomitant contraction of the urethral and/or periurethral striated sphincter muscle. DSD can result in high intravesical pressure and reflux of urine to the kidneys. The neuronal mechanisms responsible for the development of DSD after injury are unknown. Thus, no causal therapies are currently available. Here, we used antibodies against Nogo-A, a potent nerve fiber growth inhibitory protein, which have been shown to induce substantial axonal regeneration, enhanced neuronal plasticity and functional locomotor recovery after spinal cord injury in a variety of animal models. Rats were chronically implanted with a tubing system for controlled bladder filling and monitoring of bladder pressure, as well as external urethral sphincter (EUS) electromyography electrodes, allowing for repetitive urodynamic measurement and recording of EUS activity in awake animals over time. A severe but incomplete spinal cord injury was induced in all animals at the thoracic level 8. Afterwards, either control IgG antibodies or anti-Nogo-A antibodies were infused intrathecally for 14 days, and animals were investigated over a 4 weeks period. Anti-Nogo-A but not control antibody treated animals showed a significant normalization of several urodynamic parameters and EMG activity of the external urethral sphincter during voiding. Neurons in the pontine micturition center and their axons contain the neuropeptide Corticotropin Releasing Factor (CRF). Immunohistological analysis of CRF-positive fibers at sacral level S1 revealed three main regions that are densely

innervated by CRF fibers: the dorsal horn (DH), the intermediolateral nucleus (IML), and the lamina X region. Animals with a spinal cord injury had a marked decrease in CRF-fiber density in the lamina X compared to not injured animals. Interestingly, this reduction was not observed in animals treated with anti-Nogo-A antibodies. *In-situ* hybridization studies revealed that the number of GABAergic neurons located in the dorsal gray commissure decreases after injury. Yet, no reduction was observed in animals treated with anti-Nogo-A antibodies. These results suggest that the decreased supraspinal input to specific centers in the sacral spinal cord after injury leads to selective interneuron loss. These processes can be reverted/prevented by Nogo-A neutralization. In parallel, DSD is attenuated and important aspects of micturition are normalized.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.05/U6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Canada Foundation for Innovation
Natural Sciences and Engineering Research Council of Canada
Fonds de recherche du Québec – Santé (M.B. Postdoctoral Fellowship and M.M. salary)

Title: Intracortical neuroprosthesis fosters locomotor recovery after spinal cord injury

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Abstract: Spinal cord injuries (SCI) interrupt the pathways between the cortex, which controls voluntary movements, and the spinal networks that generate locomotion. Over time, both spontaneously and through training, neuroplastic changes occur and partial control of locomotion is reinstated.
First, we aimed at identifying the contribution of the hindlimb motor cortex in recovery of walking after SCI. We developed a chronic cortical mapping technique in awake rats. By using

an electrode array, we delivered targeted trains of stimulation to the hindlimb motor cortex and recorded changes in evoked responses on leg muscles before and after a unilateral thoracic hemisection. In this SCI model the contralesional cortex initially loses its contralateral connections to the leg muscles. Over time, we showed that the contralesional cortex recovers the ability to produce movements of the paretic hindlimb. Re-appearance of evoked muscles potentials paralleled the recovery of stepping, starting 5 to 10 days after injury and peaking at 3 weeks after injury.
Second, we hypothesized that applying cortical stimulation during the recovery period would increase functional cortico-spinal connectivity and facilitate locomotor recovery. We developed a neuroprosthetic system whereby trains of cortical stimulation are delivered coherently during locomotor behavior. By monitoring electromyographic patterns we could detect gait phases and delivered cortical neuromodulation in closed-loop. The stimulation increased leg flexion during treadmill locomotion. In SCI rats, motor deficits including leg dragging were immediately alleviated or abolished. The ladder crossing measures skilled locomotion in the rat. SCI impairs the rat's ability to perform this task. Our therapy cohort and two control groups shared the same level of initial deficits. We found that after 3 weeks rats treated daily with our neuroprosthetic therapy had a success rate far exceeding that of two control animals groups (n=6 per group). This improvement was retained 4 weeks after the therapy was terminated.
Our results show that the motor cortex contributes to recovery of walking after SCI. Furthermore, we proposed the first demonstration of a supraspinal intervention capable to remarkably contribute restoring precise leg control.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: WFL-UK-008/15
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CZ.02.1.01/0.0./0.0/15_003/0000419

Title: The effects of chronic paralysis on the mechanical properties and fibre-type composition of the diaphragm

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Abstract: High cervical hemisection causes a profound and robust deficit in respiratory motor function. Indeed, the disruption to supraspinal respiratory motor pathways causes a paralysis in the ipsilateral hemidiaphragm muscle which lasts from acute to chronic time points. However, we have previously shown that treatment induced recovery to normal diaphragm function can occur rapidly, within as little as two weeks following application. This would suggest that, despite the effects of atrophy and fibre type compositional change, the paralysed muscle retains functional capacity overtime. Here, we investigated how diaphragm mechanical properties change six weeks following chronic cervical spinal cord injury during isometric, isotonic, and cyclical contractions. Bilateral diaphragm electromyographic activity showed that 100% of animals with the C2 hemisection injury had complete paralysis in the ipsilateral hemidiaphragm six weeks following the initial trauma. Interestingly, isometric tetanic stress, twitch kinetics, and force-velocity relationships were similar between both the hemidiphragms in the injured animals and those in control groups. These data would suggest that injury induced paralysis did little to reduce diaphragm muscle mechanical function. However, while reproducible, these measures lack significant ecological validity to provide substantial and meaningful data relating to *in vivo* muscle function. Through the assessment of cyclic contractions, we demonstrated that the hemidiaphragm ipsilateral to the injury had a higher optimal cycle frequency for maximal net power generation compared to controls (8-10 Hz *versus* 5 Hz; $P < 0.001$). Interestingly, the shift in optimal frequency did not affect fatigue resistance during repeated cycles of work at 2 Hz, compared with all controls. Nonetheless, the principal mechanisms underpinning this alteration in optimal cycle frequency result from an increase in work performed during shortening associated with alteration in muscle fibre type. Collectively, these data show that chronic paralysis of the diaphragm adaptively and plastically alters the muscles optimal mechanical and fibre type composition. However, the muscle retains the capacity for conventional functionality, most likely due to continuous passive movement of the muscle within the thoracic cavity over time. These data explain how normal respiratory motor function can be rapidly restored following successful treatment of spinal cord injury and provide substantial information concerning how endogenous and adaptive plasticity may facilitate in this role.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Topic: C.11. Spinal Cord Injury and Plasticity

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Title: Effects of early and delayed strength training on neuropathic pain and nociceptive afferent sprouting after cervical spinal cord injury

Authors: *M. R. DETLOFF[1], A. ONG[1], A. D. TAMASHIRO-ORREGO[1], T. THAWEERATTANASINP[1], S. J. CHHAYA[2], J. D. HOULE[1]
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Abstract: Spinal cord injury (SCI)-induced neuropathic pain is associated with both nociceptor hyperexcitability as well as sprouting of primary afferent c fibers that transmit pain information to the spinal cord. We have previously that early, aerobic exercise prevents development of neuropathic pain but does not ameliorate it once established. While locomotor training is used in the clinic, the standard of care in post-SCI rehabilitation focuses on improving muscle strength. This project will determine whether early or delayed strength training after SCI can affect nociceptive afferent plasticity and pain development and persistence after cervical SCI. Female Sprague-Dawley rats received a C5 unilateral spinal cord contusion corresponding to handedness. A subset of SCI rats underwent isometric forelimb strength training 5 days/week starting at 5 or 42 days post-injury (dpi) lasting 5 weeks. Briefly, rats complete 50 successful repetitions of at least 50g force in an isometric forelimb pull task to receive a food reward. Mean pulling force returned to near normal after 10 strength training sessions regardless of early or delayed initiation of exercise . The recovery of forelimb strength corresponded to improvements in reach-to-grasp behavior as assessed using a single pellet-retrieval task. Delayed strength training reduced paw hypersensitivity and pain behavior as measured by von Frey and mechanical conflict avoidance operant tests compared to unexercised and acute strength training SCI groups. Three days before sacrifice, rats received microinjection of cholera toxin-B (CTB) into the ulnar nerve to identify large diameter sensory afferents. We are currently completing immunocytochemical and quantitative analysis of SCI lesion severity and the degree of primary afferent sprouting associated with forepaw dermatomes. Future experiments will examine the active and passive membrane properties of nociceptive neurons of SCI rats with and without strength training exercise. With the results, we hope to better understand the mechanisms underlying SCI-induced pain, allowing for possible refinement of rehabilitation protocols to reduce chronic pain after SCI.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Merit Review Award # B1005-R/1I01RX001005-01A2, from the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D)

Title: New therapies in experimental cervical spinal cord injury (C-SCI)-induced spasticity and gait disabilities

Authors: *J. HOU[1,2], R. NELSON[1], N. MOHAMMAD[1], D. PLANT[1], G. MUSTAFA[1,2], S. TSUDA[1,2], J. GODWIN[1], R. MARTIN[1], K. BUCKLEY[1], A. LERNER[1], R. J. BERGERON, Jr.[3], F. J. THOMPSON[1,2,4], P. BOSE[1,2,5]
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Abstract: C-SCI can produce life-long locomotor impairments, including spasticity disability. The objective of these therapy development studies was to amplify therapeutic impact by combining treadmill locomotor exercise (Tm) and SCI-site magnetic stimulation (TMS). To broaden the scope of potential therapeutic application, we also tested a new hexadentate monosodium iron chelator (NaHBED) therapy in this C-SCI model. Moderate $C_{6/7}$ contusion injuries (200 kdynes, Infinite Horizon Impactor) were produced in anesthetized adult rats. To evaluate acute treatment, Tm was initiated at post-SCI day 8. The treatment was performed 5 days/week for 6 weeks. Beginning at post-SCI day 14, TMS, was applied at the injury site every other day using a protocol that we recently reported (Hou et al., 2014). In a different cohort of acute treatment animals, the NaHBED was injected SC (100mg/kg/d) for 10 days starting on the day of SCI. For chronic studies, simultaneous TmTMS treatment was initiated at post-SCI week-8 and was performed for 6 weeks. Measures of lower limb spasticity (velocity-dependent ankle torques and time-locked triceps surae EMGs) and H-Reflex rate-depression were assessed using methodology that we developed and reported previously. Locomotor disabilities and therapy-induced improvements were assessed using 3-D kinematic (Vicon Motion Systems) and footprints (CatWalk, Noldus) analyses of gait. Lesion size, iron deposition in the injury site, and integrity of the descending pathways were imaged using 7.0 T MRI (MR Solutions) using T1/T2-weigted, QSM, and DTI/GQI imaging, respectively. Acute treatments using TmTMS were observed to completely blocked the development of spasticity compared to data obtained

from untreated SCI controls. Chronic TmTMS treatment yielded significant improvement in spasticity, but was not able to block it. Interestingly, the NaHBED treatment alone exhibited significant reduction in spasticity. Significant improvements in parametric measures of gait were observed in both acute TmTMS and NaHBED groups, respectively. The improvements in spasticity and gait were accompanied by greater spared spinal tissues and less iron deposition in the injury site (particularly, in NaHBED group). These data suggest that simultaneous application of TmTMS can be an effective treatment for C-SCI induced spasticity and gait impairments; acute treatments showing greater efficacy (e.g. earlier opportunity to diminish secondary injuries) than the chronic treatments. Improvements in spasticity and gait induced by treatment using a new iron chelator (NaHBED) are proposed to be associated with reductions in iron-induced toxicity and inflammation.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: CRSNG Grant

Title: Inflammation-induced attenuation of locomotor recovery is associated with decreased motoneuronal KCC2 expression

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Abstract: Following spinal cord injury (SCI), neuroplasticity in spinal network results in functional recovery as well as in hyperreflexia, spasticity and neuropathic pain development. We recently showed that pro-inflammatory injection of complete Freund adjuvant (CFA) in lumbar muscles below the level of a complete spinal transection attenuates locomotor recovery and decreases the expression of the chloride cotransporter KCC2 in lumbar spinal cord. Other studies suggest that motoneuronal expression of KCC2 could be restored by locomotor training. The

purpose of this study was to evaluate if inflammation-induced locomotor deficits were associated with decreased KCC2 expression in motoneurons assessed immunohistochemically and whether training could restore this deficit. Four groups of CD1 female mice composed of control spinal mice (n=8), spinal mice that were trained daily on a treadmill (n=10), spinal mice which received CFA injection in lumbar muscles (n=9) and trained spinal mice with CFA (n=9) were used in this experiment. Locomotion was assessed on day 2, 7, 14, 21 and 28 after a complete T7 transection. Animals were euthanized on day 28 by a transcardiac perfusion of 4% paraformaldehyde solution (PAF). Spinal cords were sampled, fixed overnight in PAF and cryoprotected in 30% sucrose and then frozen. Spinal tissue was sliced transversally between L1 and L6 in 25µm-thick sections, processed for slide-mounted immunofluorescence staining and probed for KCC2 and choline acetyltransferase (ChAT). Spinal mice with CFA showed impaired locomotor recovery compared to control spinal mice (increased drag, decreased step length, hip, ankle and MTP excursions). Also, our results show that the KCC2 expression in motoneurons was decreased in CFA spinal mice compared to control spinal mice and the observed deficit is restored in trained spinal mice with CFA. In addition, a correlation analysis revealed that locomotor recovery is associated with higher KCC2 expression in motoneurons. Considering the high prevalence of injured and inflammed back tissues in SCI patients, these results suggest that changes in KCC2 expression is a potential mechanism underlying the mutual influence of pain and rehabilitation and support the use of exercise to promote functional recovery.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

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Program #/Poster #: 297.10/U11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: LO1309
Center of Reconstructive Neuroscience CZ.02.1.01/0.0/0.0/15_003/0000419
MEYS, LTAUSA17120
GACR P304/12/G069

Title: Low level laser therapy leads to recovery from spinal cord injury by improving behavior and physiological changes

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Abstract: Low level laser therapy (LLLT) is considered as an effective treatment for central and peripheral nervous tissue regeneration by influencing numerous processes that accompany injury of the nervous tissue. LLLT restrain accumulation of inflammatory cells, modulate reactive oxygen species production, activate mitochondrial DNA replication, increase growth factor expression and alter nitric oxide levels. This study is aim to investigate the effect of LLLT on the functional recovery after spinal cord injury (SCI) and evaluate soleus muscle mass and histopathological changes of the spinal cord in rats.
Rats (Wistar male, n=26) with balloon induced spinal cord compression lesions were treated with a low-intensity MLS laser (simultaneously 808 nm continuous emission and 905 nm pulse emission, pulse-wave frequency, 10 Hz) at a light dose of 300 J. Light was applied transcutaneously at the lesion site immediately after injury for 10 days, given for 9 minutes. Functional recovery was assessed weekly by locomotor tests (BBB and Beam walking) and a sensitivity test (Plantar test). The animals were sacrificed 9 weeks after injury; the mass of soleus muscle was weighted and the spinal cord tissue was histologically evaluated. qPCR (Bdnf, Ngf, Nt3, Fgf2, Irf5, Mrc1, Olig2, Casp3, Gap43, Gfap Vegfa and Cntf) and Luminex multiplex cytokines (MIP-1α, IL-4, IL-1β, IL-2, IL-6, IL-12p70, TNF-α, and RANTES) were performed 2 months after SCI, to detect host tissue responses to LLT. Result demonstrated that LLT significantly improved functional locomotor recovery from the first week after lesioning in both BBB test as well as in advanced locomotor test, such as beam walking. Of 13 rats, 7 were able to cross the beam, compared to none in the control group. Phototherapy showed a significantly positive impact on diminishing thermal hyperalgesia after SCI. Laser treated animals displayed less atrophy in soleus muscle mass compared to the control group. Low-power laser radiation had a positive effect on grey and white matter sparing and there was a tendency to increase axonal sprouting. Changes in MIP-1α, IL-4, IL-6 were detected during first week after SCI. There were no significant changes in GFAP-positive area after laser treatment.
In conclusion, non-invasive light therapy promotes functional recovery in acute SCI and underscores use of LLLT as a promising therapy for SCI in humans.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 297.11/U12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH 1DP2NS106663

Title: Assessing corticospinal-dependent skilled forelimb movement in mice

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Abstract: Current behavioral tools in mice are not sufficient for interrogating complex, corticospinal-dependent, skilled motor behavior. The foundation for skilled motor learning and a potential mechanism for rehabilitation after neurological injury is the remodeling of cortical motor networks, including corticospinal neurons. An understanding of the organization and function of cortical motor networks is critical as neurological diseases and injuries that disrupt these networks, or network output, dramatically impair motor function. Recent advances in optical imaging have allowed for the interrogation of cortical motor network function *in vivo*, however, there is a need for a similar advance in the development of skilled behavioral tasks to use in combination with these imaging techniques. In mice, a simple lever press task has provided the initial insights into network function during learning, however, the execution of this unskilled learned behavior is unaffected by motor cortex injury. We have addressed this critical need by developing unbiased testing devices for complex behaviors to use in concert with modern *in vivo*imaging techniques.Working with Vulintus, Inc., we have adapted automated behavioral tasks of the MotoTrak system for use in head-fixed mice during two-photon imaging. We have validated these skilled motor tasks by testing the impairment of behavioral performance induced by unilateral transection of the corticospinal tract at the medullary pyramids (pyramidotomy). We recorded calcium transients in individual corticospinal neurons expressing the genetically encoded calcium indicator GCaMP6f. Imaging was performed over the course of skilled motor learning and used to determine the effects of pyramidotomy on neuronal activity. Our findings on the corticospinal neuron response to injury will open the door to future studies that focus on the plasticity of cortical motor networks, the incorporation of individual corticospinal neurons during skilled motor learning, and the recovery of motor networks after injury.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 297.12/V1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NINDS NS054894
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Craig Neilsen Foundation

Title: H reflex recorded from lumbar external oblique can be used to study effects of optogenetically mediated cortical neuromodulation after a complete T9/T10 spinal transection in rats

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Abstract: After a complete T9/T10 spinal cord injury (SCI) in adult rats, trunk control becomes very important for postural stability, and crucial for function if stepping of hindlimbs is enabled. We have developed a neuromodulatory technique aimed at promoting plasticity and motor learning in the trunk motor cortex after SCI via subthreshold optogenetic stimulation using virally delivered Channelrhodopsin (ChR2). Virally delivered enhanced yellow fluorescent protein (EYFP) is used as a control. When optogenetically mediated neuromodulation is paired with a 25 day robot assisted rehabilitation paradigm, motor mapping studies reveal a significant increase in cortical representation of trunk muscle segments below the injury (1-way ANOVA with Tukey-Kramer post-hoc comparisons, $p<0.05$) in the ChR2+robot rats, both with induced spinal stepping (N=8) and without (N=8), but not in EYFP+robot rats with (N=8) or without (N=8) spinal stepping enabled. Activation of caudal trunk enabled by these representational changes likely also causes plastic changes in spinal circuitry below the injury by influencing sensory input and motor output in the spinal cord caudal to injury. These plastic changes may be beneficial in functional recovery after injury, and understanding these effects may help direct future rehabilitation efforts. Functional tests, such as AOB or BBB scoring provide little insight into group differences at circuit levels, so a physiological probe is needed to understand the basis of functional differences.
H-reflex testing is used widely to test spinal excitability. Though an H-reflex can be initiated in any muscle if the innervating nerve can be isolated for stimulation, testing typically occurs in muscles of the low extremities since the distance between the muscle of interest and the spinal cord is sufficient to ensure complete separation of the signals representing direct motor activation of the muscle from the spinally driven reflexive activation of the muscle. Here we present a method to test the H-reflex in the lumbar external oblique, an axial muscle with short peripheral nerves and latencies, caudal to injury, in awake behaving rats, employing blind source separation technique, independent component analysis, to separate the overlapping direct motor activation of the muscle from the spinally driven reflexive activation of the muscle. Varying stimulation frequency allows the effects of neuromodulation of trunk motor cortex on spinal excitability below the injury to be revealed. This work has been supported by NIH NINDS NS054894, and NS072651 and the Craig Neilsen Foundation.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR Grant MOP119278

Title: Electrical stimulation to promote plasticity in the injured corticospinal tract

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Abstract: cAMP and its downstream effectors have long been implicated in plasticity in the nervous system, with a vast array of work showing that increases in cAMP leads to an increase in plasticity and neurite outgrowth. Following spinal cord injury (SCI), intracellular cAMP levels have been shown to decrease in the motor cortex, which has been theorized to be caused by the loss of neuronal activity. Restoration of cAMP levels has been achieved following peripheral nerve injury through electrical stimulation and rehabilitative motor therapy. Additionally, stimulation in the uninjured side of the cortex following SCI in conjunction with rehabilitative therapy has shown increases in cAMP. These increases have been shown to result in an increase in neurite outgrowth in the injured nerves in both of the peripheral and central nervous system injury models. There has been limited work on stimulation of the injured side of the cortex. Our goal is to increase motor recovery following SCI by increasing cAMP induced plasticity in the corticospinal tract through a combination of cortical electrical stimulation of the injured cortex and motor rehabilitative therapy.
Adult female Lewis rats were trained in a single pellet grasping (SPG) task for 5 weeks to a baseline success rate of 40%. Following which animals underwent an incomplete unilateral cervical spinal cord transection on the side of the dominant paw. Immediately following SCI the experimental group underwent 30 minutes of electrical stimulation in their forelimb motor cortex. One week following injury, both groups were trained in the same grasping task for an additional six weeks at which point functional recovery was compared to pre-injury levels. Success rates and limb functional scores were analyzed and tissue was processed for histological analysis following BDA tracing of the corticospinal tract, allowing us to measure distribution of collateral sprouting in the grey matter above the lesion site.
Results indicate increased functional recovery in the SPG task in stimulated animals.

Histological analysis of collateral sprouting and their distribution demonstrates that electrically stimulated animals show a significant increase in collateral sprouting immediately above the lesion site, as well as a significant increase in the distance extended from the dorsal funiculus into the grey matter. Further studies aim to investigate the parameters of stimulation required to elicit anatomical and functional changes so as to reach a more clinically feasible means of treatment.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.14/V3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ISRT STR118

Title: Combined epidural stimulation, anti-Nogo antibody treatment and training in a severe contusion injury

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Abstract: Combinatorial therapies for the treatment of spinal cord injury (SCI) are vital if a significant amount of locomotor recovery is to be achieved. Parsing out the behavioral and anatomical changes each treatment is having will allow us to effectively combine therapies needed for SCI recovery. Alone, anti-Nogo-A antibody (11C7), locomotor training, or epidural stimulation of the lumbar spinal cord have been shown to improve locomotor outcomes in animal models of SCI. However combining therapies has not always been successful, with certain treatments, such as training alongside anti-Nogo-A therapy, proving to have negative combinatorial effects. The current study attempts to show the addiditive effects of sequential anti-Nogo-A antibody treatment followed by epidural stimulation and locomotor training with body weight support. Adult Sprague-Dawley rats received a severe contusion injury at T9/T10, epidural electrodes implantation at L2 and S1, and intrathecal delivery of either the Anti-Nogo antibody 11C7 or control IgG (osmotic pumps). Animals were randomly assigned to one of cage control, locomotor training, epidural stimulation (40Hz sub threshold), or combined epidural stimulation and locomotor training. Pumps and catheters were removed after 2 weeks and

training began 3 weeks following injury in order to minimize negative outcomes seen when anti-Nogo-A therapy was simultaneously combined with locomotor training. Rats in the trained groups stepped bipedally-to-quadrupedally with varying amounts of body weight support at speeds of 7-21cm/s (5 days/week, 20 mins/day) for 8 weeks. Kinematic recordings were made and Cholera toxin-B (CTB) tracer injections into the hindlimb and cortical BDA injections were completed before terminal electrophysiology. Surprisingly, our preliminary data showed that there were no significant differences in BBB scores between groups throughout the treatment period. The fact that both drug and control groups did not show significant improvement in the open field suggests that epidural stimulation and locomotor training did not have the effects seen previously. The three week delay in treatment may be the cause for this with the critical period possibly missed. The behavioral results underline the importance of understanding the mechanisms of different treatments in order to be able to combine them in the most effective way.

Disclosures: R.G. Dickson: None. **R.W. Kissane:** None. **K.O. Chen:** None. **M.E. Schwab:** None. **S. Chakrabarty:** None. **R.M. Ichiyama:** None.

Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.15/V4

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ISRT Grant (STR118)

Title: Changes in descending drive and local spinal reflexes in rats following spinal cord injury, with combinatorial application of locomotor training, epidural stimulation and anti-Nogo (11C7) antibody

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Abstract: A few therapeutic strategies have shown promise in the recovery of locomotor function following severe spinal cord injury (SCI), however the mechanisms underpinning the recovery of functional capacity are not fully understood. Anti-Nogo antibody (11C7) has been shown to promote sprouting of cortical spinal tract (CST) axons and functional capacity in animal models. Locomotor training and stimulation at the dorsal surface of the spinal cord

(epidural stimulation) has been used as a means of modulating spinal circuits caudal to the lesion, and promoting recovery of function. We sought to explore the effect of combining locomotor training with epidural stimulation, in the presence of 11C7, to assess the supra spinal and local spinal changes involved in the loss and gain of locomotor function following a severe SCI. Simultaneous treatment of 11C7 with locomotor training interferes in the recovery of locomotor capacity. Consequently we treated with 11C7 or a Control IgG antibody for two weeks immediately following SCI and delayed initiation of training by one week. Rats received a severe contusion injury (250 kdyn) to the mid-thoracic spinal cord (T9/10). Three weeks post injury animals were randomly assigned to one of four groups; cage control, locomotor trained, epidural stimulation (40Hz across spinal segments L2 and S1), or locomotor training with epidural stimulation combined. Animals were trained for eight weeks before undergoing kinematic analysis and terminal electrophysiological experimentation. Preliminary data suggest no clear differences in the recovery of open field locomotor capacity between groups. 3D kinematics analysis of bipedal locomotion is currently ongoing. Descending drive through the CST was completely removed following SCI. There was no evidence of modulatory capacity of the CST on the monosynaptic reflex (MSR) following any of the treatment strategies. However, SCI resulted in motor neuron hyperreflexia, which was ameliorated in animals that underwent locomotor training. In the combination animals there appears to be an increased modulatory input from the reticular formation on MSR. Importantly, we have begun to identify potential spared descending pathways able to modulate motor neuron excitability in the absence of CST input.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.16/V5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH/NINDS NS083666

Title: Bumetanide differently alters spinal reflex inhibition over time after SCI

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Abstract: Spasticity affects ~70% of people with a spinal cord injury (SCI), and is attributed to an increase in neuronal excitability and a decrease ability to depress spinal reflexes below the

lesion. Neuronal inhibition in the mature CNS mostly rely on GABAergic and glycinergic induced hyperpolarization. Drugs directly targeting GABAergic receptors provide a transient improvement in alleviating spasms and exaggerated reflexes and *de facto* became the most prescribed medication for the management of spasticity (Walter et al., 2002). However, they have significant side effects by decreasing motoneuronal excitability such that the potential for motor recovery is compromised (Dietz and Sinkjaer, 2007). Therefore, restoring inhibitory mechanisms rather than depressing neuronal excitability are promising strategy to decrease spasticity without hindering motor recovery.
A shift in chloride homeostasis has been shown to be involved in the emergence of spasticity after SCI. Chloride homeostasis in CNS neurons, is mainly determined by the relative expression of two chloride transporters, the outward-rectifying KCC2 and the inwardly-directed NKCC1. The decrease in KCC2 expression in motoneurons after SCI is depolarizing the E_{IPSP} and contributes to the emergence of spasticity (Boulenguez et al 2010). We have previously shown that the beneficial effects of exercise on spastic symptoms relied on a return of chloride homeostasis in lumbar motoneurons (Cote et al., 2014).
Chloride homeostasis-related neurological disorders were shown, to be improved when blocking NKCC1 with bumetanide (Ben-Ari, 2017). Here, we explore the therapeutic effect of bumetanide and step-training on restoring chloride homeostasis and improving the locomotor pattern after SCI. Chronic EMGs were implanted into hindlimb muscles of SCI rats to monitor locomotion over the course of 4 weeks. During a terminal experiment, we evaluated the alteration of reflex modulation associated with these interventions. H-reflexes were evoked by stimulating the tibial nerve and were conditioned by PBSt stimulation at different intervals. Our results suggest that acute bumetanide treatment improves reflex modulation, most likely through a recovery of postsynaptic inhibition, when initiated early after SCI. When NKCC1 activity was blocked chronically the improvement of locomotor pattern are comparable to step-trained animals. Correlation between features of EMG bursts (timing, amplitude, etc) and KCC2/NKCC1 levels will also be presented. Together, these results suggest that bumetanide could produce beneficial effects on spastic symptoms and the recovery of locomotion after SCI.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS232644
Craig Neilsen Foundation 270383

Title: Enhancing KCC2 function attenuates hyper-excitable stretch reflex after SCI

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Abstract: After spinal cord injury (SCI), ~75% of individuals develop spasticity – a debilitating condition involving involuntary movements, co-contractions, and hyperreflexia. Most current medications to suppress spasticity act upstream of NDMA and Ca2+-dependent mechanisms, leading to serious side effects including a drastic decrease in motoneuronal excitability. Therefore, there is a pressing need for new options that will treat spasticity without hindering motor activity. We have previously shown that exercise attenuates hyperreflexia after SCI through an increase in lumbar motoneuronal expression of KCC2. KCC2 is a Cl- co-transporter that largely determines the [Cl-]i of neurons and its expression is decreased in SCI. A promising approach is to restore endogenous inhibition directly by targeting Cl- homeostasis via KCC2, which will not affect spinal excitability as current available treatments do. Recently, a novel family of compounds, CLPs, were developed to selectively enhance KCC2 activity and has been successfully used to alleviate hypersensitivity in models of neuropathic pain. We have previously found that CLP257 restores the frequency dependent depression (FDD) of the H-reflex in untrained rats to levels like those observed in exercised rats.
Here, we examine the effects of CLP257 on mechanically induced stretch reflexes and muscle forces. Adult Sprague Dawley rats underwent a complete transection (T12), and either received passive bicycle training or were left untrained. In a terminal experiment 4 weeks post SCI, the triceps surae was lengthened at different amplitudes and velocities, and the resultant forces were quantified before and after administration of CLP. Large velocities were used to induce stretch reflexes, while smaller velocities were used to quantify overall muscle force output. Our results indicate that CLP reduces the hyperexcitable stretch reflex observed in untrained animals and has no diminishing effects on force output. This indicates that CLP avoids the detrimental effects on muscle activity that often accompany current anti-spastic medication. Surprisingly, CLP appears to increase spiking activity in muscle fibers, suggesting that although CLP decreases hyperactive reflexes, it also contributes to increased excitability of certain pathways. This will need to be further investigated to determine if this activity can be used to the benefit of motor recovery. These results indicate that CLP has beneficial effects on the monosynaptic reflex in hyperreflexive rats after SCI. To investigate polysynaptic mechanisms, we will also examine the effects of CLP on long duration reflexes.

Disclosures: J. Bilchak Stroughair: None. **G. Caron:** None. **K. Yeakle:** None. **M. Cote:** None.

Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.18/V7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS101105

Title: Exploring approaches to promote respiratory motor plasticity through varied and fixed interval intermittent hypoxia

Authors: *A. L. SILVERSTEIN, K. J. RITTER, D. R. STOLTZ, L. E. HAGER, C. M. CALULOT, R. S. J. MAGGARD, E. E. HUFFMAN, W. S. WITT, W. J. ALILAIN
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Abstract: In the human population, spinal cord injury (SCI) most commonly occurs at the cervical level. Interruptions of descending pathways here can result in breathing motor deficits through paralysis of the diaphragm, sometimes necessitating mechanical ventilation for survival which greatly decreases patients' quality of life. Fixed interval intermittent hypoxia (FIH) treatment is utilized in rat models to attenuate breathing motor deficits resulting from cervical SCI. FIH consists of the repeated, alternating exposure of a subject to consistent and equal durations of hypoxic and normoxic conditions. Specifically, this treatment induces a prolonged increase in phrenic motor output, a type of respiratory motor plasticity known as phrenic Long Term Facilitation (pLTF). FIH exhibits similarity to the psychological construct of operant conditioning in which the increased incidence and persistence of a desired, spontaneous behavior is trained through reinforcement. As such, each interval of hypoxia can be construed as the period during which the subject responds with heightened respiratory drive and is subsequently reinforced by an interval of normoxia. Provided that FIH procedure is a form of operant conditioning, it can be optimized. Using the fixed or variable duration of the hypoxic interval as our independent variable, we hypothesize that Varied Interval Hypoxia (VIH) treatment will induce a greater, more prolonged increase in phrenic motor output than FIH. To test this hypothesis, we utilized electromyographic recording to assess our dependent variable of diaphragmatic activity. In naïve retired breeder rats (female, Sprague-Dawley) treated by VIH (n=2), episodic spinal cord application of serotonin, previously shown to induce pLTF independently from intermittent hypoxia treatment, depressed breathing motor output, an effect opposite from that observed after FIH (n=2). Preliminary data from C2 hemisected animals (n=3) suggests that exposure to VIH results in an increase in diaphragmatic output achieving 44.89% (stdev.p 15.76%) of maximum induced by nasal occlusion. These data suggest that VIH may paradoxically promote a lower level of respiratory motor plasticity than FIH in naïve models,

while potentially inducing significant recovery in post-injury models. Further exploration will focus on post-injury treatment, adjusting the variance of the hypoxic periods for optimum induced recovery, and more robust comparison to control.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 297.19/V8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Startup funds from University of Kentucky College of Medicine

Title: Human apolipoprotein e (apoe) isoforms differentially influence neurite outgrowth and regeneration

Authors: *R. S. MAGGARD[1], C. M. CALULOT[2], L. E. HAGER[2], K. J. RITTER[2], B. N. TURBA[2], J. D. HOFFMAN[2], A.-L. LIN[2], L. A. JOHNSON[2], W. ALILAIN[2]
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Abstract: Translating spinal cord injury (SCI) therapies from preclinical animal models into the human population is challenging. One potential explanation is that human genetic predispositions may limit the efficacy of treatments which enhance regeneration and sprouting. The clinically relevant ApoE4 (E4) allele, present in about 14% of the human population, corresponds to an increased incidence of Alzheimer's disease. Its role in recovery from SCI is poorly understood despite suggestive data implicating its involvement. Two clinical studies found that SCI individuals with the E4 allele had less motor recovery than individuals without the allele despite longer time in rehabilitation. ApoE4 may mediate this diminished recovery by limiting regeneration and sprouting. Robust regeneration is energy intensive and requires efficient mitochondria, and studies have shown that ApoE4 impairs mitochondrial function. Given these mitochondrial deficits, we hypothesize that ApoE4 can impair regeneration and sprouting. To test this hypothesis, we investigated the impact of ApoE4 on sprouting and neurite outgrowth. In our experiments, we cultured dorsal root ganglia neurons from mice expressing the human ApoE isoforms—ApoE2 (E2), ApoE3 (E3), or ApoE4—under the control of the mouse ApoE promoter. We then analyzed differences in 1) neurite complexity and 2) robustness of outgrowth between genotypes. Our results demonstrate that E3 neurons have more robust outgrowth than E4 neurons, as indicated by a higher total combined neurite length. Analysis of neurite branching

indicates that E3 neurons also have higher neurite complexity than neurons expressing ApoE4. Preliminary data from the Spot Assay, an in vitro model of the glial scar and CNS regeneration, suggest that chondroitin sulfate proteoglycans may inhibit regeneration in E4 neurons to an even greater extent than in E3 neurons. Since outgrowth, sprouting, and regeneration all partially mediate recovery after CNS injury, impairments in these processes can adversely affect recovery. These foundational studies address not only the possible genetic influence of ApoE4 on recovery from CNS injury, but also a critical gap in knowledge—whether there is a genetic contribution underlying responses to treatment in SCI individuals.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.20/V9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: UK Startup Funds

Title: Balancing neuroprotection with functional recovery: The role of the perineuronal net in preventing excitotoxicity after spinal cord injury

Authors: *D. R. STOLTZ, K. J. RITTER, E. E. HUFFMAN, A. L. SILVERSTEIN, W. J. ALILAIN
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Abstract: In spinal cord injury (SCI), initial mechanical trauma causes debilitating primary damage to neural cells and blood vessels. Following this, a secondary cascade of downstream events occur, including inflammation, ischemia, and excitotoxicity — an increase in intracellular Ca2+ concentration from overactive glutamate (Glu) receptor activity leading to cell death. Additionally, there is an upregulation of the perineuronal net (PNN), a lattice-like structure of the extracellular matrix which modulates neural communication and homeostasis. The PNN is partially composed of highly negatively charged chondroitin sulfate proteoglycans (CSPGs). While the PNN and CSPGs can support plasticity and neuronal growth during development, after injury these ECM molecules are inhibitory to regeneration, sprouting and plasticity. However, administration of the bacterial enzyme chondroitinase ABC (ChABC) can digest these inhibitory factors and promote functional recovery. What remains unknown is the impact of removing these inhibitory factors soon after injury. We hypothesize that negatively charged CSPGs are

upregulated after SCI as a neuroprotective response that attenuates excitotoxicity by acting as a sink for Ca2+. To test our hypothesis, we induced excitotoxicity by injecting rats with a threshold dose of Glu with or without ChABC utilizing the well defined respiratory motor system. 59% of SCI occurs at the cervical level, and leading causes of death and restriction of independence in these cases stem from mechanical ventilation. Therefore, we administered the dose instraspinally at the C4 level and paired treatment with intrapleural injection of cholera toxin-B to retrogradely label the phrenic motor neuron pool (which innervates the diaphragm). Preliminary results suggest that animals treated with both Glu and ChABC had more extensive phrenic motor neuron loss. Histological analysis of apoptosis with TUNEL staining will further reveal whether CSPGs serve our proposed role in promoting survival after SCI in additional cells. In conclusion, our early findings suggest that following SCI, the body's main focus is to survive and not necessarily to preserve function. CSPG upregulation could promote survival and CNS tissue preservation at the expense of plasticity and functional regeneration. Future directions will investigate the optimal timing of CSPG digestion to balance neuroprotection with alleviation of the inhibitory environment to promote recovery.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 297.21/V10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: University of Kentucky College of Medicine Excellence in Graduate Research Fellowship
National Science Foundation Graduate Research Fellowship

Title: Apolipoprotein E4 as a barrier to respiratory motor plasticity

Authors: *L. HAGER, R. S. J. MAGGARD, D. R. STOLTZ, K. J. RITTER, E. E. HUFFMAN, B. N. TURBA, C. CALULOT, A. L. SILVERSTEIN, W. J. ALILAIN
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Abstract: More than 50% of spinal cord injuries (SCI) occur at the cervical level. These injuries can disrupt axons that descend from medullary respiratory centers to the phrenic motor nucleus at C3-C6. Since diaphragmatic innervation originates from the phrenic motor nucleus, loss of these descending inputs leads to impairment of breathing function in cervical SCI patients. One approach to promote functional recovery is by enhancing plasticity through activation of spared

but latent pathways or strengthening of synapses. One form of respiratory motor plasticity is long term facilitation (LTF), which is characterized by a prolonged increase in breathing activity. LTF can be induced by intermittent bouts of hypoxia (IH) or through intermittent doses of serotonin (5-HT) applied to the spinal cord. Increased signaling through 5-HT receptors and upregulation of glutamate receptor expression in excitatory synapses mediate LTF. In preclinical animal models of SCI, IH has been successful in promoting breathing recovery. However, human patients have exhibited varying degrees of response to IH treatment, indicating that there is an additional factor influencing plasticity that must be considered. We propose that genetic diversity among the human SCI population could be a key factor in determining an individual's potential for plasticity. Apolipoprotein E (ApoE) is a promising gene of interest since the ApoE4 protein has been shown to reduce synaptic plasticity by decreasing the expression of glutamate receptors on the neuronal surface in vitro. In the present study, long term facilitation was induced in rats in the presence of human ApoE3 and E4 proteins to determine their influence on plasticity in vivo. In animals that received E4, diaphragmatic EMG recordings demonstrated that LTF was abolished and immunohistochemistry revealed that fewer glutamate receptors were localized in synapses. To investigate the effect of ApoE4 on respiratory motor plasticity after injury, C2 hemisections were performed on a second cohort of rats and LTF was induced at a 20-week post injury time point in the presence of human ApoE3 or E4. In ApoE3 treated animals, diaphragmatic activity ipsilateral to the injury increased in response to serotonin dosing, whereas this increase was abolished in Apo4 treated animals. Collectively, these experiments demonstrate ApoE4's ability to inhibit plasticity, emphasizing that genetic diversity is an important factor to consider in the development of therapies for the human SCI population.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

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Topic: C.11. Spinal Cord Injury and Plasticity

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Start-up funds Libin Cardiovascular Institute of Alberta/Hotchkiss Brain Institute, University of Calgary.

Title: Harnessing spinal electrical stimulation to modulate autonomic function after spinal cord injury

Authors: *J. SQUAIR[1,3,4], N. CHO[2], K.-A. BARTHOLDI[2], S. ANIL[2], M. ANDERSON[2], J. GANDAR[2], A. ROWALD[2], C. KATHE[2], Z. K. SARAFIS[2], M. GAUTIER[2], X. KANG[5], N. VACHICOURAS[5], S. LACOUR[5], Q. BARRAUD[2], G. COURTINE[2,5,6], A. A. PHILLIPS[4]
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Abstract: Severe spinal cord injury interrupts descending sympathetic projections that modulate cardiovascular function. This interruption leads to frequent bouts of hypertension (autonomic dysreflexia) and orthostatic hypotension, conditions that lead to increased risk for cardiovascular disease and potentially death. Here, we developed a conceptual and engineering framework to design an electrical spinal cord neuroprosthesis that targets the sympathetic circuitry within the spinal cord to prevent the development of these conditions. We first developed a rodent model of sympathetic dysfunction after spinal cord injury. For this, we visualized catecholaminergic fibers originating from the brainstem autonomic centers in TH:Cre rats who underwent a severe upper thoracic contusion. We found a near complete interruption of TH+ descending sympathetic axons, which led to an immediate decrease in resting hemodynamics and to the development of aberrant cardiovascular reflexes. To target the sympathetic circuitry within the spinal cord with epidural electrical stimulation, we mapped the hemodynamic responses to stimulation applied at each level of the thoracic and lumbar segments. We identified highly-specific hotspots that effectively modulated hemodynamics. We then used intersectional neuroanatomical tracing and activity-dependent signaling pathways to uncover the connectome of the spinal cord and splanchnic ganglia circuits engaged by the stimulation. Using optogenetic manipulations, we established causal relationships between the modulation of these circuits and the hemodynamic response to the stimulation. We then combined CT scans, MRI sequences and computational modelling to design a neuroprosthesis that targets cardiovascular hotspots in the spinal cord. This neuroprosthesis was fabricated using e-dura technology. We therefore have termed this implant *autonomic e-dura*. The therapeutic efficacy of the *autonomic e-dura* is under investigation.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

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Topic: C.11. Spinal Cord Injury and Plasticity

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Swiss National Science Foundation subside 310030_130850
Human Brain Project

Title: Mechanisms through which epidural electrical stimulation restores locomotion after spinal cord injury

Authors: K. BARTHOLDI[1], *Q. BARRAUD[1], E. FORMENTO[2], A. ROWALD[1], N. D. JAMES[1], N. CHO[1], C. KATHE[1], L. BAUD[1], T. H. HUTSON[3], S. MICERA[2,4], S. DI GIOVANNI[3], P. MUSIENKO[5], M. CAPOGROSSO[6], G. COURTINE[1]
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Abstract: Epidural electrical stimulation (EES) of the lumbar spinal cord restored locomotion in rodents, nonhuman primates and humans with spinal cord injury (SCI). However, the neural structures through which EES enables motor pattern formation remain poorly understood. Using calcium imaging and chemogenetic inactivation experiments, we demonstrate that the activation of proprioceptive feedback circuits contributes to motor pattern formation during EES. However, EES also recruits cutaneous low-threshold mechanoreceptor feedback circuits. Modeling experiments showed that the activation of these pathways with EES is detrimental to the production of locomotion. To augment the facilitation of movements with EES, we thus reasoned that these two types of circuits should be targeted with opposing neuromodulators. This understanding translated into a circuit-specific electrochemical neuromodulation therapy based on noradrenergic receptor modulation that enabled robust locomotion in paralyzed mice and rats. These findings establish a mechanistic framework for the design of targeted neuromodulation therapies in human patients.

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Courtine: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GTX medical.

Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.24/V13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ERC 588133
SNF Sinergia 513843

Title: Cortico-reticulo-spinal circuit reorganization reverses paralysis after severe spinal cord contusion

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Abstract: Severe spinal cord contusions interrupt nearly all brain projections to lumbar circuits producing leg movement. Failure of these projections to reorganize leads to permanent paralysis. Here, we modeled these injuries in rodents. We found that a severe contusion abolishes all motor cortex projections below injury. Using mice expressing light-sensitive channels in cortical projection neurons, we found that electrochemical neuromodulation of the lumbar spinal cord enabled the hindlimb motor cortex to regain a graded control over hindlimb locomotor movements in otherwise paralyzed animals. Virus-mediated tract tracing and circuit-specific inactivation techniques revealed that the cortical drive accessed the lumbar spinal cord through glutamatergic reticular neurons with residual projections below the injury. Gravity-assisted rehabilitation enabled by electrochemical neuromodulation reinforced these reticulospinal projections, rerouting cortical information through this pathway. This cortico-reticulo-spinal circuit reorganization mediated a motor cortex-dependent recovery of walking and swimming without requiring neuromodulation. Similar mechanisms may improve functional recovery in humans.

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Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.25/V14

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS R21-1R21NS096571-01

Title: Subcutaneous maturation of neural stem cell-seeded scaffolds to treat spinal cord injury

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Abstract: Neural stem cells (NSCs) represent a promising treatment approach to restore neurologic function following spinal cord injury (SCI). However, survival and engraftment must be maximized to coax them into achieving their full regenerative potential, while simultaneously promoting a permissive microenvironment by reducing inhibitory cues. Here, we formed 3D scaffolds from a biomimetic polysaccharide (methacrylamide chitosan), containing immobilized interferon-γ and rat NSCs. Previously, we have shown that these scaffolds generate both neurons and neural rosette-like structures from encapsulated NSCs when matured in subcutaneous tissue. To harness this phenomenon and prime the cells for regeneration we subcutaneously matured (SubQ) our scaffolds prior to transplanting them into a subacute (2w post-injury) T10 right lateral hemisection. To reduce chondroitin sulfate proteoglycan inhibition, we also administered intracellular σ peptide (ISP) after SCI for 16w while assessing functional improvements over time through BBB score and a novel open-source gait analysis technique which captures gait data using high-speed imaging (AGATHA). Statistical analysis (ANOVA, $\alpha = 0.05$) of week 4 BBB scores found that the interaction between NSCs, SubQ, and ISP was significant ($p = 0.001$, $n = 8$), while NSCs ($p = 0.03$) and ISP ($p = 0.014$) alone also made significant differences. Tukey's *post-hoc* analysis indicated that the full treatment group (NSCs + SubQ + ISP) scored significantly higher (14.2 ± 1.3, mean ± SD) than all other groups (11-12 range) after 4w: we will monitor the rats weekly for the remaining 12w to see if improvement continues. Additionally, we took advantage of the open-source and high-resolution (we can generate images of each paw showing individual digits during stance phase) nature of AGATHA to calculate additional SCI-specific parameters, which we show are sensitive and track recovery: paw placement accuracy (the distance between ipsilateral fore/hind paw placement), and phase dispersion (% step cycle difference between diagonal limb placement), alongside more general parameters: duty factor, step width, stride length, etc. After 16w, we will confirm locomotor improvements by retrograde tracing and immunohistological (IHC) staining to assess tissue-level integration between the scaffold and surrounding cord, and examine the contributions of our

implanted (GFP+) NSCs. Overall, we show that our approach has promise for improving functional recovery after SCI, as well as highlight a new, open-source technique for gait analysis of SCI animal models.

Disclosures: T.R. Ham: None. **D.D. Pukale:** None. **N.D. Leipzig:** None.

Poster

297. Spinal Cord Injury and Plasticity: Training, Rehabilitation, and Repair: Animal Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 297.26/V15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: IRP fellowship P165F
SNSF Ambizione
ERC Grant ERC588133

Title: Understanding the underlying neuronal circuitry and spatial specificity of epidural cervical spinal cord stimulation

Authors: *N. D. JAMES[1], S. ODOUARD[1], B. BARRA[3], N. GREINER[3], N. CHO[1], M. CAPOGROSSO[4], G. COURTINE[2]
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Abstract: MC and GC contributed equally to this work
Contusion of the cervical segments is the most common form of spinal cord injury (SCI). Patients surveys have identified improvements in upper limb function as a top priority for individuals that have suffered this type of injury, but no clinical solution is available for improving the recovery of skilled arm movements. Electrical neuromodulation therapies of the spinal cord have enhanced lower limb function in numerous preclinical models, from rodents to primates, as well as a number of clinical case studies. Despite this success, and the high priority of improved upper limb function for the SCI patient community, efforts to translate this promising technique to the cervical spinal cord and upper limbs have so far been limited. Given the complex patterns of muscle activation required for the execution of skilled arm movements, adaptation of epidural electrical stimulation (EES) to the cervical spinal cord necessitates a thorough understanding of the functional specificity that can be achieved using this technique, as well as the neuronal circuitry that underlies its effect. Here we present functional and anatomical data indicating that lateralised epidural stimulation of the rodent cervical spinal cord effectively targets specific upper limb motor pools, dependent on the rostrocaudal location of the stimulation site. Further to this, we have assessed how the specificity and efficacy of this stimulation is

affected following a clinically relevant cervical contusion injury. To gain a greater understanding of key neuronal circuitry we have utilised targeted pharmacological and chemogenetic manipulations in transgenic rats, allowing us to demonstrate the pivotal role of proprioceptive feedback circuits in the generation and modulation of motor responses during cervical EES. Taken together, these results establish a conceptual framework for the design and optimisation of targeted cervical implants to facilitate upper limb movements after spinal cord injury.

Disclosures: N.D. James: None. **S. Odouard:** None. **B. Barra:** None. **N. Greiner:** None. **N. Cho:** None. **M. Capogrosso:** None. **G. Courtine:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.01/V16

Topic: C.11. Spinal Cord Injury and Plasticity

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Craig H. Neilsen Foundation Grant 338132

Title: Anatomical asymmetries in the injured human spinal cord

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Abstract: Most injuries to the human spinal cord results in bilateral damage. The aim of our study was to assess to which extent both sides of the spinal cord are affected after injury using the Human Spinal Cord Injury Tissue Bank at The Miami Project to Cure Paralysis at the University of Miami. Spinal cords were removed from donors and fixed in paraformaldehyde. The injured segments were dissected out, embedded in paraffin, and cut on a microtome in 8 um thick transverse or sagittal section. The sections were stained with hematoxylin and Eosin (H&E) to recognize cells or H&E combined with luxol fast blue (LFB) to recognize cells and myelin. The cytoarchitecture of the damaged tissue was evaluated under the light microscopy. We found that the degree of damage as well as the location of the injured tissue was largely variable between specimens. In all cases, the damage to white and grey matter was asymmetric. We observed pronounced asymmetric presence of cells resembling Schwann cells, indicating that Schwannoma formation showed signs of asymmetries after injury. In most cases, some white matter was spared at the periphery of the spinal cord indicating continuity between the segments

rostral and caudal to the injured area. Our observations indicate that white and grey matter undergo bilateral asymmetric changes regardless of the extent of the injury, supporting the view that most spinal cord injuries in humans are asymmetric and anatomically incomplete.

Disclosures: Y. Lei: None. **M. Oudega:** None. **M.A. Perez:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.02/W1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Swedish Science Research Council Grant K2014-62X-12190-19-5

Title: Contralesional hindlimb motor response induced by unilateral brain injury: Evidence for extra spinal mechanism

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Abstract: BACKGROUND. The neurological dogma states that motor deficits secondary to traumatic brain injury and stroke arise due to the aberrant activity of neural pathways descending from injured brain to the spinal cord. We tested this dogma by analyzing hindlimb motor response to unilateral brain injury in the rats with completely transected spinal cord. METHODS. The spinal cord was first transected at T2/T3 levels, and then the cortical hindlimb representation area was unilaterally ablated. Motor outputs were analyzed under pentobarbital anesthesia during 3-4 hours. Formation of hindlimb postural asymmetry was assessed as differences between the contra- and ipsilesional legs in *a*) their position; *b*) hip, knee and ankle joint angles, and *c*) stretch forces. The nociceptive withdrawal reflexes, quantified as EMG responses evoked by electrical stimulation of digits and heel, were compared between the ipsi- and contralesional hindlimb muscles. Expression of plastic genes was analyzed in the lumbar spinal cord, i.e. below the transection level by qRT-PCR. RESULTS. Behavioral, electrophysiological and molecular evidence demonstrated the development of the contralesional-side specific response to the unilateral brain injury. The spinal rats, which then received cortical ablation but not sham operation, developed asymmetric hindlimb posture with flexion of the contralesional leg. The hindlimb withdrawal reflexes of the flexor muscles (the extensor digitorum longus and

semitendinosus) were enhanced on the contralesional side while extensor muscle (the interosseous) on the ipsilesional side. Unilateral cortical ablation in spinal rats produced robust changes in the expression of neuroplastic genes in the lumbar spinal cord. mRNA levels were elevated on either the ipsilesional (*c-Fos*) or contralesional (*TGF-beta*) side resulting in the asymmetric expression patterns, or bilaterally (*Gap43*). Unilateral brain injury failed to induce postural asymmetry in the hypophysectomized spinal rats. CONCLUSIONS. These results demonstrate that, in parallel with neural pathways, signals elicited by injured brain are transmitted to the lumbar spinal cord by alternative, likely endocrine mechanism. Spinal plastic and hindlimb motor responses induced by these signals are side specific.

Disclosures: L. Carvalho: None. **H. Watanabe:** None. **M. Zhang:** None. **D. Sarkisyan:** None. **O. Kononenko:** None. **I. Bazov:** None. **T. Iakovleva:** None. **J. Schouenborg:** None. **N. Lukoyanov:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.03/W2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life (WFL-UK-008/15)
European Union (Operational Programme Research, Development and Education) in the framework of the project "Centre of Reconstructive Neuroscience" (CZ.02.1.01/0.0./0.0/15_003/0000419)

Title: Enhancement of plasticity for functional recovery after spinal cord injury

Authors: *S. F. IRVINE[1], S. GIGOUT[1], P. M. WARREN[1,2], J. C. F. KWOK[1,3]
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Abstract: To promote recovery after spinal cord injury (SCI), treatments aim to enhance regeneration of severed axons and the plasticity of surviving circuitry. Enzymatic removal of perineuronal nets (PNNs), a plasticity brake in the adult central nervous system (CNS), using intrathecal chondroitinase ABC (ChABC) injections successfully enhances plasticity and functional recovery, particularly in SCI models. PNNs envelop neuronal sub-populations throughout the CNS providing stabilisation of circuitry and thus regulation of plasticity. Whilst ChABC has proven beneficial to recovery alongside other treatments including rehabilitation, there are significant hurdles in regards to clinical application. This study aims to investigate an

alternative method of PNN removal via non-invasive systemic PNN inhibition (PNNi) in combination with rehabilitation and its efficacy to enhance motor recovery after acute SCI. Firstly, as much of the PNN-associated neuronal populations are still relatively unknown in the spinal cord, we characterised normal PNN expression in the ventral motor pools using immunohistochemistry alongside specific motoneurone (Mn) markers. Compared to the acclaimed universal PNN marker *Wisteria floribunda* agglutinin lectin, the major PNN component aggrecan denoted significantly more PNNs around Mns. Selective Mn labelling revealed that PNNs encircled ~90% of alpha Mns, likely reflecting the population involved in the above mentioned motor recovery after SCI. To test the therapeutic efficacy of PNNi, adult female Lister Hooded rats received a moderate contusion to the T9 spinal cord and were assigned to treatment groups receiving PNNi or vehicle, with or without combination of rehabilitative treadmill training. Recovery was assessed using behavioural tests such as open field test hindlimb tests (BBB), horizontal ladder and von Frey assay. Preliminary results suggest that the systemic PNNi predominantly removes PNNs from the spinal cord, rather than the brain. Hindlimb motor functions were improved following rehabilitation. However, systemic plasticity enhancement seems to affect the forelimb function. Current experiments focus on defining the therapeutic window for optimal plasticity. Our data suggests that chronic PNNi application may provide a non-invasive strategy to enhance plasticity and regeneration after SCI.

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Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.04/W3

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Self-tracing human neural stem cells to map transplant integration

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Abstract: In North America alone, spinal cord injury (SCI) leaves more than 1 million patients with life-long sensory, motor, and autonomic deficits. Stem cell therapies offer an attractive approach to repairing and regenerating the injured spinal cord. While previous studies have shown that human induced pluripotent stem cell-derived neural stem cells (hiPSC-NSCs) can improve locomotion, few have been able to demonstrate graft-host integration. Viral and non-viral tracing methods have been used to map neural circuits; however, they often require additional invasive procedures and tracing may not overlap with grafted cells. Furthermore, viral tracing causes neurotoxicity; therefore, long-term tract tracing is not feasible. To overcome these

challenges, we aimed to engineer hiPSC-NSCs to express both antero- and retrograde trans-synaptic tracers to map transplant integration. A bicistronic vector encoding ANTERO-mCherry and GFP-RETRO was non-virally integrated into hiPSC-NSCs and sorted into monoclonal lines. The resultant self-tracing NSCs were characterized for self-renewal and proliferation potential by neurosphere assay, and pluripotency by immunocytochemistry of neuroglial markers following in vitro differentiation. Neurons derived from self-tracing NSCs were co-cultured with wild-type neurons and monitored under fluorescent microscopy to assess the extent of tracing. Functional connectivity of traced neurons will be determined by patch clamp recording. To assess tracing in vivo, T-cell deficient rats with a chronic C6/7 SCI were randomized to receive (1) self-tracing NSCs, or (2) GFP-hiPSC-NSCs followed by viral tracing. NSCs retained typical hiPSC-NSC properties and they traced synaptic connections more precisely than conventional techniques. This work provides exciting proof-on-concept data demonstrating how self-tracing NSCs can be used as a tool to delineate synaptically integrated sensorimotor pathways involved in stem-cell mediated recovery.

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Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

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Program #/Poster #: 298.05/W4

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2018RIA2AIA05020292
2014M3A9B6034224

Title: Molecular determinants of macrophages with a proregenerative phenotype supporting axonal growth

Authors: *E. KIM
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Abstract: Although intrinsic capacity of CNS axon regeneration is highly limited, injuries to the peripheral nerves frequently result in successful axon regeneration. We have previously shown that macrophage activation in the dorsal root ganglia (DRGs) following peripheral nerve injury contributes to the enhanced axon regeneration capacity. We further demonstrated that neuron-macrophage interaction occurring in the DRGs is essential linking injury-triggered neuronal chemokine expression with the proregenerative macrophage activation. However, it is not known how activated macrophages, which we defined as regeneration-associated macrophages (RAMs), in turn contribute to the enhanced capacity of axon regeneration in DRG neurons. The present study sought to characterize molecular signatures of RAMs and to identify key signaling

pathways that drive the activation of the proregenerative phenotype in RAMs. To generate RAMs, we employed an in vitro neuron-macrophage interaction model where co-cultures of DRG neurons and peritoneal macrophages are treated with cAMP. In this model, conditioned medium of primed macrophages promotes robust neurite outgrowth. We performed transcriptomic profiling using RAMs obtained in this co-culture paradigm. Ingenuity Pathway Analysis indicated that genes related to cancer and wound healing processes, which are known to increase in tumor-associated macrophages, were highly upregulated in RAMs. Furthermore, analysis of upstream transcriptional networks suggested that beta-catenin and Hif1-alpha could play a role in shaping the transcriptomic signatures. To verify the upregulated genes in an in vivo neuron-macrophage interaction setting, CX3CR1-GFP mice were utilized to isolate activated macrophages in DRGs following peripheral nerve injury using Fluorescence-Activating Cell Sorting (FACS). Ongoing experiments involving analysis of the FACS-isolated macrophages with immunohistochemistry and real time PCR will characterize the molecular determinants of RAMs promoting capacity of axon regeneration in vivo.

Disclosures: E. Kim: None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.06/W5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH 17323

Title: Subtle changes in intrinsic properties of V1 and V0c interneurons after spinal cord injury

Authors: *K. M. LETT, B. R. JOHNSON, R. M. HARRIS-WARRICK
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Abstract: Spinal cord injury (SCI) causes a loss of descending and modulatory inputs to spinal locomotor networks; this deafferentation could cause changes in the intrinsic firing properties of network neurons. Spinal interneurons (INs) are critical in shaping patterned locomotor output, but little is known about changes in their electrophysiological properties after SCI and more importantly, their possible role in spasticity. Using perforated patch recording and a mouse SCI model, we explored the effects of SCI on the intrinsic properties and excitability of lumbar V1 and V0c INs. We previously reported that after SCI, the V1 INs show a slight increase in bistability marked by a significant negative hysteresis during ramp current injections, while the V0c INs did not show any change in bistable behavior. In this study, we explore other firing properties of these neurons after SCI. Both IN types showed a mix of tonic or phasic behavior during current steps: the percentage of tonic and phasic INs was unchanged after SCI. We

measured excitability using increasing current steps and f/I plots: for both IN types there was no significant change in excitability (measured either as initial instantaneous spike frequency or average frequency during the step) after SCI. There was also no significant change in input resistance or rheobase in both IN types after SCI. Our previous studies in mice have also found no significant increase in the intrinsic excitability and bistability of lumbar spinal motoneuron excitability. Both V1 and V0c IN types have direct synaptic connections onto motoneurons. Our results show only subtle changes in the intrinsic properties of V1 and V0c INs after SCI, limited to a slight shift in persistent firing in V1 INs during ramp current injection. These results could have implications in identifying changes in locomotor circuitry driving lower limb spastic behavior after SCI. Supported by NIH grant NS17323 to RHW.

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Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS076589-01
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VA Grant I01RX000815
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Title: Long-term effects of spike-timing dependent plasticity in humans with severe paralysis due to spinal cord injury

Authors: *A. WILSON[1,2], H. JO[1,2], M. A. PEREZ[1,2]
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Abstract: A single session of repeated non-invasive stimulation using the principles of spike-timing dependent plasticity (STDP) improved voluntary motor output in hand muscles in humans with cervical spinal cord injury (SCI). Here, we examined the effects of repeated sessions of STDP on residual motor output and corticospinal excitability in proximal arm muscles in humans with high severe cervical SCI. During STDP, we used 180 pairs of stimuli where corticospinal volleys evoked by transcranial magnetic stimulation (TMS) over the shoulder representation of the primary motor cortex were timed to arrive at corticospinal-motoneuronal synapses of the bicep brachii or deltoid muscle ~1-2 ms before antidromic potentials were elicited in motoneurons by electrical stimulation of the brachial plexus. Participants were randomly

assigned to the stimulation (STDP+exercise) or sham (sham STDP+exercise) groups for 10 sessions in 2-3 weeks, which were followed by an upper-limb exercise program for ~40 min. We found that the group of SCI participants that received STDP+exercise increased maximal voluntary contraction of the targeted muscle to a larger extent than the group that received sham STDP+exercise. The size of motor evoked potentials elicited by TMS in the biceps brachi or deltoid increased only in the group that received STDP+exercise. Our findings demonstrate that STDP-like changes at residual spinal synapses combined with exercise enhances voluntary motor output in proximal arm muscles in humans with severe paralysis representing a new strategy to potentiate its therapeutic effects.

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Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.08/W7

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Arm cycling increases corticospinal excitability of trunk muscles in spinal cord injured subjects

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Abstract: Impaired trunk motor control is seen in the majority of individuals with spinal cord injury (SCI) and this can severely compromise upper limb and locomotor function. Evidence has shown that increasing corticospinal drive to impaired muscles after SCI can improve motor function, leading to greater independence and improved performance of activities of daily living. We have shown that the excitability of corticospinal drive to muscles of the trunk is increased during voluntary contractions of the upper limb muscles in healthy subjects and, more recently, in some individuals with SCI. Whether arm exercise can increase corticospinal excitability of the impaired trunk muscles in SCI remains unknown and was hence the aim of this study. Subjects with incomplete SCI undertook unilateral arm cycling for 30 minutes in an upright seated position. Electromyographic (EMG) activity was recorded bilaterally from erector spinae (ES). Motor evoked potentials (MEPs) from ES were examined prior to (baseline) and 20 minutes into the arm cycling, and immediately and 5 minutes following the arm cycling using transcranial magnetic stimulation over the hotspot for contralateral ES. We found that ES MEPs were greater immediately (mean ± standard deviation: 138.72±58.74% MEP at baseline) and 5 minutes (131.62±44.70%) following the arm cycling compared with the baseline, whereas the ES MEPs

obtained at 20 minutes (123.74±44.10%) into the arm cycling did not differ from that at the baseline. This indicates that arm cycling for 30 minutes can increase the corticospinal drive to the trunk muscles in SCI. In addition, EMG activity of the ES was comparable across all time points, suggesting that the changes in ES MEPs are likely due to increases in the excitability of corticospinal projections to ES. Further, there was no difference in the change in ES MEPs between subjects who showed increases in ES MEPs during the arm contractions and those who did not. The changes in ES MEPs following the arm cycling did not relate to the level of injury. Our results demonstrate the potential of using arm exercise for increasing the excitability of the corticospinal drive to the trunk muscles after SCI. Whether arm cycling has therapeutic effects on improving trunk motor function following SCI remains to be investigated.

Disclosures: S. Chiou: None. **A. Gall:** None. **P.H. Strutton:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.09/W8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: PVA

Title: Cervical excitatory interneurons sustain breathing after spinal cord injury

Authors: *K. SATKUNENDRARAJAH[1], S. K. KARADIMAS[2], A. M. LALIBERTE[3], G. MONTANDON[5], M. FEHLINGS[4]
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Abstract: Traumatic cervical spinal cord injury (SCI) leads to significant ventilatory impairment. Non-traumatic SCI (ntSCI), in which the cervical spinal cord is progressively compressed over time, results in milder respiratory dysfunction despite the significant disruption of the cervical neural network. Using a mouse model of ntSCI, we found a significant loss of phrenic motoneurons (PMNs) that innervate the main inspiratory muscle, without severe respiratory insufficiency similar to what is observed in human ntSCI patients. Progressively increased Vglut2 positive boutons on the preserved PMNs indicates that despite the significant loss in the number of PMNs, respiratory motor output is maintained via compensatory and progressive increases in glutamatergic input onto preserved PMNs. While the PMNs were decreased there was an increase in the number of prephrenic cervical interneurons connected to the PMNs. To confirm the role of the cervical glutamatergic interneurons in promoting respiratory plasticity and preservation of ventilation in ntSCI we injected *AAV-FLEX*-

PSAML141F–GlyR-IRES-eGFP in the ventromedial area of C3-7 spinal levels of *Vglut2::cre* mice two weeks prior to the induction of ntSCI. Subsequently, PSEM mediated silencing of these neurons disrupted ventilation in ntSCI mice. Further, chemogentic stimulation of cervical glutamatergic neurons following SCI promoted diaphragmatic motor recovery. In conclusion, this study provides novel insights into respiratory plasticity that occur in the setting of ntSCI and a greater understanding of the neural control of breathing. Further, the data indicates that this neurons can be manipulated to promote respiratory recovery following traumatic SCI.

Disclosures: K. Satkunendrarajah: None. **S.K. Karadimas:** None. **A.M. Laliberte:** None. **G. Montandon:** None. **M. Fehlings:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.10/W9

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Cholinergic modulation of postnatal cell proliferation in the spinal cord

Authors: *N. ALTUWAIJRI, S. A. DEUCHARS
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Abstract: There are numerous ailments that ultimately lead to demyelination and neurodegeneration. Most commonly, spinal cord injury; during which loss of neurons and demyelination are followed by inflammation and cyst formation (Profyris et al., 2004) and the progressively debilitating form of demyelination; multiple sclerosis.
While current treatments aim to manage the symptoms and modifying the course of demyelination, a relatively new field investigates the spinal cord neurogenic niche to determine its overall neuroregenerative potential. The ependymal cells of the spinal cord are thought to be the neural stem/progenitor cells of this niche. Since ependymal cells respond to manipulation of nicotinic acetylcholine receptors (Corns et al., 2015); we aimed to investigate the effect of an acetylcholinesterase inhibitor on neural and glial cell proliferation and differentiation *in vivo* and *in vitro*.
Adult C57BL/6 -6 week old mice (N=4 experimental group, N=4 control) received daily i.p injections of *donepezil* (1mg/kg) or vehicle (0.1ml saline) along with the thymidine analogue 5-ethynyl-2'-deoxyuridine (EdU) (10mM) for 7 days. Spinal cord sections were treated for EdU detection then immunohistochemically analysed for astrocytic and oligodendrocytic differentiation using antibodies against S100β and PanQkI respectively. In the central canal of *donepezil* treated animals there were significantly lower (mean 2.56 ± SEM 0.311, N=4 animals, n=88 sections; P=0.002) numbers of EdU positive cells compared to control (mean 3.95 ± 0.36, N=4 animals, n= 75 sections). The differentiation of EdU positive cells into astrocytes but not

oligodendrocytes was modulated by *donepezil.* The positive control to this experiment was the hippocampus of each animal. The cholinergic modulatory effect of *donepezil* on the hippocampus was clearly discernable; significantly increasing proliferation in the dentate gyrus (P=0.0054).
The effects of *donepezil* were tested *in vitro* by the addition of (5μM) of *donepezil* and (1μM) EdU to 500 *μm* spinal cord slices and compared to a control group. The numbers of EdU positive cells around the central canal in *donepezil* treated slices were significantly lower (P=0.002, mean 3.95 ± 0.38 SEM, N=3, n=23) in comparison to control (mean 5.05 ± 1.57 SEM, N=3, n=17). Slices treated with cytisine (20 μM; a partial nicotinic acetylcholine receptor agonist had significantly lower (P=0.016, mean 1.1875 ± 0.22 SEM, N=3, n=16) numbers of EdU positive cells in the central canal compared to those in control. Thus it is clear that the identity and role of each receptor subtype needs to be elucidated in the spinal cord.

Disclosures: N. Altuwaijri: None. **S.A. Deuchars:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.11/W10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: the Edward Jekkal Muscular Dystrophy Association Fellowship (TB)
Craig H. Neilsen #338432(ML)
NIH Grant R01NS081112 (ML)

Title: Sleep-disordered breathing following experimental cervical spinal cord injury

Authors: *T. BEZDUDNAYA, A. OSHOBAJO, V. MARCHENKO, M. A. LANE
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Abstract: Sleep-disordered breathing (SDB) is a common deficit in patients with spinal cord injury (SCI). Clinical studies show that individuals with cervical SCI can develop symptoms of SDB within few weeks/months post-injury indicating SCI as an independent risk factor for this disorder. However, the anatomical and physiological underpinnings of SDB are not well defined. The goal of the current study was to determine sleep-related respiratory deficits following C2 cervical spinal cord hemisection (C2Hx) in adult female rats. C2Hx results in a unilateral interruption of bulbospinal inputs to phrenic motoneurons and immediate ipsilateral paralysis of the diaphragm - the main muscle of inspiration. Here, we monitored diaphragm activity, before and during 6 weeks post-injury in awake and sleeping rats. All animals were chronically implanted with bilateral diaphragm electromyogram (EMG) electrodes and recorded for at least 4 hours on a weekly basis. In addition, neck EMG and electrocorticogram activities were recorded

to identify different stages of sleep (awake, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep). Our data show spontaneous recovery of the ipsilateral hemidiaphragm within a few weeks post-injury. However, despite recovery seen in awake animals, the activity of the ipsilateral hemidiaphragm can be significantly attenuated and abolished in the course of NREM and REM sleep. Moreover, we observed an increased number of arousal events during sleep often accompanied by episodes of hyperexcitation on the injured side of the diaphragm. Overall, our data demonstrate that C2Hx leads to sleep-disordered diaphragm activity which can result in an intermittent decrease of tidal volume and oxygenation during sleep in adult rats.

Disclosures: T. Bezdudnaya: None. **A. Oshobajo:** None. **V. Marchenko:** None. **M.A. Lane:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.12/W11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: VAMC Merit Award
Craig H. Nielsen Foundation
NYS DOH SCIRB (PI VLA)
NYS DOH SCIRB (PI SAS)

Title: Combined administration of electro-magnetic stimulation (EMS) at spinal level and at leg muscles to modulate neurophysiological properties at spino-muscular circuitry in healthy and SCI humans

Authors: *V. L. ARVANIAN[1], H. A. PETROSYAN[1], A. TESFA[1], M. FAHMY[1], C. ZOU[2], S. SISTO[3]
[1]Res. Services, Norhtport VAMC, Northport, NY; [2]StonyBrook Univ., Stony Brook, NY; [3]Univ. of Buffalo, Buffalo, NY

Abstract: H-reflex is recognized as an important neurophysiology tool used in evaluation of spino-muscular circuitry. H-reflex is sensitive to conditions and activity. For example, H-reflex diminishes after several days in zero gravity and is modulated differently depending on muscle activity. Spinal cord injury (SCI) reportedly affects threshold intensity and frequency dependent depression (FDD) of H-reflex. We examined 4 healthy and 3 SCI participants; study was approved by the IRB and conducted in accordance with the Declaration of Helsinki. We measured soleus M-wave and H- reflex recruitment curves using peripheral tibial nerve stimulation after each following condition: (i) baseline, (ii) initial 25 min session of EMS over spinal L5 level (SEMS; 0.2 Hz frequency, 70% coil intensity), (iii) additional 15 min session of

SEMS, (iv) 15-min session of EMS at leg muscles. FDD of H-reflex (stim current was set to evoke 40% of H-max, using 0.2, 1, 2 and 5 Hz stim rate) was examined after taking baseline measures and then after end of muscle stimulation. Baseline measurements (prior SEMS]) revealed a less steep (flatter) rise phase and more prolonged plateau of the recruitment curve of H-reflex, as well as a lesser depression rate of FDD in SCI vs healthy participants. In both healthy and SCI subjects, 1st application of SEMS for 25mins induced substantial facilitation of both M-response and H-reflex; this associated with a significant leftward shift of the recruitment curves for M- and H-responses and a marked decrease in the threshold currents to evoke H- and M-responses. 2nd follow-up application of SEMS for 15 min did not induce further changes, thus indicating that effects of SEMS reached its maximum after initial 1st 25 min of SEMS. However, EMS application over leg muscles induced further facilitation of M-wave and H-response. These results suggest that EMS over spinal level and leg muscles exert their effects on H-reflex through different mechanisms. Results also revealed improvement of FDD rate following SEMS/leg stimulation in SCI participants. Importantly, one SCI participant was engaged in 20 min exercise training sessions (NUSTEP exercise machine) after completion of SEMS/leg stimulation protocols; after 5 sessions the subject, who is 12 years post SCI, reported an increase in sensation and function for the first time. It is important to note that this subject had been performing similar exercise on a regular basis prior to this study without functional changes. Results suggest that spinal/leg EMS stimulation combined with exercise may be a potential approach in clinics for a variety of spinal or peripheral nerve conditions.

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Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.13/W12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Department of Veteran Affairs Center Grant B9253-C
Paralyzed Veterans of America

Title: Viral-mediated gene therapy targeting Rac1 alleviates spasticity after SCI

Authors: *C. BENSON[1,2], M. HILL[1,2], S. LIU[1,2], L. AKIN[1,2], S. G. WAXMAN[1,2], A. M. TAN[2,1]
[1]Neurol., Yale Univ., New Haven, CT; [2]Ctr. for Neurosci. and Regeneration Research, VA Connecticut, West Haven, CT

Abstract: Spasticity is a significant complication associated with SCI, and is a clinical symptom of hyperexcitability within the spinal cord reflex system, e.g., H-reflex. Up to 90% of SCI patients, including US Veterans, experience clinically significant spasticity, which can negatively impact quality-of-life, e.g., hinder personal hygiene and intimate relationships. Spasticity can be incapacitating, triggered at any time by a variety of stimuli, and can exacerbate other SCI complications, e.g., pressure ulcers, infection. Poorly treated, spasticity often leads to permanent deformity and contractures (hardening of soft tissues in joints and muscle), which can be painful. A major hurdle facing novel therapeutic development for spasticity is the lack of mechanistic insight into the cellular and molecular factors that contribute to spinal reflex circuit pathology after injury. Maladaptive changes to motor reflex function after injury, e.g., SCI, TBI, or stroke, can lead to excessive H-reflex excitability associated with spasticity. Previous studies have demonstrated that changes to dendritic spines within the motor reflex circuit leads to loss of H-reflex rate-dependent depression (RDD), indicative of increased excitability. This hyperexcitability can occur from an increase in spine density, a redistribution of spines to regions closer to the cell body, and an increase in spine head surface area on alpha-motor neurons. Over the past decade, we have gathered considerable evidence that supports two core premises for our proposal: 1) the Rac1-Pak1 signaling pathway contributes to spasticity, and 2) dendritic spine dysgenesis serves as a morphological correlate that predicts spasticity and drug response. The overall objective of this study is to deconstruct the mechanisms underlying spasticity at the circuit-level and provide novel opportunities for developing more effective and safe treatments for spasticity after SCI. Here, we hypothesize that using a gene therapy that disrupts Rac1 function will reduce the formation abnormal dendritic spines and restore normal RDD and spasticity after SCI. To test this hypothesis, we delivered an adeno-associated virus (AAV) 2/9-cre intramuscularly into the soleus muscle group of the left hind limb of Rac1 floxed mice. This delivery method specifically infects alpha-motor neurons comprising the monosynaptic spinal stretch reflex (e.g., H-reflex). Cre-expression in these neurons selectively ablates Rac1 expression. As expected, we observed that viral-mediated knockout of Rac1 normalizes RDD compared to control animals in EMG recording, demonstrating a reduction in H-reflex hyperexcitability.

Disclosures: C. Benson: None. **M. Hill:** None. **S. Liu:** None. **L. Akin:** None. **S.G. Waxman:** None. **A.M. Tan:** None.

Poster

298. Spinal Cord Injury and Plasticity: Neurophysiology I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 298.14/W13

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Edonerpic maleate boosts motor function recovery from spinal cord injury

Authors: *M. SATO[1], S. JITSUKI[1], H. MASUYAMA[2], H. MURATA[1], T. YAMAMOTO[1], T. TAKAHASHI[1]
[1]Yokohama City Univ., Yokohama-Shi, Japan; [2]Toyama Chem. Co., Tokyo, Japan

Abstract: Spinal cord injury (SCI) is a miserable neurological condition that often causes permanent sensory, motor, and bladder-bowel dysfunction. Despite the needs of treatments, clinical options for treatments is limited. Neuronal plasticity is a mechanism underlying the recovery process of motor function after the injury of central nervous systems, and the experience-dependent synaptic AMPA (α-amino-3-hydoroxy-5methyl-4-isoxazole-propionic-acid) receptor (AMPAR) delivery is a molecular and cellular mechanism of neural plasticity. We recently found that a small compound, edonerpic maleate (also known as T-817MA), facilitated experience-driven synaptic glutamate AMPA receptor delivery and resulted in the acceleration of motor function recovery after brain damage in mice and monkeys in a training-dependent manner (Abe et al. Science 2018). Here, we report that edonerpic maleate also facilitates the motor function recovery after spinal cord injury in rats.

Disclosures: **M. Sato:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Toyama Chemical Co., Tokyo, 160-0023, Japan. **S. Jitsuki:** None. **H. Masuyama:** None. **H. Murata:** None. **T. Yamamoto:** None. **T. Takahashi:** None.

Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.01/W14

Topic: D.03. Somatosensation: Pain

Support: Instituto de Salud Carlos III: FIS PI14/00141, FIS PI1700296, RETIC RD16/0008/0014
Generalitat de Catalunya: 2017SGR737
MINECO: BFU2017-83317-P

Title: TRESK background K^+ channel regulates sensory neuron excitability and contributes to mechanical and cold pain

Authors: A. CASTELLANOS[1,2,3], A. ANDRES-BILBE[1,2,3], A. NEGM[4,5], G. CALLEJO[1], N. COMES[1,2,3], D. SOTO[1,2,3], A. GUAL[1,2,3], J. NOËL[4,5], *X. GASULL[1,2,3]
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Abstract: TRESK (K2P18.1) is a background K^+ channel highly expressed in spinal cord, dorsal root and trigeminal ganglia sensory neurons, where it has been involved in modulating sensory neuron excitability and firing. Changes in channel expression and function have been reported to enhance nociceptor excitability after injury or inflammation. To determine the role of TRESK in sensory transduction, we first compared the excitability and membrane properties of small/medium-sized sensory neurons in whole cell patch clamp recordings of cultured DRG neurons from wild type and TRESK knockout mice, which presented a reduced action potential threshold, increased membrane resistance and enhanced repetitive firing upon depolarization. Recordings of skin nociceptive fibers showed strong activation in response to cold in the absence of TRESK channel. In agreement, behavioral experiments in TRESK ko mice revealed a decreased mechanical threshold to von Frey hairs and an enhanced cold sensitivity. No significant changes were found for thermal sensitivity to warm or hot temperatures. Nocifensive behavior after capsaicin injection was unaltered while the response to AITC was slightly diminished. Interestingly, TRESK ko mice presented a reduced response to hypertonic and hypotonic stimuli even after sensitization with PGE_2. During inflammation, ko mice showed a decreased phase I response in the formalin test, while phase II was unaltered. In the CFA-induced inflammatory model, both mechanical and thermal sensitivity were enhanced compared to wt animals. Mechanical and thermal hyperalgesia were also enhanced in the sciatic nerve cuffing model of neuropathic pain. Finally, the oxaliplatin-induced cold sensitization was absent in ko mice, probably due to the already enhanced cold sensitivity. In summary, our results indicate that TRESK has a significant contribution regulating the excitability of certain populations of sensory neurons mainly involved in mechanical and cold pain sensing. Moreover, a down-regulation of its expression as occurs after nerve injury might contribute to the generation of the hyperalgesia and allodynia observed during chronic pain.

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Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.02/W15

Topic: D.03. Somatosensation: Pain

Support: DFG Grant RE 704/2-1
DFG Grant SFB1158(TP-A04)

Title: Sodium channel $Na_v1.9$ enables ongoing activity in single mouse C-fibres during zero extracellular potassium

Authors: C. WEIDNER[1], T. HOFFMANN[2], K. KISTNER[2], J. PAKALNISKIS[3], R. DE COL[2], K. MESSLINGER[2], M. A. NASSAR[5], P. W. REEH[2], *R. W. CARR[4]
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Abstract: Bouts of spontaneous pain associated with chronic pain are attributed to aberrant action potential activity in primary somatosensory neurons. To explore the mechanistic underpinnings of spontaneous activity animal models have been developed to mimic neuropathic and inflammatory pain states. Dependent upon the prevailing injury this leads to differential regulation of signaling proteins and their transcription. To circumvent this heterogeneity we developed an experimental paradigm for the reversible induction of sustained burst activity in single cutaneous C-fibres using nominally zero extracellular potassium. Low extracellular potassium induced sustained firing in 83% (19 of 23) naive C-fibres in mice. The ongoing discharge was bursting in character comprising bursts of 26±6.5 action potentials at 11.6±15.4 Hz separated by interburst periods of 62.5±167s. Ongoing firing began within tens of minutes (23±6.1 minutes) and persisted throughout the period of exposure to zero potassium for up to 6 hours. Ongoing C-fibre activity subsided upon re-establishment of the extracellular potassium concentration at 3.5mM without lingering effects on heat and mechanical thresholds. Induction of ongoing activity was dependent upon the voltage-gated sodium channel $Na_v1.9$. None of five C-fibres tested from $Na_v1.9$ -/- mice developed ongoing activity during exposure to zero potassium for periods of up to 2 hours. In C-fibres from wild type animals, blockade of hyperpolarization-activated cyclic-nucleotide gated (HCN) channels with ZD7288 (10-30 μM) reduced burst incidence and the number of action potentials in each burst. The data highlight $Na_v1.9$ and HCN as instrumental for the induction of ongoing activity in unmyelinated axons.

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Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.03/W16

Topic: D.03. Somatosensation: Pain

Support: MRC grant

Title: Mapping the functional expression profile of Kv7 channels in somatosensory neurons of different sensory modalities

Authors: *F. P. JONES, N. GAMPER
Univ. of Leeds, Leeds, United Kingdom

Abstract: Voltage dependant potassium (K+) channels (Kv) are important in controlling excitability and repolarising neurons after depolarisation has occurred. One subset of these channels is the Kv7 family, which is composed of Kv7.1-7.5 subunits as homo- or heteromers. Kv7 channels are promising targets for treating excitability disorders, including epilepsy and pain, as they are active at negative voltages, thus clamping the resting potential and reduce the excitability of the neuron. Kv7 channels are expressed in many excitable cells, including neurons and muscle cells, though subunit differences exist in different tissues. Therefore, identifying the expression pattern of Kv7 subunits in different cell types will aid development of more targeted therapeutic strategies. Here we used we used immunofluorescent techniques and electrophysiology to identify Kv7 expression profile within rat peripheral somatosensory system, which is responsible for detection and transmission of somatic and visceral stimuli, including these resulting in pain and itch sensations. To this end, rat dorsal root ganglia (DRGs) were co-labelled with antibodies against Kv7.1 - Kv7.5 and modality-specific markers (NF200 for A fibres, Peripherin for C fibres). Kv7.1 showed very limited expression in the DRG (4%±1.5 of total neurons), whereas 85% and 80% of Peripherin positive neurons were Kv7.2 positive and Kv7.3 positive respectively, suggesting that the majority of small diameter neurons are Kv7.2 and/or Kv7.3 positive. Kv7.3 is also expressed in around 50% of NF200 positive neurons. Kv7.5 was expressed in around 60% of NF200 positive neurons and a similar number of Peripherin positive neurons, suggesting that Kv7.5 is similarly distributed between large, medium and small diameter neurons. This data was supported by recording of Kv7 current (M-current) in capsaicin responsive (presumed nociceptive) DRG neurons in the presence of Kv7.2/7.3 heteromer selective agonist, ICA-27243. ICA-27243 increased outward current at -20mV by 67%±6.8 ($p<0.05$ $n=6$) compared to baseline; non-selective Kv7 channel agonist retigabine, when applied after ICA-27243, produced no further current augmentation (while being as efficacious as ICA-2743, when applied alone). Outward current was also reduced by application of Kv7 channel antagonist. In sum, Kv7.2 and 7.3 are predominant Kv7 subunits expressed in small-diameter DRG neurons, these subunits are also responsible for the majority of M current in these cells. Kv7.5 is also expressed in subpopulations of small, medium and large diameter neurons.

Disclosures: F.P. Jones: None. **N. Gamper:** None.

Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.04/W17

Topic: D.03. Somatosensation: Pain

Title: Examination of the role of Nav1.7 and Nav1.8 in the generation of action potentials both in-vivo and in-vitro

Authors: L. H. DENG[1], V. JOSEPH[2], K. L. STARK[1], S. LARDELL[3], R. WEIMER[2], P. KARILA[3], *D. H. HACKOS[1]
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Abstract: Aim of investigation: Loss-of-function mutations in Nav1.7 lead to complete insensitivity to pain (CIP) in humans and a CIP-like phenotype in Nav1.7 KO mice. On the other hand, CIP patients have not been identified with loss-of-function mutations in Nav1.8 and Nav1.8 KO mice show a minimal pain phenotype, suggesting that Nav1.8 plays little if any role in sensory neuron action potential generation or propagation in vivo. Using laser speckle imaging, we established an in vivo assay sensitive to peripheral action potential generation, allowing us to examine the role that Nav1.7 and Nav1.8 play in action potential generation under resting and inflammatory conditions.
Methods: Laser speckle imaging allows real-time detection of blood flow in the glabrous skin of the mouse hind-paw. In this method, AITC (mustard oil) is applied to the skin, which activates TRPA1 channels, allowing calcium influx and depolarization of sensory fibers. Such depolarization is sufficient to generate action potentials, allowing opening of voltage-gated calcium channels that allows more calcium influx, which results in release of peptide neurotransmitters and increased blood flow. Recordings of DRG excitability (using electrophysiology and calcium influx) were also used to examine the interplay between Nav1.7 and Nav1.8 channels in cultured sensory neurons under different conditions.
Results: We observed that AITC-induced increase in blood flow in the mouse hind-paw is dependent on TRPA1 as expected (since AITC is a direct activator of TRPA1 channels). We further observed that the action potential component of this response is Nav1.7-dependent but not dependent on Nav1.8. Recordings of DRG neurons in culture show that the dependence on Nav1.7 vs Nav1.8 can be modified depending on the condition of the experiment (resting membrane voltage and inflammation state).
Conclusions: Here we demonstrate a novel assay that allows indirect examination of action potential generation within the peripheral sensory fibers in the skin. We use this assay to determine the role that Nav1.7 and Nav1.8 play in this process and demonstrate that action potential generation is fully dependent on Nav1.7.
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Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.05/W18

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01NS100788
NIH Grant R01GM102575
NIH Grant R01NS065926

Title: The landscape of nascent protein synthesis in the DRG at single codon resolution

Authors: *P. BARRAGAN-IGLESIAS[1], T.-F. LOU[2], J. B. DE LA PEÑA[2], A. WANGZHOU[1], B. J. BLACK[3], S. MEGAT[1], J. K. MOY[1], P. RAY[1], J. J. PANCRAZIO[3], T. J. PRICE[1], Z. T. CAMPBELL[2]
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Abstract: Pro-inflammatory cytokines are harbingers of persistent pain. As a model for probing their effects on nociceptors, we focus on NGF and IL-6. Together, they trigger a rapid induction of cap-dependent translation and promote long-lasting changes in nociceptor plasticity. Accompanying behavioral changes require *de novo* protein synthesis but not transcription. To identify the targets of regulated protein synthesis in cultured dorsal root ganglion (DRGs), we applied the method of translational profiling by ribosome footprinting. This approach yields a global snapshot of ribosomes poised over mRNA fragments at a specific moment in time. We use footprinting to identify the action of NGF and IL-6 on nascent protein synthesis after only 20 minutes. The data provide a comprehensive view of the substantial changes in translation that are induced by these cytokines. From the dataset, we identify motifs which confer preferential translation in response to NGF and IL-6 treatment. We provide evidence for S6 driven translation of immediate early genes following cytokine treatment. Additionally, conserved segments present in 5'UTRs corresponding to key players in sensory detection and nociception, including CGRP and EGR2, are selectively translated. These upstream open reading frames, termed uORFs, do not appear to require the integrated stress response. Peptides derived from CGRP and EGR2 uORFs produce mechanical hyperalgesia when injected into the paw. We propose that non-canonical translation provides a vast and unanticipated potential source of endogenous signaling peptides that may contribute to nociceptor plasticity in response to inflammatory mediators.

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Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.06/X1

Topic: D.03. Somatosensation: Pain

Support: JP25351001
2015-PM11-23-01

Title: Nociceptive stimuli suppress reactions of somatosensory stimuli regardless the location

Authors: *N. TAKEUCHI
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Abstract: The sensory repetition suppression, refers to the attenuation of neural activity in response to a second stimulus and plays a pivotal role in inhibition of redundant sensory inputs. Using magnetoencephalography (MEG) recordings, we examined the somatosensory suppression induced by preceding several types of sensory stimuli. Thirteen healthy volunteers participated in this study which was approved in advance by the Ethics Committee of the National Institute of Physiological Sciences, Japan and written consent was obtained from all participants. As the Test stimuli, the intensity of somatosensory stimulus abruptly increased at 1200 ms from onset of somatosensory stimulus lasting 1500 ms and were applied to the dorsum of the left hand. Three types of prepulse stimulus, i.e., auditory stimulus, nociceptive stimulus (using IES: intra-epidermal electrical stimulation) and somatosensory stimulus applying to the dorsum of the right foot were inserted before 600 ms from onset Test stimulus. That is, there were four stimulus conditions: (1) Test alone, (2) Test + auditory stimulus, (3) Test + somatosensory stimulus, (4) Test + nociceptive stimulus. The results showed the amplitude of Test stimuli in each condition were significantly smaller for (3) and (4) conditions in contralateral and ipsilateral SII compared to Test alone. While there were no significant amplitude change for all condition in cSI. Auditory prepulse stimulus condition did not affect the somatosensory suppression in cSI, cSII and iSII. These findings suggested the somatosensory suppression was observed by other sensory stimulus, such as nociception and even though conditioning stimulating body part was far from test stimulating part.

Disclosures: N. Takeuchi: None.

Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.07/X2

Topic: D.03. Somatosensation: Pain

Title: Influence of repeated mechanical stimuli on pain threshold of nociceptor

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Abstract: It is well known that pain receptor is tonic or slowly adapting and it is generally thought that pain receptor is non-adapting type. There is little report about pain sensory and adaptation mechanism of Aδ fiber, and it is not clear of pain sensory mechanism of Aδ fiber. This study focused on the adaptation of pain sensory by measuring the influence of repeated mechanical pain stimuli on pain thresholds. The algometer used in the experiments measured pressure in units of 1g and in the range of 1g-10g. A total of 16 participants took part in this study (ranging from 20 to 22 years; 8 males and 8 females). The author asked the participants that they took their meal more than 2 hours before experiments. The experiments were conducted from 2:00pm-4:00pm at room temperature (24°C). In the experiments participant sat down on a chair and closed eyes. All experiments were done at intervals more than one week. The participant was pricked with the pressure algometer at the same point of right forearm medial cutis. Control was the average of pressure pain thresholds (PPTs) measured 3 times at the same point. After the measurement of control, the participant was stimulated at the same point 15 times every 5 seconds successively, and measured a change of PPTs. In the experiments at 5-second intervals, PPTs significantly increased. PPTs were also measured at 7, 10, 12, 15, 20 and 30-second intervals. In the experiments of more than 7-second intervals PPTs increased in the 2nd and the 3rd stimulus after control, but hardly increased after the 4th stimulus PPTs. In addition, PPTs were further measured by the similar method 1 hour, 4 hours and 24 hours after the first experiments. Then the control was measured in all cases and PPTs were measured by the similar method at the same point of the participant. PTTs of the 6th and the 12th stimulus increased 1hour later and 4 hours later, compared with the first experiments. A tendency of decrease was seen in PTTs of the 6th and the 12th stimulus 24 hours later. These results showed that repeated mechanical stimuli at short time intervals increased PPTs. It was suggested that Aδ fiber was adapted by the repeated mechanical stimuli at short time intervals.

Disclosures: S. Nagahama: None.

Poster

299. Nociceptors

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Topic: D.03. Somatosensation: Pain

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Title: Interferon gamma acutely evokes action potential discharge from vagal c-fibers in mouse lungs

Authors: *M. J. PATIL[1], M. KOLLARIK[2], F. RU[3], B. J. UNDEM[4]
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Abstract: Aim of Investigation: The inflammation associated with airway inflammatory diseases (e.g. asthma COPD, bronchitis, pulmonary fibrosis) can activate vagal airway C-fibers leading to negative symptoms including reflex bronchoconstriction and mucus secretion that can threaten lung function, as well as sensations of dyspnea and urge-to-cough. Type 1 and type 2 interferons are elevated in respiratory viral infections and inflammatory airway diseases. The vast majority of research attention on the role of interferons in the lungs, and elsewhere, has focused on their ability to orchestrate anti-viral defenses and other immunological responses. We previously noted that receptors for both type 1 and type 2 interferons are richly expressed by vagal C-fiber neurons (PLoS One. 2017 Oct 5;12). Here, we show that interferon γ acutely activates airway vagal C-fibers.**Methods:** We used low input RNA sequencing of nodose neurons retrogradely labeled from the lungs to detect the presence of Interferon receptors in presumed capsaicin-sensitive airway afferent C-fibers. To study action potential discharge from C-fiber terminals we isolated the lungs, vagus nerve, along with vagal ganglia from Pirt-cre/GCamp6s mice. The ganglion was positioned beneath a 2-Photon microscope that assessed the elevation in calcium that were caused by action potentials that were conducted from the terminals in the lungs to cell bodies in the nodose ganglion. This allowed us to monitor the activity of hundreds of vagal ganglion neurons in response to interferon γ infused specifically into the trachea/lung compartment.**Results:** The interferon γ receptors (ifngr1 and ifngr2) were richly expressed in airway-specific TRPV1-positive nodose neurons. In our 2 Photon imaging of the nodose ganglion we found that within only a few minutes of exposing the trachea/lungs to Interferon γ action potentials were discharged from more than 70% of capsaicin-sensitive C-fibers (n=4 experiments). **Conclusions:** This study supports the hypothesis that interferon γ, in addition to playing key roles in orchestrating the immune response by regulating chemokine and cytokine gene expression in immune cells, can also more acutely recruit the nervous system by

activating visceral sensory nociceptors. If dysregulated this may contribute to the nocifensive reflexes and symptoms of visceral inflammatory diseases.

Disclosures: M.J. Patil: None. **M. Kollarik:** None. **F. Ru:** None. **B.J. Undem:** None.

Poster

299. Nociceptors

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Program #/Poster #: 299.09/X4

Topic: D.03. Somatosensation: Pain

Title: Characterization of dental pulp innervation using transgenic reporter mice

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Abstract: Trigeminal ganglia (TG) neurons are heterogeneous and have been broadly classified, based on their degree of myelination and conduction velocity, into C, A**β,** and Aδfibers. Several elegant studies using indirect immunohistochemistry and electrophysiological recordings have demonstrated that dental pulp is mainly innervated with C- followed by Aδ- fibers. However, recent studies have demonstrated that TG neurons can be further classified into: peptidergic (CGRP+) and non-peptidergic C fibers (MrgprD+), low threshold mechanoreceptor (LTMR) Aδ(TrkB+) and LTMR Aβ(TrkC+) fibers, high threshold mechanoreceptor (HTMR) Aδand Aβfibers (Nav1.8+; CGRP-). We hypothesized that the dental pulp is primarily innervated by Aδand Aβfibers, including LTMR subclasses. To test this hypothesis, we employed transgenic reporter mice expressing either GFP or TdTomato under the promoter of either Nav1.8, CGRP, MrgprD, TrkB and TrkC. Mandibular en-bloc sections containing molars were harvested from genotyped mice (8-10 week old) for each reporter line (n=6), demineralized and processed for direct detection of immunofluorescence. Images were acquired using laser scanning microscopy with standardized settings from sequential slides from each sample. The greatest majority of fibers innervating the dental pulp are Aδand Aβfibers, including LTMR subclasses, not previously reported. These fibers innervate the most coronal aspects of the pulp and project extensions into the dentinal tubules. C-fibers are more apically positioned than Aβand Aδfibers. This is the first demonstration of the distribution of LTMR myelinated fibers in the dental pulp. The presence of these fibers, that are typically non-nociceptive, into dentinal tubules sheds light on the uniqueness of dental pulp innervation and neurophysiology and might have potential applications in vital pulp therapy.

Disclosures: O. Austah: None. **K. Metwalli:** None. **S. Ruparel:** None. **A.R. Diogenes:** None.

Poster

299. Nociceptors

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Program #/Poster #: 299.10/X5

Topic: D.03. Somatosensation: Pain

Support: DFG UE171/3-1

Title: Induced pluripotent stem cells generated from skin fibroblasts of a female patient with Fabry disease are susceptible to cell death during nociceptive differentiation

Authors: T. KLEIN[1], K. GÜNTHER[2], J. SCHLEGEL[2], F. EDENHOFER[2], M. SAUER[2], *N. ÜÇEYLER[1]
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Abstract: Background and Objective: Fabry disease (FD) is an X-linked lysosomal storage disorder that mainly affects the heart, kidneys, and the nervous system. Due to deficiency of the alpha-galactosidase A (GLA), the glycolipid globotriaosylceramide (Gb3) accumulates in cells, including human dermal fibroblasts (HDF). The major neurological symptom in FD is acral burning pain. The pathophysiology of pain in FD is unknown and research is hindered by the lack of suitable biomaterial. Using patient-derived HDF we generated induced pluripotent stem cells (iPSC) and differentiated peripheral neurons including nociceptors for further investigation of potential intracellular effects of Gb3 accumulations.
Methods: iPSC from a 25 year old female FD patient (FD-iPSC) carrying a missense mutation in *GLA* were generated and characterized using standard procedures. iPSC were differentiated into nociceptors following an established protocol. The gene expression of key markers was analyzed during the first ten days of differentiation and after seven weeks of maturation using quantitative real-time PCR (qRT-PCR). Gb3 load was investigated using Shiga toxin 1, subunit B conjugated with SeTau-647 (StxB-SeTau) for iPSC and neurons and bioorthogonal click chemistry for neurons. Cells were fixed and incubated with the labelled toxin, washed and analyzed. Click chemistry was performed on seven weeks matured neurons by incubation of the cells with 25 µM tetraacylated N-azidoacetylgalactosamine and subsequent incubation with DBCO-sulfo-Cy5. For comparison, a control-iPSC line was used generated from neonatal BJ HDF (Ctrl-iPSC).
Results: FD-iPSC showed typical embryonic stem cell-like morphology, gene expression, and a normal karyotype. The diagnosed heterozygous mutation of *GLA* was retained. Some FD-iPSC displayed Gb3 clusters, as detected by StxB-SeTau whereas Ctrl-iPSC had none. On day eight of differentiation, qRT-PCR revealed lower gene expression of key sensory markers like islet-1 ($p<0.001$), peripherin ($p<0.01$), transient receptor potential vanilloid 1 ($p<0.05$) compared to

Ctrl-iPSC. Gb3 signal continuously declined during the differentiation and was absent in neurons after seven weeks of maturation.
Conclusions: We successfully generated FD-iPSC with a Gb3 positive subpopulation. Altered gene expression of key markers during nociceptive differentiation in combination with declined neuronal Gb3 signal may point to enhanced apoptosis of affected cells e.g. via Gb3 associated enhanced cellular stress. Neuronal cell death *in vitro* might be caused by similar mechanisms as the loss of nerve fibers *in vivo*, associated with the small fiber pathology in FD.

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Poster

299. Nociceptors

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Topic: D.03. Somatosensation: Pain

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Title: DNA methylation as a regulator of nociceptive sensitization in Manduca sexta

Authors: *J. KIM[1], M. FUSE[2]
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Abstract: Nociception is the basic neural process that encodes threatening stimuli and is seen even in animals with primitive sensory systems. Activation of nociceptors in response to specific insults triggers the higher-order emotional and psychological perception of pain in organisms with more complex nervous systems. Organisms respond to harmful stimuli with defensive behaviors and maintain heightened behavioral responses, a form of non-associative learning known as nociceptive sensitization. While this behavioral plasticity has been observed across the animal kingdom, little is known about how conserved the molecular mechanisms underlying this response are, an understanding that is critical to improving pain treatments and pharmacological testing to target specific points in nociceptive pathways. DNA methylation (DNAm) has been shown in different species to be critical for memory formation and learning, including nociceptive sensitization in some instances. Using the tobacco hornworm, *Manduca sexta*, to study nociception offers a unique approach because its defensive striking response is well-characterized, and there exist standard *in vivo* and *in vitro* bioassays to directly assess nociceptive sensitization in *Manduca*. This study explores the hypothesis that DNAm is a critical regulator of nociceptive sensitization in *M. sexta*. We have identified putative DNAm genes from the available *Manduca* genome, and use a behavioral assay to determine changes in the threshold

force to elicit a defensive strike. We test individual animals by poking a proleg with von Frey filaments of increasing force before and after a strong pinch, using our established up-down protocol. After a pinch, animals become sensitized, where subsequent testing results in a strike threshold that is significantly lower than baseline. Preliminary results indicate that coupling the pinch with an injection of RG108, a DNAm inhibitor, counters or completely blocks the decrease in nociceptive threshold typically seen in sensitized animals. Thus, RG108 appears to have a direct effect on behavioral sensitivity to a harmful stimulus in *Manduca*. These results demonstrate that DNAm may regulate nociceptive sensitization in *M. sexta*. Methylation and bioinformatics analyses will corroborate findings on a molecular level and help identify genes that are differentially methylated during nociceptive sensitization.

Disclosures: J. Kim: None. **M. Fuse:** None.

Poster

299. Nociceptors

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Title: Effects of bupivacaine-encapsulated PLGA nanoparticles on the compressed dorsal root ganglion in mice

Authors: *T. WANG[1], J. TAO[1], F. LIU[1], Y. FANG[1], W. QIU[2], C. MA[3]
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Abstract: Bupivacaine is a commonly used local anesthetic in postoperative pain management. We evaluated the effects of a prolonged, local delivery of bupivacaine on pain behavior accompanying a chronic compression of the dorsal root ganglion (CCD). Poly(lactide-coglycolide) (PLGA) nanoparticles encapsulating bupivacaine were injected unilaterally into the L3 and L4 DRGs of mice just before producing CCD by implanting a stainless-steel rod in the intervertebral foramen of each ganglion. Behavioral sensitivity to punctate mechanical stimuli (Von Frey filaments) of different forces of indentation, delivered to each hind paw, was measured before and on subsequent days of testing after the CCD. Nanoparticles were spherical in morphology and 150±10 nm in diameter. Bupivacaine was steadily released as measured in

vitro over 35 days. A dye that was encapsulated in the nanoparticles was found in the intact DRG after 2 weeks. CCD alone or with injection of blank (control) nanoparticles produced a behavioral hypersensitivity to the punctate stimuli on the ipsilateral paw without affecting sensitivity on the contralateral, over a period of 7 - 14 days. The hypersensitivity was manifested as an increased incidence of paw-withdrawal to indentation forces normally below threshold (allodynia) and an increased shaking to a filament force that always elicited withdrawal prior to CCD (hyperalgesia). In contrast, nanoparticles with bupivacaine prevented any manifestation of allodynia or hyperalgesia on the ipsilateral hind paw while leaving normal nociceptive responses largely intact on both hind paws. We hypothesize that bupivacaine-loaded PLGA nanoparticles may prevent the occurrence of this neuronal hyperexcitability without reducing the nociceptive information normally conducted from the periphery to the central nervous system. The slow, sustained delivery of bupivacaine by nanoparticles may provide a means of preventing the occurrence of postoperative neuronal hyperexcitability that could develop into chronic neuropathic pain.

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Poster

299. Nociceptors

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Program #/Poster #: 299.13/X8

Topic: D.03. Somatosensation: Pain

Title: Dexmedetomidine inhibits voltage-gated sodium channels via α2-adrenoceptors in trigeminal ganglion neurons

Authors: *Y. KIM[1], S.-T. IM[2], S.-M. HWANG[3]
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Abstract: Dexmedetomidine, an α2-adrenoceptor agonist, is widely used as a sedative and analgesic agent in many clinical applications. However, little is known about the molecular mechanisms responsible for its analgesic properties in the trigeminal system. Two types of voltage-gated sodium channels, $Na_v1.7$ and $Na_v1.8$ as well as α2-adrenoceptors are expressed in primary sensory neurons of the trigeminal ganglion (TG). Using whole-cell patch-clamp recordings, we investigated the effects ofdexmedetomidine on voltage-gated sodium channel currents (I_{Na}) via α2-adrenoceptors in dissociated small-sized TG neurons. Dexmedetomidine caused a concentration-dependent inhibition of I_{Na} in small-sized TG neurons. The I_{Na} inhibition by dexmedetomidine was blocked by yohimbine, a competitive α2-adrenoceptor antagonist. Dexmedetomidine-induced inhibition of I_{Na} was mediated by G protein-coupled receptors

(GPCRs) since this effect was blocked by intracellular perfusion with the G protein inhibitor GDPβ-S. Our results suggest that the I_{Na} inhibition in small-sized TG neurons, which is mediated by the activation of Gi/o protein-coupled α2-adrenoceptors, might contribute to the analgesic effects of dexmedetomidine in the trigeminal system. Therefore, these new findings highlight a potential novel target for analgesic drugs in the orofacial region.

Disclosures: Y. Kim: None. **S. Im:** None. **S. Hwang:** None.

Poster

299. Nociceptors

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Topic: D.03. Somatosensation: Pain

Title: Identification of a population of peripheral sensory neurons projecting to blood vessels

Authors: *C. MORELLI, L. CASTALDI, S. BROWN, A. WEBSDALE, B. CERRETI, A. BARENGHI, P. A. HEPPENSTALL
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Abstract: Sensory neurons have the fundamental role of detecting stimuli from the periphery and are therefore considered afferents. Their endings are located in skin, muscles, joints and vessels and they are important to detect touch, itch, heat, cold and pain sensations, while their cell body is located in Dorsal Root Ganglia (DRG). We have identified a population of sensory neurons that project to blood vessels that have instead an efferent function. Like motor and sympathetic neurons, they directly act on blood vessels to regulate blood flow. Using transgenic mouse lines expressing fluorescent reporters, DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) or optogenetic activators, we have characterised this new population from a histological and a functional point of view. These neurons account for around 10% of all DRG neurons and when they are specifically activated they act on arteries and arterioles regulating the blood flow. These results have been confirmed both with *ex vivo* live imaging experiments and with behavioural studies. The discovery of a new population of sensory neurons innervating blood vessels to regulate blood flow is an important step towards a better understanding of the relationship between the peripheral nervous system and the cardiocirculatory system. This in turn may help to develop new therapeutics for diseases like hypertension or fibromyalgia, where the nervous component seems to play an important role.

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Poster

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Title: Cellular and behavioral requirements for calcium induced calcium release mechanisms in cold nociception

Authors: *A. A. PATEL[1], N. J. HIMMEL[2], J. J. YANG[3], D. N. COX[2]
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Abstract: Calcium (Ca^{2+}) plays a pivotal role in modulating neuronal-mediated responses to multimodal sensory stimuli. Recent studies in *Drosophila* reveal class III (CIII) multidendritic (md) sensory neurons function as multimodal sensors regulating distinct behavioral responses to innocuous mechanical and nociceptive thermal stimuli. Functional analyses reveal that CIII-mediated multimodal behavioral output is dependent upon activation levels with stimulus-evoked Ca^{2+} displaying relatively low vs. high intracellular levels in response to gentle touch vs. noxious cold, respectively. However, the mechanistic bases underlying modality-specific differential Ca^{2+} responses in CIII neurons remains incompletely understood. We hypothesized that noxious cold evoked high intracellular Ca^{2+} responses in CIII neurons may rely upon Ca^{2+}-induced Ca^{2+} release (CICR) mechanisms to promote noxious cold nociceptive behavior. Neurogenomic analyses revealed that ER localized Ca^{2+} channels including the Ryanodine receptor (RyR) and Inositol triphosphate receptor (IP_3R) are enriched in CIII neurons. CIII-specific knockdown of the RyR or IP_3R results in a specific impairment in noxious cold evoked behavior, whereas gentle touch behavior was unaffected. Likewise, disruptions in both RyR and IP_3R in CIII neurons leads to significantly lower levels of cold evoked Ca^{2+} responses as revealed by the cytoplasmically localized Ca^{2+} integrator CaMPARI suggesting these channels are required in CICR from the ER. To more directly investigate how Ca^{2+} localization is altered when disrupting RyR or IP_3R, we generated novel transgenic strains bearing the ER localized Ca^{2+} sensor CatchER^{+}. As predicted, CIII-specific RyR knockdown results in significantly higher ER luminal Ca^{2+} indicative of a role in regulating Ca^{2+} release from intracellular stores. We further demonstrate that CIII-specific knockdown of RyR or IP_3R results in dramatic reductions in cold-evoked GCaMP cytoplasmic Ca^{2+} responses further supporting a role for CICR. Morphological analyses revealed that RyR or IP_3R knockdown in CIII neurons results in varied, but subtle reductions in dendritic arborization. To differentiate potential roles of RyR and IP_3R in general excitability vs. sensory transduction, we combined CIII-specific knockdown with optogenetic

activation revealing that these molecules appear to act in the sensory transduction stage rather than in action potential propagation. Collectively, these analyses support novel, modality-specific roles of RyR/IP_3R function and CICR mechanisms in regulating intracellular Ca^{2+} levels and cold evoked behavioral output from multimodal CIII neurons.

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Poster

299. Nociceptors

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Title: Different coding strategies for heat and cold by primary sensory afferents

Authors: *F. WANG[1], E. BÉLANGER[1,2], S. L. CÔTÉ[1], P. DESROSIERS[1,3], S. A. PRESCOTT[4,5], D. C. CÔTÉ[1,2,3], Y. DE KONINCK[1,2,6]
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Abstract: Primary somatosensory afferent neurons transduce environmental stimuli into electrical activity that is transmitted into central nervous system to be decoded into corresponding sensations. How different stimuli are encoded by a population of afferents remains poorly studied. To address this, we performed video-rate two-photon functional imaging from thousands of dorsal root ganglion (DRG) neurons in anesthetized mice, and applied natural mechanical and thermal stimuli to the hind paws. We found that approximately half of the DRG neurons were polymodal (including >30% being both mechano- and thermoceptive). Further parametric analysis revealed that thermoceptive neurons displayed distinct encoding behaviours in the heat vs. cold ranges. As temperature increased, more heating-sensitive neurons were

activated and most individual neurons responded more strongly. It is consistent with graded coding at population and single-neuron levels, respectively. In contrast, most cooling-sensitive neurons responded in an ungraded fashion, which is inconsistent with graded coding and instead suggests combinatorial coding based on the co-activation pattern of an ensemble of DRG neurons. Thus, our study found that polymodality is a common phenomenon of DRG neurons, and thermoceptive afferents use different strategies to encode heat and cold.

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Poster

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Title: Conserved strategy for nociceptive stimulation by animal venom

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Abstract: The induction of pain by animal venom discourages predation and competition, and is therefore crucial to natural selection. Despite the common pain-evoking property of many animal venoms, an evolutionarily conserved algogenic substance has not been identified. Here we show that citrate sufficiently recapitulated the biphasic nociceptive effects of crude rattlesnake venom when injected in mice. The initial nociceptive response (P1N) was reconstituted by citrate at native venom pH, and occurred through potentiation of acid-sensing ion channel. The delayed and prolonged nociceptive responses (P2Ns) were caused by stimulation of a novel pain receptor on peripheral terminals of nociceptors, and were abolished by its genetic deletion or pharmacological inhibition. Intriguingly, the abundance of citrate in most animal venoms explains their common pain-evoking nature, and the lack thereof explains how some species, such as the brown reclusive spider, bite painlessly to produce intoxication in stealth.

Disclosures: Y.L. Yang: None. **T.W. Lai:** None.

Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.18/X13

Topic: D.03. Somatosensation: Pain

Support: Queen's University School of Medicine
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Title: Immunohistochemical characterization of sensory neurons surrounded by postganglionic sympathetic baskets in the mouse trigeminal ganglia

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Abstract: Following peripheral nerve injury, postganglionic sympathetic axons sprout into affected sensory ganglia and form perineuronal plexuses around a subpopulation of primary sensory neurons. These sympathetic basket-like structures have been shown to play an important role in the development and maintenance of chronic pain. In this study, we sought to determine a more precise phenotype trigeminal ganglia neurons surrounded by sympathetic plexuses. Here we utilized mice that express nerve growth factor (NGF) under the control of glial fibrillary acidic protein promoter, as these mice display the spontaneous formation of sympathetic baskets in sensory ganglia (i.e., in the absence of nerve injury). Preliminary immunostaining results show that the vast majority of those sensory neuronal cell bodies surrounded by sympathetic plexuses in the trigeminal ganglia are immunopositive for 1) the NGF receptor trkA, 2) a second NGF receptor p75, 3) calcitonin gene-related peptide, and 4) neurofilament heavy chain (NF200). These same sensory neurons with sympathetic basket lack immunostaining for NGF receptor trkB, isolectin B4, substance P, TRPV1, aquaporin, and ASIC3. These results reveal that the nociceptive sensory neurons surrounded by sympathetic plexuses are NGF-sensitive, peptidergic, and heat insensitive. This study begins to shed light on the mechanisms that provide specificity in the formation of sympathetic plexuses following peripheral nerve injury. This knowledge is imperative for developing targeted interventions for sympathetically maintained chronic pain conditions. This work is funded by Queen's University School of Medicine to (MK), and King Saud bin Abdulaziz University for Health Sciences Scholarship to (HA).
Keywords: chronic pain, nerve growth factor, sympathetic plexuses

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Poster

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Topic: D.03. Somatosensation: Pain

Support: Wellcome Trust

Title: Functional and molecular characterisation of cold-responsive DRG neurons *in vivo* using GCaMP

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Abstract: The ability to sense environmental cold serves as an essential survival tool. The ablation of the Trpm8 or $Na_V1.8$-expressing sensory neurons causes a profound deficit in noxious cold sensation in mice, despite these populations having limited overlap. To explore this further, we used mice expressing Pirt-GCaMP3, $Na_V1.8$-Cre and a Cre-dependent reporter to investigate the population of sensory neurons responsive to different cooling stimuli, *in vivo*. Plantar application of a variety of cooling stimuli down to 1^oC caused the activation of distinct, threshold-specific cold-responsive neurons. Interestingly, the majority of cold-responsive neurons were negative for $Na_V1.8$ expression, and the deletion of $Na_V1.8$ did not affect the relative number, distribution or maximal response of cold-sensitive neurons. Furthermore, the genetic deletion of $Na_V1.8$ had no observable effect on cold-induced behaviours in mice, as measured by the cold plantar, cold plate or acetone tests. Fluorescent-activated cell sorting (FACS) and subsequent microarray analysis of putative cold-sensitive sensory neurons, highlighted an enriched repertoire of ion channels that is potentially required for cold sensing in mouse DRG neurons. These data demonstrate the complexity of cold sensing mechanisms in sensory neurons, and reveal a major role for $Na_V1.8$-negative neurons in sensing innocuous and noxious cooling.

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Poster

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant F30AT009949

Title: Effect of high omega-6 diet on sensory neuron excitability and pain behavior

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Abstract: Background: Physicians recommend dietary interventions for management of cardiovascular disease, diabetes and many autoimmune diseases; however, there is a large gap in knowledge on the role of diet as a risk factor or potential therapy for chronic pain. Our group and others have demonstrated that oxidized metabolites of the omega-6 polyunsaturated fatty acids (PUFAs) lead to increased activation of transient receptor potential vanilloid 1 (TRPV1) expressed on nociceptive neurons, as shown in several pain models. Since these are essential fatty acids, tissue levels of omega-6 PUFAs are regulated by dietary intake; however, the mechanisms by which dietary omega-6 lipid modulates pain is not understood. The current study characterizes changes in sensory neuron signaling and its contribution to increases in thermal and mechanical nociception. **Methods:** Male C57BL6 mice were placed on isocaloric diets with high (10%) and low (0.5%) levels of omega-6 PUFAs for 8 weeks. Thermal and mechanical nociceptive thresholds were measured pre and post-diet. Patch clamp electrophysiology was used to determine changes in excitability in different dorsal root ganglion (DRG) sensory neuron subgroups, while calcium imaging was used to assess alterations in capsaicin-induced calcium accumulation, post diet. Data were analyzed with two-way ANOVA with Bonferroni post hoc test. **Results**: Thermal nociceptive thresholds decreased by 30% in the high omega-6 group ($p<0.001$, $n=25$), and baseline mechanical thresholds decreased by 15% ($p<0.001$, $n=25$) as compared to pre-treatment levels. Hyperexcitability of DRG sensory neurons, due to high omega-6 diet, was observed within specific sensory neuron subgroups but not all subgroups. Capsaicin induced calcium influx in DRG neurons increased by 50% in the high omega-6 group ($p<0.05$, $n=53$) compared to control. **Conclusions:** Collectively, these novel data suggest that chronically elevated dietary omega-6 PUFAs lead to increased thermal and mechanical pain response as well as neuronal hyperexcitability within specific subclasses of sensory neurons. Future work will focus on mechanisms by which omega-6 PUFAs contribute to increased neuronal signaling and nociception.

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Poster

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant GM115384
NIH Grant NS100065

Title: Touch device for accurate detection of acute mechanical pain stimulus

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Abstract: Pain poses a major clinical, social, and economic problem. Approximately one in three adults suffer from chronic pain and the economic cost associated with chronic pain management is estimated to be about $600 billion annually. Despite the critical importance of pain management, the diagnosis of pain remains poorly developed. In either the laboratory setting or the clinical setting, there is currently no means of assessing acute mechanical pain. We meet this need through a device that records the onset and offset of painful mechanical stimulations. The device allows for a needle, syringe, or any metal item to act as both the stimulus and touch trigger. With an item such as a needle, when applied properly, one can use contact time as a surrogate for stimulus onset. Additionally, withdrawal times can be accurately and precisely determined by the loss of contact. A tool for accurately assessing these parameters of painful stimuli has both research and clinical applications. Such a tool allows for accurate analysis of neuronal reactions to pain where exact timing is crucial, advancing the field of pain research. And this tool provides a unique insight into the conditions of patients with pain related ailments such as peripheral neuropathy, and chronic pain by providing a means of measuring and monitoring patient's mechanical pain thresholds. Our data show observable differences in withdrawal speeds elicited by different needle gauges. This shows the device's ability to measure pain thresholds to a level of sensitivity previously not possible. Additionally, data shows that there are differences in response to painful stimulus in rats under normal and chronic pain conditions, demonstrating the tool's ability to be used not only to assess pain thresholds, but to also assess hypersensitivity. There are currently no other means to objectively detect hypersensitivity and is thus a boon to the study and treatment of pain.

Disclosures: J.A. Dale: None. **J. Wang:** None.

Poster

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS087542

Title: Phenotyping of somatosensory afferents mediating cold and cold pain sensations

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Abstract: Ion channels of the Transient Receptor Potential (TRP) superfamily are non-selective cation channels that mediate the influx of small ions, as well as larger positively-charged molecules. This ability to permeate large cations has been used to cell-specifically target local anesthetics to afferent nerve fibers expressing these channels, thereby allowing a functional phenotyping of these cells *in vivo*. We have previously shown that the principle mediator of neuronal cold responses, the menthol receptor TRPM8, permeates large cations *in vitro*. Additionally, *in vivo*, nerve block by selective entry of the cell-impermeant sodium channel blocker QX-314 with cold stimuli (both chemical and thermal) blocks cold and cold pain. Thus, these cells are critical mediators of this somatosensory modality. However, afferents expressing the ion channels TRPV1 and TRPA1 have also been implicated in mediating cold and cold pain. Therefore, using QX-314-specific nerve block via cell permeation after activation of TRPV1 and TRPA1 channels, we have examined the role of these afferents in cold perception. Our findings show that both channels, depending on stimulation conditions and pathological state, are components of a cold sensory pathway.

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Title: Identification of pyruvate dehydrogenase as a target of prostaglandin E2-induced Epac signaling in mouse dorsal root ganglion neurons

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Abstract: The phenomenon of hyperalgesic priming has been used to investigate molecular mechanisms underlying the transition from acute to chronic pain. In this model, an initial injury produces a persistent "primed" state in which a second mild insult (injection of the prostaglandin PGE2) produces prolonged hyperalgesia. Priming is caused in part by a switch in cyclic adenosine monophosphate (cAMP) effectors from protein kinase A (PKA) to exchange protein activated by cAMP (Epac). Epac is a guanine nucleotide exchange factor that activates Rap1, and Epac/Rap1-dependent activation of protein kinase C (PKC) epsilon has been implicated as a critical pathway for some forms of hyperalgesic priming. A significant challenge has been to identify proteins downstream of Epac that may contribute to nociceptor sensitization. We characterized Epac-dependent PKC activity in dorsal root ganglion (DRG) neurons from male mice by first enriching total phospho-protein by immobilized metal affinity chromatography (IMAC), then analyzing samples by Western blot using an antibody recognizing serine residues phosphorylated by PKC. Application of PGE2 or the Epac agonist 8-pCPT-2-O-Me-cAMP-AM (8Cpt) to dissociated DRG neurons produced a consistent profile of phospho-protein bands that were reversed by inhibitors of PKC (GF109203X) or Epac (ESI09), but not of PKA (cAMPS-Rp and KT5720). A major band ~41kD was excised from the polyacrylamide gel and processed for liquid chromatography-mass spectrometry, identifying the major protein as pyruvate dehydrogenase Pdha1. Multiplex Western blot staining showed that the band for Pdha1 overlapped completely with the PKC phospho-serine band at 41 kD. The Pdha1 band was depleted in phospho-enriched samples from neurons treated with 8Cpt plus ESI09 compared to 8Cpt alone, indicating that ESI09 suppresses phosphorylation of Pdha1 and supporting the identification of the 41kD band as Pdha1. Phosphorylation of Pdha1 by pyruvate dehydrogenase kinases (PDK) at S293 inhibits conversion of pyruvate to acetyl-CoA and the production of energy through the TCA cycle; inhibition also reduces mitochondrial buffering of intracellular calcium and production of reactive oxygen species. However, analysis of predicted PKC-phosphorylation sites in the mouse Pdha1 sequence revealed several sites, but did not include S293. This suggests that Epac-dependent PKC phosphorylation of Pdha1 may represent a novel mechanism for the regulation of Pdha1 and mitochondrial function in response to Gs-coupled receptor signaling. Regulation of mitochondrial function by GPCR-induced Epac signaling may contribute to the critical role of Epac in hyperalgesic priming.

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Poster

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Title: DRG cell-type enriched TSS usage and alternative splicing in humans and mouse implicate important sensory genes

Authors: *P. R. RAY, J. KHAN, A. WANGZHOU, S. MEGAT, V. RAJESH, T. J. PRICE
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Abstract: Problem: Whole gene expression profiles of human and mouse sensory tissues have been comprehensively characterized in recent works (Flegel et al, PLoS One 2015; Usoskin et al, Nat Neuro 2015) at varying resolutions (whole tissue, small cell pool and single cell) identifying genes enriched in sensory cell types. However, only a handful of studies (Lerch et al, PLoS One 2012) have analyzed gene expression profiles in the mammalian dorsal root ganglia (DRG) or trigeminal ganglia (TG) at the level of individual isoforms and none have performed such analysis on a whole genome basis in mammalian single cell studies or in human datasets. To remedy this, we created a genome wide map of alternative splice (AS) variants and transcription start site (TSS) usage in human and murine DRG and TG. Methods: Based on publicly available human and mouse whole tissue, and mouse DRG single cell RNA-seq datasets, we computationally contrast these isoform expression maps between DRG, TG and several central nervous system tissues to identify differential isoform usage in human and mouse DRG and TG , and in sensory neuronal subpopulations in the mouse DRG. SpliceTrap, rMATS, Tophat/Cufflinks, STAR and Salmon toolkits were used to analyze RNA-seq datasets. 6 kinds of alternative isoform usage (alternative TSS, alternative 5’ and 3’ splice sites, retained intron, skipped exon and mutually exclusive exons) were analyzed. Information theoretic measures based on Shannon's entropy were used to identify differential isoform enrichment. Results: We identified several sensory tissue enriched isoforms in both humans and mouse. WNK1 (lysine deficient protein kinase 1), has a skipped exon alternative splicing event known to be associated with peripheral neuropathy enriched in both the human and mouse DRG. OGT (O-GlcNAc Transferase), essential for sensory neuron maintenance, also has a differential alternative splicing event in the human DRG. In the mouse DRG, we characterized isoform enrichment across sensory neuronal subpopulations (neurofilament, peptidergic, non-peptidergic, Tyrosine hydroxylase positive cells) including Trpv1, Piezo2, and Trpa1, whose splice variants have been linked to specific functions. We also analyzed alternatively spliced regions of the genes in terms

of their content of RNA binding sites, motif and secondary structure, and protein domains (from PFAM and Interpro), and Short Linear Motifs (from ELM). Discussion: Our results yield the first comprehensive multi species map for isoform expression in mammalian sensory tissues, that can be mined for diagnostic and therapeutic studies in human disease, and mechanistic and functional single gene studies in rodent models.

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Poster

299. Nociceptors

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Topic: D.03. Somatosensation: Pain

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Title: Palmitic acid induces pain behavior via toll-like receptor-4 (TLR4) on sensory neurons

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Abstract: New studies reveal that western diet (WD) consuming populations experience pain states independent of diabetes or obesity. It appears as if components of the diet sensitize the body. Saturated fats, which are a large component of WD, lead to obesity and have a role in insulin resistance and diabetes. A subset of free fatty acids (FFA), which are formed from the breakdown of saturated fats, are proposed to interact with Toll-like receptor 4 (TLR4). TLR4 is a receptor that recognizes lipid components of bacteria, and similarly, the lipid-A backbone of FFAs. In particular the FFA, Palmitic Acid (PA), has been shown to directly activate TLR4. To determine how PA could activate sensory neurons via TLR4, we utilized a novel transgenic model that allows for specific expression of TLR4 in peripheral sensory neurons in otherwise whole-body null animals. In order to re-express TLR4 in these cells we used a cre recombinase animal that is driven by the $Na_v1.8$ promoter. We hypothesize that PA through action on TLR4 on sensory neurons is important for mediating pain plasticity. Male and female: wild-type (WT), TLR4 null-or knock-out mice (KO), and mice that had TLR4 re-expressed in peripheral nociceptors (SNS^{React}), were used in all experiments. For behavioral assessments, mice underwent intraplantar injection of PA into the hind paw; both mechanical hypersensitivity and spontaneous pain measurements were assessed 1hr, 3hr, 24hr, 3d, 5d, and 7d post injection of PA. Dorsal root ganglia neurons were treated with a 100μM dose of PA followed by 50mM KCl as a positive identifier of neurons. In both sexes, WT and SNS^{React} mice that received an intraplantar injection of PA had a lowered paw withdrawal threshold and higher grimace score,

indicating the animals were hypersensitive. While the KO animals had mechanical thresholds and grimace scores similar to vehicle treated animals. In calcium imaging experiments, PA was able to activate a subset of about 30% of WT neurons indicated by a calcium influx. The 30% of cells that responded to PA also responded to application of capsaicin demonstrating they were TRPv1+ cells. These experiments demonstrate that the breakdown of saturated fatty acids in food can lead to pain-states in the absence of diabetes or other gross conditions.

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Poster

299. Nociceptors

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Topic: D.03. Somatosensation: Pain

Title: Characterizing YPEL3 gene function in *Drosophila melanogaster*

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Abstract: The Yippee-like gene family is a group of genes that show high conservation through many different types of organisms including various animal, bacterial, and fungal species. This uncharacterized gene was recently associated with a disease found in a human patient that showed neurological defects including areflexia and hypotonia. An ortholog of YPEL3 was found in *Drosophila melanogaster* (dYPEL3) that showed 85% amino acid identity. We successfully generated mutants of dYPEL3 similar to the human mutation in *Drosophila*. Here we show that the nociceptive circuit is the likely target for dYPEL3 mutations due to optogenetic manipulation of dYPEL3 mutants using Channel Rhodopsin II (ChR2) to activate nociceptive circuitry, thus displaying a phenotype of increased rolling behavior in larva. We also show through the use GRASP (GFP Reconstitution Across Synaptic Partners), that the synaptogenesis between the nociceptive neurons and their immediate projection neuron target, Basin-4, is reduced in strength in the mutants compared to wild-type. Calcium influx analyzed using GCaMP live imaging showed increased total Basin-4 activation in the mutant lines. Thus, dYPEL3 has role in regulating the nociceptive circuit in *Drosophila* which could have definite implications in sensory response and neurological defects.

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Poster

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Title: Effects of the VGF-derived peptide TLQP-62 on primary afferent neurons

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Abstract: The neurosecretory protein VGF (non-acronymic) is rapidly and robustly upregulated by primary somatosensory afferent neurons following peripheral nerve damage. VGF is proteolytically processed to yield a number of bioactive peptides, including the C-terminal peptide TLQP-62. This peptide has been shown to induce BDNF-dependent synaptic plasticity in the hippocampus and function during learning and memory. We have demonstrated that spinal TLQP-62 is increased after nerve injury and that immunoneutralization of C-terminal VGF peptides attenuates the development of mechanical allodynia. Furthermore, calcium imaging in spinal cord slices from naïve mice revealed TLQP-62-induced potentiation of glutamatergic responses in a subset of dorsal horn neurons. This effect was inhibited by the non-selective TrkB inhibitor K252a, and exposure of spinal cord slices to TLQP-62 increased TrkB phosphorylation. These observations suggested that TLQP-62 may facilitate BDNF release. Since primary afferent neurons are a potential source of spinal BDNF, we examined the effects of TLQP-62 on these neurons. Using mice that express a genetically encoded calcium indicator restricted to primary afferent neurons (Pirt-GCamp3 mice), we observed that TLQP-62 induced calcium transients in a subset of primary afferent fibers in the dorsal horn of spinal cord slices. The responses occurred immediately after TLQP-62 exposure and were sustained during prolonged exposure. TLQP-62 also induced calcium transients in DRG cultures. These responses were seen in a subset of capsaicin-responsive neurites as well as in neurites that did not respond to capsaicin.

Ongoing work is investigating the functional consequences of these TLQP-62 effects and their relationship to BDNF via patch-clamp and BDNF-pHluorin imaging, respectively. Our observations of TLQP-62-induced calcium responses in the processes of primary afferent neurons are consistent with the idea that the peptide may modulate release of signaling mediators.

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Poster

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Title: GABAergic system in the spinal sensory ganglia

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Abstract: Peripheral nerves convey to the brain versatile information about the body's environment and report the state of the muscle, joints and viscera. Brain interprets this information in terms of haptic, somatic and visceral experiences including that of pain. Healthy nerves conduct action potentials from their peripheral endings to the dorsal spinal cord, where synaptic transmission first takes place. It is assumed that the peripheral somatosensory signals are first integrated in the spinal cord (the 'Gate Control' theory) and subsequently analyzed in higher brain centers. Our recent work challenged this view (1). We focused on cell bodies of sensory neurons, which are situated in the dorsal root ganglia (DRG), outside of the main nerve conduction pathway. Surprisingly, these DRG cell bodies express receptors for classical CNS neurotransmitters, such as glutamate and GABA, even though there is no known synapses in

DRG. We report that DRG cell bodies contain a fully functional GABAergic system that can modulate nociceptive signals before these enter the CNS. Thus, *i)* DRG neurons express the proteins necessary for GABA synthesis and release; *ii)* DRG neurons release GABA in response to depolarization; *iii) in vivo* infusion of GABA into DRG dramatically reduced acute and chronic pain while application of GABAA antagonists induced pain or exacerbated peripherally-induced pain; *iv)* chemogenetic or optogenetic depolarization of GABAergic DRG cell bodies *in vivo* reduced acute and chronic pain. In a follow-up study we performed simultaneous *in vivo* recordings of firing in the peripheral (spinal nerve) and central (dorsal root) branches of L5 spinal nerve of a rat, which allowed to focally apply drugs to DRG during the recording. We show that hind paw injection of capsaicin induced firing in both peripheral and central branches of the nerve. DRG application of GABA strongly reduced capsaicin-induced firing in the dorsal root without any effect in the peripheral branch. In contrast, DRG injection of GABAA antagonist bicuculline significantly increased tonic firing rate in the dorsal root. Intriguingly, basal firing rates were consistently lower in the dorsal root as compared to the spinal nerve but after bicuculline the difference disappeared, suggesting existence of tonic GABAergic filtering at DRG, which can be modulated via endogenous and exogenous mechanisms. Collectively, our findings indicate that peripheral somatosensory ganglia may represent a new type of a 'gate' within the somatosensory system.

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Poster

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Title: Failure of somatic spike invasion in primary afferent neurons

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Abstract: The peripheral terminals of primary afferent neurons convert the external somatosensory stimuli into action potentials, or spikes, that propagate centrally into the central nervous system (CNS). Primary afferent neurons have a unique pseudounipolar structure in which a single axon protrudes from the soma and splits into one central and one peripheral

branch, thus forming a T-junction. For spikes to reach the CNS, they must pass through the T-junction, which can impede spike propagation. Computational work suggests that spikes continue to propagate towards the central terminals even if they fail to invade the soma. However, it is not an uncommon practice for researchers to record from the soma when characterizing different primary afferent neurons and (at least some) spikes do invade the soma. By recording extracellular spikes from the soma in response to sustained mechano- and photo-stimulation of the peripheral terminals *in vivo* in transgenic mice that express channelrhodopsin-2 in all primary afferents, we observed three types of spike patterns: irregular, regular and an unexpected semi-regular pattern. The semi-regular pattern was characterized by what appeared to be missing spikes from an otherwise regular spike pattern. We confirmed this observation computationally in an abstract mathematical model and a biophysical neuron model. Both models show that a noisy spike initiation process cannot reproduce the semi-regular spike pattern, but that subtraction of a random subset of the spikes from a regular pattern, generated via either model, does. We therefore hypothesized that the missing spikes occur as a result of failure of spike propagation into the soma. To investigate this, we encouraged spike propagation failure by blocking sodium channels with lidocaine. As predicted, lidocaine converted the regular spike pattern into the previously observed semi-regular pattern. These results confirm that spikes intermittently fail to propagate into the cell soma in vivo. These findings demonstrate that spike propagation failure occurs in vivo and that this is important to consider when characterizing primary afferent response properties.

Disclosures: D. Al-Basha: None. **S.A. Prescott:** None.

Poster

299. Nociceptors

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 299.30/Y11

Topic: B.06. Synaptic Transmission

Support: 4-VA

Title: Identifying the molecular components of cold nociception in *Drosophila melanogaster*

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Abstract: Nociception, the central nervous system's processing of noxious stimuli, gives rise to conscious perception of pain and protective reflexes. This study aims to explore the molecular mechanisms of nociception by researching the potential role of *Drosophila melanogaster* Innexin gap junction proteins in cold nociception. Invertebrate Innexins are functionally analogous to mammalian Connexins. To screen for a possible role of these Innexins in cold nociception, the

expression of each Innexin was knocked down by cell-specific expression of *innexin* RNAi constructs in the class III dendritic arborization (da) neurons. Wild type (WT) third instar *Drosophila* larvae exhibit a characteristic "cringing," or shortening, response when exposed to noxious cold (6°C). Larvae were subjected to a cold plate and their behavior was video recorded. 100 larvae were tested for each genotype. The larval images were processed using Image J software to quantify the "percent cringe". By comparing the percent cringe of the protein-lacking larvae to the WT, the involvement of the knockdown protein in the cold nociceptive pathway was inferred. A control was established using Oregon-R WT larvae (positive for WT cringe response). Tetanus toxin, a potent neurotoxin, was expressed specifically in class III da neurons and significantly inhibited cringing. This provided evidence that class III da neurons function in cold nociception and moving forward this test served as a negative control. To date, every Innexin has been tested with at least one RNAi construct, and six of the eight Innexins have been tested with two different RNAi constructs. In class III da neurons, down regulation of four Innexins - Inx2, Inx5 (with both RNAi constructs), Inx1 and Inx3 (only tested with one construct) - significantly inhibited cringing. This provides evidence that these four Innexins function in the cold nociception pathway of third instar larvae, and also, therefore, that this pathway utilizes electrical synapses. Down regulation of Inx4, Inx6, Inx7, and Inx8 significantly inhibited cringing with one RNAi construct but not the other. To clarify the potential role of these Innexins, mutant flies lacking a functional Innexin will be tested to eliminate confounding variables that may exist with the RNAi constructs.

Disclosures: R.M. Barborek: None. **K. Combs:** None. **A. Neighbors:** None. **M. Knick:** None. **S. Halsell:** None.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.01/Y12

Topic: D.03. Somatosensation: Pain

Support: NIH Grant AR057194

Title: TRPV1 and TRPV4 involvement in cinnamaldehyde-evoked itch in female and male mice

Authors: T. FOLLANSBEE[1], M. IODI CARSTENS[1], T. NGUYEN[1], A. NGUYEN[1], M. CHEN[1], D. DOMOCOS[1], *E. E. CARSTENS[2]
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Abstract: Cinnamaldehyde (CA) elicits itch sensation in humans (Namer et al., Neurorep 16:955-9, 2005; Hojland et al., Acta Derm Venereol 95 :798-803, 2015). We presently

investigated CA-evoked scratching behavior in male (M) and female (F) mice and potential TRP channel involvement. Female (F) and male (M) C57BL6 wildtype (WT) and TRPV1 knockout (KO), TRPA1KO and TRPV4KO mice were used. CA (1-5% in 5% Tween80) was delivered unilaterally to the cheek via intradermal (id) injection (10 μL). Mice were videotaped and numbers of hindlimb scratch bouts and forelimb wipes directed to the injected cheek, and bilateral facial groom bouts, were scored offline by blinded observers. To test for alloknesis, 40% CA was applied topically to the rostral back. At 5-min intervals, a von Frey monofilamant (0.7 mN bending force) was applied 3 times to the treatment area and occurrences of immediate hindlimb scratch bouts directed to the stimulus, and wet dog shakes, were counted. CA elicited a dose-dependent increase in numbers of scratch bouts that peaked at 10-25 min post-CA and then declined. There was no sex difference in the numbers of CA-evoked scratch bouts in WTs. Importantly, CA elicited significantly fewer scratch bouts in both F and M TRPV1KO and TRPV4KO mice ($p<0.05$ for both) compared to WTs. Counts of CA-evoked scratch bouts were not significantly different in F or M TRPA1KOs, or in M mast-cell deficient (Sash) mice, compared to WT counterparts. CA did not elicit any significant increase in forelimb wiping or facial grooming behavior compared to vehicle controls, and there were no sex or genotype differences in these behaviors. As TRPV1 and TRPV4 are associated with histaminergic itch, we tested if CA-evoked scratching was suppressed by the histamine H1 antagonist cetirizine. Neither a low (1.5 mg/kg) nor a high (15 mg/kg) dose of cetirizine significantly affected the number of CA-evoked scratch bouts, indicating a lack of involvement of histamine receptors. Topical application of CA resulted in a significant increase in alloknesis scores in M and F WTs, as well as wet dog shakes. We are currently investigating if CA-evoked alloknesis scores are different in various KO groups. The data indicate that CA elicits itch via a novel non-histaminergic pathway that partly involves TRPV1 and TRPV4 ion channels.

Disclosures: T. Follansbee: None. **M. Iodi Carstens:** None. **T. Nguyen:** None. **A. Nguyen:** None. **M. Chen:** None. **D. Domocos:** None. **E.E. Carstens:** None.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.02/Y13

Topic: D.03. Somatosensation: Pain

Title: Novel morphine delivery technique with rat pain model -subpial injection-

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Abstract: Introduction: The subarachnoid administration is one of the most effective drug delivery methods in clinical, especially opioids delivery. But the pia matter which is a cell layer cover the spinal parenchyma.We established more effective AAV9 injection method than the subarachnoid administration, which is “sub-pial injection”. The goal of the present study was to show the effectiveness of sub-pial opioid injection as compare with the subarachnoid administration in rat pain model.Methods: All studies are approved by the Institutional Animal Care Committee. Adults SD rats (male 250-310 g) had formalin test. The sub-pial group (Morphine group n=4/dose, Control n=4) were received laminectomy at Th13/L1. Following the laminectomy, animals were received the sup-pial morphine injection or saline injection. The subarachnoid group (Morphine n=4/dose, Control n=4) were implanted with chronic intrathecal catheter (PE-5) 5 days prior to morphine injection. The formalin tests were started 30min after morphine injection (2% paraformaldehyde injection subcutaneously into the hindpaw). In both group, the quantitative bioassay for the analgesic effect of sub-pial / subarachnoid morphine on formalin tests was performed to calculate 50% effective dose values (ED50) for induced pain 30min after morphine administration.Results: The scoring of stereotypical behaviors such as flinching, licking, and biting of the affected hindpaw were decreased in sub-pial / subarachnoid morphine administration in comparison with saline injection. $ED50_{SubPial}$were 0.003ug/ml on the early stage and 0.004ug/ml on the late phase. On the other hand $ED50_{subarachnoid}$were 0.10ug/ml on the early stage and 0.17ug/ml on the late phase. The sub-pial injection can decrease the value of ED50 in comparison with subarachnoid administration ($p<0.05$ on the early stage and the late phase).Conclusion : These data show the efficiency of sub-pial morphine injection. The novel morphine injection can give more strong analgesic effect than the traditional subarachnoid morphine administration.

Disclosures: K. Kawamitsu: None. **K. Kamizato:** None. **M. Kakinohana:** None.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.03/Y14

Topic: D.03. Somatosensation: Pain

Support: BonePain Network. Marie Sklodowska-Curie Grant 642720

Title: Does behaviour in rats change over the time course of MIA induced osteoarthritis?

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Abstract: Osteoarthritis (OA) is a chronic condition characterized by cartilage damage around the joints, resulting in pain, swelling and stiffness. There is currently no cure for OA. Treatments vary from non-steroidal anti-inflammatory drugs, opioids and capsaicin creams to alleviate pain and knee replacement surgery in severe cases. 13% of patients that undergo surgery still suffer from pain. Patients report the pain as burning, shooting pain with wide spread sensitization, suggestive of pain with neuropathic features. Studies have found these patients to have nerve damage in areas surrounding the joint. Together this suggests that OA pain can have both nociceptive and neuropathic features, having implications for future treatment. Here we studied animals subjected to the monoiodoacetate (MIA) model of OA. Behavior was assessed in 12 MIA and 6 sham control rats to address differences between two different stages of the disease: early inflammatory stage with nociceptive features (2-4 days post-injection) and late stage with neuropathic features (14 days post-injection). Animals were habituated and trained for two tests: Catwalk Gateway System and LABORAS. Behavior was tested before injection of MIA (OA animals; 2mg/animal) or saline (sham animals; 0.9%) and post injection at days 2, 4, 7 and 14. LABORAS measurements were taken over the course of 20h, allowing for the recording of naturalistic behavior over both dark and light circle. In addition, blood samples were processed at each time point to measure the level of cytokines in serum. The Catwalk system revealed a decrease in Print Area hind paw ratios of OA animals at day 2, day 4 and day 14. Hind paw ratios of OA animals were also significantly different for Swing, Swing Speed and Single Strance. Differences in rearing at day 2 post-MIA and locomotor duration at day 4 post-MIA were observed during the light cycle. No differences were observed in sham animals in both Catwalk or LABORAS. The cytokine profile revealed higher levels of anti-inflammatory cytokines IL-10 and IL-4 at day 14 post-MIA injection than at baseline. TNFα was increased at day 4 post MIA injection. These data suggest that OA animals use the injured limbed less during the early stages of inflammation (day 2 and 4) and during later stages (day 14) where neuropathic components may start to appear. No difference in walking is observed at day 7 where inflammation has thought to be resolved. Cytokine profile revealed an increase in TNFα in the inflammatory stage as previously reported but not in the later stage. Anti-inflammatory cytokines appear increased at day 14, suggesting that their action is necessary to aid the decrease in inflammation in the late stage.

Disclosures: C. Montagut-Bordas: None. **A. Fisher:** None. **A.H. Dickenson:** None.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.04/Y15

Topic: D.03. Somatosensation: Pain

Support: PAPIIT-RA205018

Title: Task switching impairment under chronic neuropathic pain: Role of the intralaminar thalamus

Authors: *C. D. MONTES-ANGELES[1], E. PERRUSQUIA-HERNÁNDEZ[2], A. HERRERA-VALDIVIA[2], I. PÉREZ-MARTÍNEZ[2]
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Abstract: Chronic pain involves central and peripheral changes in neural activity, impairing processes including attention, adaptation and action selection. The affected structure underlying this impairment might be the intralaminar thalamus, known as a mediator of the affective dimension of pain, of attention to salient stimuli and decision-making as an outcome, as well. The aim of this study is to assess the processing of action task switching under the influence of chronic neuropathic orofacial pain following a behavioral and physiological approach.
Methods: C57BL/6 male mice were divided in two groups: (1) mental nerve constriction injury (MnC) and (2) sham surgery. Spontaneous and evoked orofacial responses were measured in order to assess persistent pain and mechanical allodynia. The action selection process was evaluated during a switch-task and a
two-alternative forced choice task, in both freely moving and head restrained mice. Both evaluations will allow an adequate manipulation of different variables, and the precise control of neural circuits for its electrophysiological characterization and further optogenetic manipulation.
Results: Trigeminal injury increased the latency to correct switch responses to a stimulus. MnC decreased its responses frequency during an early phase of the task, and increased it in a late phase, as a sign of a lack of adaptation to the choice of the response to emit. Two alternative forced choice task was performed in order to test this impairment was due to disturbance in a cognitive but not in a sensory process.
The behavioral assessment of the cognitive impairment induced by chronic orofacial pain and a psychophysical approach of the mentioned processes will allow its study from a physiological and structural perspective, in order to find therapeutic alternatives, and to achieve the precise modulation of neuronal circuits commanding specific cognitive processes.
This project was supported by PAPIIT-RA205018

Disclosures: E. Perrusquia-Hernández: None. **A. Herrera-Valdivia:** None. **I. Pérez-Martínez:** None.

Poster

300. Pain Models: Behavior

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant DAO18151
Cancer Society of New Zealand
Health Research Council of New Zealand

Title: Evaluation of novel kappa opioid receptor agonists 16-ethynyl salvinorin A and 16-bromo salvinorin A in preclinical models of acute and chronic pain

Authors: *B. M. KIVELL[1], K. PATON[1], A. CULVERHOUSE[1], S. WILLIAMSON[2], T. E. PRISINZANO[2]
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Abstract: Current pain medications that activate mu-opioid receptors have high abuse potential and are limited in their ability to effectively treat chronic pain. Here we evaluate the novel kappa-opioid receptor (KOPr) salvinorin A (SalA) analogues, 16-Ethynyl SalA and 16-Bromo SalA, alongside the prototypical KOPr agonist U50,488, for their ability to modulate both acute and chronic pain alongside behavioural side-effects. Dose-response warm water tail-withdrawal assays in mice shows SalA and the novel analogues 16-Ethynyl SalA and 16-Bromo SalA were more potent than the traditional KOPr agonist U50,488 with 16-Ethynyl SalA being more efficacious than U50,488. Both 16-Ethynyl SalA and 16-Bromo SalA had improved duration of action of analgesic effects evaluated in hot plate and tail-withdrawal assays compared to SalA. In the intraplantar formaldehyde test, both 16-Ethynyl SalA and 16-Bromo SalA significantly reduced nociceptive and inflammatory pain, paw oedema and infiltration of neutrophils in a KOPr dependent manner. In a mouse model of paclitaxel-induced neuropathic pain 16-Ethynyl SalA and 16-Bromo SalA were potent in reducing both mechanical and cold allodynia when administered acutely. In paclitaxel-treated mice administered KOPr agonists daily for 22 days, U50,488, 16-Ethynyl SalA, 16-Bromo SalA all significantly reduced paclitaxel-induced neuropathic pain with reduced tolerance effects compared to morphine. 16-Ethynyl SalA and 16-Bromo SalA have fewer aversive and anxiogenic side-effects when compared to SalA and U50,488 in conditioned place aversion and light dark tests. However, 16-Ethynyl SalA and 16-Bromo SalA showed significant impairment of motor co-ordination in the accelerating rota rod tests. Overall, our data suggests that 16-Ethynyl SalA and 16-Bromo SalA are effective in modulating nociceptive, inflammatory and neuropathic pain with reduced KOPr mediate side-effects and hold promise for development of effective pain medications without abuse liability.

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Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 300.06/Y17

Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS045594
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Title: Pain-like withdrawal responses to conditioned auditory cues associated with repeated von Frey stimuli in two rat models of neuropathic pain

Authors: *B. R. BERKEMEIER, Q. R. SHIM, W. XIE, J. A. STRONG, J.-M. ZHANG
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Abstract: Von Frey filaments are nylon monofilaments used to exert varying amounts of force to specific test sites by stimulating mechanoreceptors. The animal typically exhibits a behavioral paw withdrawal response when the filament is pressed against the paw. The question remains: does the von Frey filament evoke a reflex or is it an effective tool in measuring pain, which is a higher-order brain function? In order to test this we examined whether withdrawal responses evoked by von Frey filaments (unconditioned stimulus) could be conditioned by pairing with a conditioned stimulus (auditory tone). Groups of male Sprague-Dawley rats (n=4 rats per group) underwent surgeries to implement a neuropathic pain model - either Chronic Constriction Injury (CCI) or the longer-lasting Spared Nerve Injury (SNI). Control rats were uninjured. The rats were then tested as to whether or not they could learn to associate the conditioned stimulus (a 5 kHz sine wave played at approximately 60-65 dB for 10 seconds) with the unconditioned stimulus (von Frey poke) which was administered during the last second of the tone. Rats could avoid the von Frey poke by withdrawing the paw in response to the sound, prior to the filament application. Conditioning occurred 2 days per week and consisted of 3 sets of 10 trials. Rats with either neuropathic pain model, but not control rats, could learn to associate the tone with the von Frey poke. Behavioral responses to the tone included withdrawal of the paw, sometimes with licking and flicking of the paw, and sometimes other behaviors such as trying to bite the filament on sight. CCI rats had a peak in learned associations around day 20 and could no longer make associations by day 40. SNI rats could make associations for longer than the CCI rats, continuing to at least day 60. In another experiment, control rats were also tested with modified von Frey filaments with sharp pricking tips. These rats still could not make the learning association. We suggest that these findings demonstrate that von Frey filaments evoke pain, as spinal reflexes cannot generate these higher-order learning connections made within the brain. If these pathways

of association could be identified, we could potentially disrupt them, allowing for a new approach to alleviating neuropathic pain.

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Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 300.07/Y18

Topic: D.03. Somatosensation: Pain

Support: PAPIIT-UNAM IN200415
PAPIIT-UNAM IA2013117
CONACyT 597467
CONACyT 164536

Title: Paraventricular hypothalamic stimulation restores spontaneous day/night activity in rats with neuropathic pain through spinal oxytocin receptors activation

Authors: *A. D. MANZANO GARCÍA, A. GÓNZALEZ HERNÁNDEZ, A. ESPINOSA DE LOS MONTERO ZÚÑIGA, G. MARTÍNEZ LORENZANA, M. CONDÉS LARA
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Abstract: Background and aims: Loose sciatic nerve ligation (LSN) induces hyperalgesia and allodynia, pain behaviors evoked by mechanical or thermal stimuli. Nevertheless, spontaneous (ongoing) pain is also relevant, but, little attention has been paid to this topic. In this context, we analyzed the changes in spontaneous day/night behavior (distance traveled, movement time, rest time, stereotypy time, vertical activity) in rats with LSN induced neuropathic pain. Then, we evaluated if hypothalamic paraventricular nucleus (PVN) electrical stimulation (with parameters to induce antinociception) restored the impaired spontaneous day/night behavior. Finally, we studied the role of spinal oxytocin receptors (OTR) in PVN-mediated antinociception.
Methods: At day 1 (D1) we did the LSN (left sciatic nerve) to male Wistar rats (180-220 g). Seven-days later (D7), we implanted a bipolar electrode into the left PVN; in the groups used to assess the role of OTR we implanted an intrathecal canula reaching the lumbar spinal cord also at D7. Fourteen-days after LSN (D14), spontaneous behavior was assessed 23-h/day/5 days using an automated open-field monitoring system. We performed the electrical PVN stimuli (1-ms, 60Hz, 6s, 100-300 µA) 3 times a day (9:00, 14:00 and 19:00); with the same schedule, we administered the OTR antagonist L368,899 (2µg/10µl) intrathecally.
Results: We found that the LSN diminished all the spontaneous behaviors except for the rest time, those behavioral changes were more notorious at night. PVN stimulation restored all the

behaviors; however, the sole electrode implantation (Sham group) had behavioral effects too. Data suggest the OTR participation in the PVN-mediated restoration of some behaviors (distance traveled, rest time) but not in others (stereotypy time). Moreover, OTRs seem to participate in a tonic way in antinociception since the sole antagonist L368,899 administration potentiated the behavior diminish produced by neuropathic pain. Finally, by using locomotor activity plots and heat-maps, we found that healthy animals tend to move in the periphery of plexiglass box avoiding the center of it, neuropathic animals tend to stay in one corner avoiding movement, and stimulated rats seem to stay more time in the center of the box.
Conclusions: The present data demonstrate that LSN diminishes spontaneous behaviors, preferentially at night. PVN stimulation (an antinociceptive procedure) restores those behaviors. Finally, data suggest the tonic antinociceptive participation of the oxytocinergic system in neuropathic pain.Acknowledgments: Special thanks are due to Dr. Daisy Gasca-Martínez for her technical assistance.

Disclosures: A.D. Manzano García: None. **A. Gónzalez Hernández:** A. Employment/Salary (full or part-time):; Universidad Nacional Autónoma de México. **A. Espinosa de los Montero Zúñiga:** None. **G. Martínez Lorenzana:** A. Employment/Salary (full or part-time):; Universidad Nacional Autónoma de México. **M. Condés Lara:** A. Employment/Salary (full or part-time):; Universidad Nacional Autónoma de México.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.08/Z1

Topic: D.03. Somatosensation: Pain

Title: Probing roles of sensory neuron subtypes in nociception via chemo-optogenetics

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Abstract: Clinically, pain can be divided into evoked pain and spontaneous pain. Evoked pain is pain behaviors triggered by noxious thermal stimuli (thermal nociception), mechanical stimuli (mechanical nociception) or chemical stimuli (chemical nociception); spontaneous pain is pain behaviors without external stimuli such as flinching or guarding behaviors. Accumulated evidence has shown that several nociceptive neuron populations involved in different evoked pain sensation such as thermal nociception, mechanical nociception and chemical nociception. However, little is known about the nociceptive neuron populations contribute to spontaneous pain. In formalin test, we found that formalin-induced mechanical hyperalgesia resolved earlier

than guarding pain behaviors in mice. Therefore, we hypothesized nociceptive neurons contribute to evoked pain are distinguishable from those contributed to spontaneous pain. Here, we aim to develop a chemo-optogenetics method to activate specific nociceptive neuron subtypes from periphery, in which channelorhodosin is activated via a chemical ligand. Thus this chemo-optogenetics approach allows us to probe the roles of all neuron subtypes in evoked pain or spontaneous pain. We first generated a Cre-dependent reporter mouse line that carries a luminopsin 3, a fusion protein of channelorhodosin and luciferase. We then used coelenterazine (CTZ), a natural subtract of luciferase to activate LMO3-positive dorsal root ganglion neurons via peripheral nerve terminals and tested the evoked and ongoing pain behaviors in neuron subtype-specific Cre-line::LOM3 mice. Results showed that CTZ dose-dependently increased both von Frey responses (evoked pain) and flinching behaviors (spontaneous pain) in TRPV1-Cre::LMO3 mice. We then further tested the roles of different neurons subtypes (e.g., neurons expressing tyrosine hydroxylase, ASICs, Nav1.8, etc.) in evoked pain and/or spontaneous pain. Together, we have successfully established a mouse model ideal for probing the roles of sensory neuron subtypes in nociception via chemo-optogenetics.
Key words: spontaneous pain, ctz, luminopsin 3, chemo-optogenetics, TRPV1

Disclosures: B. Jiang: None. **C. Chen:** None. **S. Lin:** None. **C. Lee:** None.

Poster

300. Pain Models: Behavior

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Program #/Poster #: 300.09/Z2

Topic: D.03. Somatosensation: Pain

Support: NHRI-EX107-10508NI
MOST 106-2320-B-010-011-MY3
MOST 106-2923-B-010-001-MY3)

Title: Perturbation of central amygdala neuron excitability reduces pain- and anxiety- like behaviors

Authors: *Y.-L. LIN[1], C.-C. LIEN[2]
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Abstract: Chronic pain disorder is associated with anxiety- and depression-like behavior. Although the amygdala is thought as a key node of the neural circuits mediating emotions, it also serves a major receiver of purely nociceptive signals. However, the circuit mechanisms by which the amygdala contributes to the pain-related anxiety has remained unclear. Here, we investigated circuit mechanisms underlying comorbid symptoms in chronic pain mouse models, including

acid-induced muscle pain. We first found that the phosphorylated ERK (pERK) level increased in the lateral subdivision of central amygdala (CeL) after chronic pain development. To address the role of the CeL in chronic pain, we attempted to manipulate CeL neurons using chemo- and opto-genetic approaches. We hypothesized that silencing of somatostatin-positive (SOM^+) neurons in the CeL, which may activate CeL output neurons (i.e., SOM^- neuron) and thereby suppresses the CeM projecting neurons, which reduces mechanical sensitivity and chronic pain-related behavior. In chemogenetic part, selective expression of designer receptors exclusively activated by designer drugs (DREADDs) was achieved by injecting a virus encoding Cre-dependent inhibitory DREADDs (i.e., hM4Di receptor) into a SOM-Cre driver, a mouse line specifically expressing Cre recombinase in a major population of the CeL. In optogenetic part, we expressed inhibitory halorhodopsin (eNpHR) in SOM^+ cells in the CeL. Consistent with this hypothesis, we found that both chemo- and opto-genetic silencing of SOM^+ neurons in the CeL reduced mechanical sensitivity and comorbid anxiety-like behavior.

Disclosures: Y. Lin: None. **C. Lien:** None.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.10/Z3

Topic: D.03. Somatosensation: Pain

Support: Al-Ahliyya Amman University

Title: Antinociceptive action of achillea biebersteinii methanolic flower extract is mediated by interaction with cholinergic receptor in mouse pain model

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Abstract: *Achillea biebersteinii* is a perennial aromatic herb that grows in the Mediterranean area. In folk medicine, it is used for the treatment of abdominal pain and stomach ache. In this study, *A. biebersteinii* flowers were collected from Al- Bukaan, Jordan and the extract was prepared in methanol. The analgesic effect of *A. biebersteinii* methanolic flower extract was tested in three pain models namely: writhing, hot plate and formalin tests in BALB/c mice. The intraperitoneal (ip) administration of *A. biebersteinii* extract (300 mg/kg and 500 mg/kg) inhibited acetic acid induced abdominal cramps. The effect of 300 mg/kg *A. biebersteinii* was comparable to that of 70 mg/kg indomethacin. No effect of the extract was observed in a thermal pain model. In formalin test, *A. biebersteinii* extracts (300 mg/kg and 500 mg/kg) decreased paw-licking and flinching responses in the early and late phases. Atropine (5 mg/kg, ip) blocked

the action of *A. biebersteinii* extract in late phase only. This indicates the involvement of cholinergic receptor in the antinociceptive action of this plant. Other mechanisms are currently being investigated in the lab. In conclusion, our study supports the use of *A. biebersteinii* as a painkiller in folk medicine.

Disclosures: S.M. Jaffal: None. **M. Abbas:** None.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.11/Z4

Topic: D.03. Somatosensation: Pain

Support: the Ministry of Science of Korea 2014M3C1B2048632

Title: Behavioral changes after sieve type neural electrode implantation in sciatic nerve injured rats

Authors: J. HONG[1], W. CHOI[2,3], M. KWON[4], H. PARK[2,5], J. KIM[2], *J. KIM[1,4,6]
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Abstract: A long term functional and reliable coupling between neural tissue and implanted neural electrodes are the key issue to acquiring neural signals or to restore neural functions after peripheral nerve injury. Prior to the clinical application neural electrode for patients with neurological disorders to restore their sensory and motor functions in patients with neurological disorders, the behavioral and histological consequences of these devices must be investigated. In the present study, we investigate changes in the sensory and motor functions in sciatic nerve injured rats after the implantation of neural electrode, sieve type neural electrodes that can acquire bidirectional neural signals with multi channels and high selectivity. The sciatic nerve injury (SNI) was made by the ligation in right side sciatic nerve and neural electrode was implanted above the injured site 2 weeks after injury. The overall consequences of implantation including motor and sensory function were performed in rats with SNI, skin incision (SI: sham) and sieve type neural electrode implantation after SNI. Motor function was assessed by physical activity such as total distance, mean of velocity. Mechanical sensitivity was assessed by Paw withdrawal threshold (PWT) to von Frey filaments in the hind paw. After the SNI, total distance and mean of velocity were significantly decreased and then spontaneously recovered from 4 days

after injury. In the skin incision group, there was no significant difference in both total distance and mean of velocity when it compared to those of pre-values. After the sieve type neural electrode implantation, rats showed a significant decrease in total distance and mean of velocity. The decreased velocity of movement and the decreased total distance of movement were maintained to 28 days after implantation. In the skin incision group, there was no significant difference in both total distance and mean of velocity when it compared to those of pre-values. In sensory function, rats with skin incision did not show a significant change in PWT compared to that of pre-value. PWT in rats with electrode implantation was decreased from 7 days but there was no significant difference compared to those of SNI group. These results indicated that the general physical activity was slightly decreased after the sieve type neural electrode implantation but neural electrode implantation does not exacerbated mechanical sensitivity.

Disclosures: J. Hong: None. **W. Choi:** None. **M. Kwon:** None. **H. Park:** None. **J. Kim:** None. **J. Kim:** None.

Poster

300. Pain Models: Behavior

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Program #/Poster #: 300.12/Z5

Topic: D.03. Somatosensation: Pain

Support: NIH Clinical Center IRP
NICHD IRP

Title: Haploinsufficiency of the brain-derived neurotrophic factor (BDNF) gene causes reduced pain sensitivity in an animal model and humans with the WAGR copy number variant

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Abstract: Rare pain insensitive individuals offer unique insights into how pain circuits function, and have led to the development of new strategies for pain control. We investigated pain sensitivity in humans with WAGR (Wilms tumor, aniridia, genitourinary anomaly, mental retardation) syndrome, who have variable-sized hemideletion of the 11p13 region. The deletion region can be inclusive or exclusive of the brain-derived neurotrophic factor (*BDNF*) gene, a crucial trophic factor for nociceptive afferents. By mapping the deletion boundaries, and by using trancriptomic analyses of gene expression, we narrowed the possible causal genes to a small locus shared by the pain insensitive individuals, supporting that *BDNF* deletion was the most likely candidate to explain the pain insensitivity phenotype. Nociceptive responses assessed by quantitative sensory testing (QST), demonstrated pain insensitivity only in the WAGR subjects whose hemideletion included the *BDNF* gene. This pain insensitivity was present in

both hot and cold modalities. At highly noxious stimuli, the pain insensitive WAGR subjects were able to rate these stimuli as noxious, suggesting some degree of preservation of the nociceptive circuit. Analogous experiments in heterozygous *Bdnf* mutant rats revealed impairment in a variety of tests for cold and Aδ- and C-Fiber mediated heat nociception similar to what was observed in the human. These rats also responded to highly noxious stimuli but showed insensitivity to pain in the mildly noxious hot and cold range. Many pain insensitivity phenotypes to date have been localized to ablation or inactivation of primary afferent sensory neurons in the dorsal root ganglia. RNA-Seq analyses were performed on rat dorsal root ganglia and spinal dorsal horn, together containing the first two neurons in the pain circuit. In these analyses, *Bdnf*+/- rats showed gene signatures indicative of normal sensory neurons but a greater degree of abnormality in the spinal cord, consistent with the idea of altered spinal circuits related to processing and transmitting painful sensory inputs. Our parallel observations in humans and rats assign causality to the heterozygous loss of the *BDNF* gene and establish BDNF as a major determinant of nociceptive sensitivity.

Disclosures: M.R. Sapio: None. **M.J. Iadarola:** None. **A.J. Mannes:** None. **J.C. Han:** None.

Poster

300. Pain Models: Behavior

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Program #/Poster #: 300.13/Z6

Topic: D.03. Somatosensation: Pain

Support: CONACYT Grant 165994

Title: D2-like agonist enhances the antinociceptive effect of spinal mu-opioid agonist in inflammatory and neuropathic pain

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Abstract: Background. Opioidergic drugs are the most potent and efficacious treatment for pain relief, but its use is limited by the adverse effects that the chronic use entails. D2-like receptor (RD2) agonist induces significant analgesia at spinal cord level, but its effectiveness is more modest compared with opioids. At synaptic level, between C-fibers and dorsal horn neurons, it has been reported a synergic effect of quinpirole co-administrated with the mu-opioid receptor (MOR) agonist. Increased expression of MOR and RD2 has been observed in dorsal root

ganglion (DRG) and the superficial laminae of the dorsal horn in rats after sciatic nerve injury, also there were more DRG neurons co-expressing both receptors when neuropathy was installed. There is no evidence at behavioral level if intrathecal (i.t.) co-administration of D2-like agonist (quinpirole) potentiates the analgesic effect of a MOR agonist (DAMGO) in nociceptive (NOC), inflammatory (IF) and neuropathic (NP) models of pain. *Methods*. Male Wistar rats were used (250-350 g) for the study. Hargreaves' apparatus and aesthesiometer were used for the thermal and mechanical behavioral test respectively. Drugs were i.t. administrated at lumbar level. Intraplantar injection of complete Freund's adjuvant (CFA) was used to induce the IF model, and sciatic nerve loose ligation for the NP model. All the experiments were approved by our Institutional Ethics Committee. *Results*. Dose-response curves were obtained for both agonists; maximal analgesia was seen at 15 min. Analgesia produced by DAMGO was statistically significant in thermal and mechanonocicepive tests meanwhile quinpirole was significant only in mechanonociception. Quinpirole co-administration (1 nmol; this dose produced the 50% of the maximal effect) potentiated the DAMGO analgesic effect diminishing its ED_{50} 6-fold only in mechanonociception. In the IF model, we used the first dose that produced analgesia in the synergy assay and was compared with the agonists administrated alone. Co-administration reverted hyperalgesia and returned latencies to its basal levels in both behavioral tests, which didn't happen when agonists were administrated alone. In NP, the results were similar. Co-administration produced partial reversion of allodynia, but drugs alone did not. *Conclusions*. I.t. co-administration of quinpirole and DAMGO potentiated the analgesia produced by MOR activation in NOC, IF and NP pain models. The results suggest that the combination of sub-effective doses of D2-like agonist could increase the analgesic effects of μ-receptor agonists, in a dose-specific manner and could reduce the secondary effects mediated by the same receptor.

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Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.14/Z7

Topic: D.03. Somatosensation: Pain

Support: NIH NS014624 (RHL)
DFG 326726541 (NM)
CNNSF 81373993 (HN)

Title: Behavioral scaling of the intensity of mechanical and heat stimulation of the cheek in mice

Authors: N. M. MALEWICZ[1], Z. ZHANG[1], N. KUMOWSKI[1], O. HURWITZ[1], S. G. SHIMADA[1], H. NIE[2], *R. H. LAMOTTE[1]

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Abstract: Sensory testing of the cheek in mice with mechanical and thermal stimulation is not standardized nor validated and difficult to apply. We developed a stimulation procedure and a discomfort rating score (DRS) to evaluate behavioral responses of mice to innocuous and nociceptive heat and punctate mechanical stimuli, of different intensities applied to the cheek. C57BL/6 mice (6 - 8 weeks old) were stimulated on the cheek in a meshed test chamber with Von Frey-type filaments (VFFs) delivering different bending forces (2 - 40 mN) but with the same tip diameter (either 0.1, 0.2 or 0.4 mm), or with a contact thermode (2 x 3 mm, 38 °C, warmth; 52 °C, noxious heat) (n=10-12 per group). Behavioral responses were video recorded and scored with experimenters blinded as to treatment condition. The DRS differentiated between no reaction, looking, withdrawal, flinching, biting, shaking, jumping and vocalizing with each wipe added into each score. Additional tests were conducted with the 0.1 mm VFFs to validate the DRS as a means of using aversive behaviors to scale graded nociceptive stimuli by measuring 1) facial grimaces using the Mouse Grimacing Scale (MGS, after Langford et al. 2010) (n=12) 2) Withdrawal latencies (measuring skin contact electrically) (n=14) and 3) by measuring the changes in DRS produced 48 hrs after intradermal injection of a desensitizing dose of capsaicin (n=8) or by the development of allergic contact dermatitis (ACD) produced by sensitizing the abdomen and subsequently challenging the cheek with topical 1% squaric acid dibutyl ester (n=10). All procedures were consistent with IASP guidelines and approved by Yale IACUC.

The thermode evoked a significantly different DRS for 52 vs. 38 °C. VFFs of a given tip diameter elicited monotonically increasing DRS scores with increases in force. The force required to elicit a given DRS decreased with tip diameter. Responses to VFFs with a 0.1 mm tip resulted in best statistically distinguishable behaviors and DRS. For the 0.1 mm tip VFFs, higher DRS values correlated with increased MGS ratings and shortened withdrawal times. A significant increase of DRS correlating with higher MGS and shortened withdrawal times was detected for heat vs warmth. DRSs in response to the 0.1 mm VFFs or to warmth and to noxious heat decreased significantly after capsaicin (desensitization) and increased after ACD (hyperalgesia).

The findings provide a validation of methods to score aversive behavioral responses that can be used to differentiate between and scale different intensities of punctate mechanical and heat stimuli delivered to the cheek.

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are a PI for a drug study, report that research relationship even if those funds come to an institution.; ork was supported by NIH NS014624.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.15/Z8

Topic: D.03. Somatosensation: Pain

Support: PAPIIT RA205018

Title: Mental nerve injury induces novelty-seeking behavior leading to increasing ethanol intake in wistar rats

Authors: E. PERRUSQUIA, R. C. ACEVEDO, C. D. MONTES-ANGELES, *I. O. PEREZ-MARTINEZ
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Abstract: The chronic neuropathic orofacial pain (CNOP) is freque ntly induced by dental treatment and orofacial surgeries. This kind of pain affects the adaptability to environmental changes in both model animals and humans.
Part of adaptation process depends on the ability to recognize between familiar and novel stimuli. CNOP induces novelty-seeking behavior as a deficit in environmental adaptation. Another side, the novelty-seeking is a sign for susceptibility to development abuse of drugs. Evidence shows that CNOP leads to alcoholism in animal models. The behavioral relationship between CNOP, novelty seeking behavior, and substance abuse is unknown. In this article, we address if CNOP produces increasing in novelty seeking and leads to alcoholism. At first, we used the mental nerve injury as neuropathic orofacial pain model; we evaluate both thermal and mechanical allodynia. We used the novel recognition task to determine the novelty-seeking behavior and the drink-in-darkness protocol to assess binge ethanol intake. Our results show that mental nerve constriction increases the novelty-seeking behavior ($p=0.01$) and correlates with ethanol binge consumption ($r2=0.68$, $p=0.0008$). The increasing of novelty-seeking behavior can serve as a predictor of risk to developing drug abuse. The treatment of chronic neuropathic orofacial pain involves the high risk to produce addiction when is used opioids. The level of novelty-seeking evaluation in patients with neuropathic pain before treatment is critical. The present study demonstrates for the first time that trigeminal injury, which induces CNOP, is enough to provide the novelty-seeking behavior and lead to ethanol binge intake.
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Poster

300. Pain Models: Behavior

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Program #/Poster #: 300.16/Z9

Topic: D.03. Somatosensation: Pain

Support: Start-up funds to WRR

Title: Spinal mobilization mitigates NGF induced reduction of rat exploratory behavior

Authors: *W. R. REED[1], J. W. LITTLE[5], T. J. NESS[2], R. E. SORGE[3], P. LI[4]
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Abstract: Low back pain (LBP) is a complex and poorly managed global health problem with lifetime prevalence rates ranging from 60-80%. Spinal mobilization (SM) is a commonly used non-pharmacological approach for the treatment of non-specific LBP. However, greater utilization and clinical optimization of SM has been hampered by a lack of knowledge regarding its underlying physiological mechanisms and good preclinical models in which to study the development and/or treatment of chronic LBP. Nerve growth factor (NGF) is a naturally occurring neurotrophin implicated in the regulation of mechanical/thermal hyperalgesia in both animals and humans. Damaged or overworked skeletal muscles experience increased NGF levels which likely contribute to the physical complaints associated with non-specific LBP. To determine the impact of SM on rat exploratory behavior in a LBP model, two unilateral L5 multifidus injections of NGF (0.8µM, 50µL) or Phosphate buffered saline (PBS; 50 µL) were delivered at an interval of 5 days (on Day 0 and Day 5) in experimental groups with or without 10 minutes of daily SM. Four groups (PBS, PBS+SM, NGF, NGF+SM) of adult female Sprague-Dawley rats were used (n=8 per group). SM (1.2Hz, 0.9N) was delivered under isoflurane anesthesia beginning on Day 1 using a computer controlled feedback motor. All experimental animals regardless of group received 10 minutes of daily isoflurane to control for this experimental variable. The change between baseline and day 11, a time point of established persistent LBP, for each group was evaluated using paired t tests and the difference across groups was evaluated with an ACOVA model and post hoc t tests. Compared to 10 minutes of baseline open field testing, at Day 11 the number of rearing events decreased for all groups ($P<0.05$), where the NGF group decreased more than the PBS group (24±9 vs 11±11, $P=0.04$) and the NGF+SM group had a significantly greater number of rearing events compared to the NGF group (36±13 vs 16±5, $P<0.01$). Similarly at day 11, the total distance (in) traveled significantly decreased for all groups ($P<0.05$), where the NGF+SM group traveled significantly greater distances than the NGF group (953±171 vs 675±192, $P=0.01$). While the physiological

mechanisms responsible for these SM-related effects on exploratory behavior are currently unknown; clinically, the therapeutic effect of spinal manual therapy is thought to be related to the diverse cutaneous and musculoskeletal mechanoreceptor stimulation inherent to manual therapy delivery. Future work using this LBP animal model will investigate potential peripheral/central mechanisms of SM and other manual therapies.

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Poster

300. Pain Models: Behavior

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Topic: D.03. Somatosensation: Pain

Support: BSB Research Enhancement Funding
ATA
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Title: Sex-dependent age-differences in response to an acute model of post-surgical pain

Authors: *N. DOS SANTOS, L. T. THOMPSON, M. D. BURTON
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Abstract: Aging-related studies in animal models of pain plasticity leading to chronic pain remain rare. This is in spite of the prevalent association of aging with chronic pain in human populations. Several studies show significant age differences in the onset and development of chronic pain. Young males develop more robust mechanical allodynia than old males in response to spared nerve injury and to chronic inflammation. Decreased spontaneous activity of C-fibers from aged animals has also been reported. In the present study, to explore both sex- and age-differences in the development of acute pain, we modified the traditional Brennan incision model to involve a more extensive injury to underlying muscle, to mimic a more severe trauma. This involved incision of skin and musculature of the plantar aspect of the hind paw in both young (4-5 mo) and aged (>22 mo) male and female FBN hybrid rats. To reveal differences in the plasticity circuitry to chronic pain, we utilized a hyperalgesic-priming model. All groups of animals received a sub-threshold dose of prostaglandin E2 (100 ng) in the plantar aspect of the surgerized hind paw 21 d after incision. Withdrawal threshold to mechanical stimuli was tested using von Frey filaments around the surgery site. Thermal hyperalgesia was assessed using the Hargreaves apparatus. Additionally, to assess post-surgical inflammation, temperature of the plantar aspect of the hind paw was recorded using a forward-looking infrared (FLIR) camera. Preliminary data reveals sex- and age-differences in response to the incision. Males in both age

groups resolve mechanical hypersensitivity and thermal sensitivity within 7 d after injury, but females present more variability on the resolution of pain. Temperature of the plantar skin is significantly higher during 7 d post-injury, with no significant difference between groups. Old males take longer to exhibit mechanical sensitization, showing aggravated response 3 d after incision in comparison to 1 d after incision in young males. No age-related differences in mechanical allodynia were seen between old and young females. There is no significant difference in the hyperalgesic-priming phase across all groups. FBN rats show sex-dependent thermal sensitivity: Females have greater thermal hyperalgesia following incision than males. These studies are the first of their kind to assess models of acute pain and the transition to chronic pain in aged male and female animals. The results suggest that the age-related delay of the onset of acute pain is exclusive to males.

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Poster

300. Pain Models: Behavior

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Program #/Poster #: 300.18/Z11

Topic: D.03. Somatosensation: Pain

Title: A low dose of quercetin modifies the antialodynic effects of BD-1063

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Abstract: BACKGROUND. The treatment of neuropathic pain is performed according to the etiology. The most used drugs are neuromodulators; however, exist others pharmacological strategies that may be potentially useful. The aim of this study was study the anti-allodynic effects of a sigma-1 antagonist (BD-1063) and quercetin in combination using a model of neuropathic pain. **METHODS**: Wistar male rats were employed and subjected to chronic constriction injury (CCI), 10 days after surgery the anti-allodynic effect (acetone test) after single-dose of BD-1063 (5.6 - 56.2 mg/kg s.c.), quercetin (5.6 mg/kg) and the combination of BD-1063 and quercetin 5.6 mg/kg were tested. **RESULTS**: The anti-allodynic effect of BD-1063 increased in a dose-dependent manner. The effect of quercetin (5.6 mg/kg) was 15.85 ± 14.6 au. The time-course shows that BD-1063 (56.2 mg/kg) reached its maximum effect at 30 min, producing an anti-allodynic effect of 89.8 ± 2.4 %, whereas BD-1063 (17.8 mg/kg) + QUER (5.6 mg/kg) produced their maximum effect at 90 min with 77.1 ± 4.2 %. It is possible to observe that the curve of the combination moves to the left. The comparison of the ED_{50} shows that a smaller amount of BD-1063 is required in combination (10.8 mg/kg) to achieve the same level of effect

that the individual administration (22.7 mg/kg). Of the different doses in combination, 2 resulted in supra-additive effects when compared with the theoretical sum. The association of BD-1063 (17.8 mg/kg) with quercetin (5.6 mg/kg) showed a higher percentage of potentiation (182%) with an effect of 192.2 ± 8.3 au. **CONCLUSION**: The pharmacological association of a sigma-1 antagonist and the flavonoid quercetin may be useful in the treatment of neuropathic pain. The anti-allodynic effects shown by BD-63 individually administered were modified when combined with a dose of quercetin which alone did not show anti-allodynic effects.

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Poster

300. Pain Models: Behavior

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Topic: D.03. Somatosensation: Pain

Support: Peggy and Avinash Ahuja Foundation and the Helen Buchanan and Stanley Joseph Seeger Endowment at The University of Texas MD Anderson Cancer Center

Title: Losartan, an angiotensin II type 1 receptor antagonist, alleviates mechanical hyperalgesia in a rat model of chemotherapy-induced neuropathic pain by inhibiting inflammatory cytokines in the dorsal root ganglia

Authors: *E. KIM[1,2], H. KIM[2], S.-H. HWANG[2], H.-K. KIM[1], S. ABDI[2]
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) adversely impacts quality of life and a challenge to treat with existing drugs used for neuropathic pain. Losartan, an angiotensin II type 1 receptor (AT1R) antagonist widely used to treat hypertension, has been reported to have analgesic effects in several pain models. In this study, we assessed losartan's analgesic effect on paclitaxel-induced neuropathic pain (PINP) in rats and its mechanism of action in dorsal root ganglion (DRG). Rats received intraperitoneal injections of 2 mg/kg paclitaxel on days 0, 2, 4, and 6 and received single or multiple intraperitoneal injections of losartan potassium dissolved in phosphate-buffered saline at various times. The mechanical thresholds, protein levels of inflammatory cytokines, and cellular location of AT1R and interleukin 1β (IL-1β) in the DRG were assessed with behavioral testing, Western blotting, and immunohistochemistry, respectively. Data were analyzed by two-way repeated measures analysis of variance for the behavioral test or the Mann-Whitney U test for the Western blot analysis and immunohistochemistry. Single and multiple injections of losartan ameliorated PINP,

and losartan delayed the development of PINP. Paclitaxel significantly increased, and losartan subsequently decreased, the expression levels of inflammatory cytokines, including tumor necrosis factor α and IL-1β, in the lumbar DRG. AT1R and IL-1β were expressed in both neurons and satellite cells and losartan decreased the intensity of IL-1β in the DRG. Our results indicate that losartan may ameliorate PINP by decreasing inflammatory cytokines. Its use as a new or add-on therapy for CIPN patients should be investigated.

Disclosures: E. Kim: None. **H. Kim:** None. **S. Hwang:** None. **H. Kim:** None. **S. Abdi:** None.

Poster

300. Pain Models: Behavior

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Topic: D.03. Somatosensation: Pain

Support: NSERC

Title: Investigating the comorbidity of chronic pain and depression

Authors: *V. MICHAILIDIS, C. CHO, M. SIVASELVACHANDRAN, E. ACLAND, N. LIDHAR, C. CHAN, L. J. MARTIN
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Abstract: Chronic neuropathic pain patients experience drastic changes in quality of life. In particular, 30%-50% of chronic neuropathic pain patients report depression as a side effect, suggesting a link between chronic pain and depression. Of the patients experiencing the comorbid disease, almost half are female. However, most of clinical research conducted on this comorbidity use male inbred rodent strains, which may not be as transferable to the affected female population. As such, our study aimed to characterize any sex differences in the depressive phenotype following peripheral nerve injury of an outbred mouse strain. We used male and female CD-1 mice (6-8 weeks) characterized on a battery of tests designed to assess sensory thresholds, learned helplessness, anhedonia and anxiolytic behavior for 4 weeks following peripheral nerve injury. Our results indicate that peripheral nerve injury caused mechanical pain sensitivity in both male and female mice. Further, peripheral nerve injury induced anxiety in male mice as evinced by decreased time spent in open areas of the open field test. Conversely, injury caused a depressive phenotype in both sexes, 2 weeks following surgery as determined by the forced swim test. Interestingly, males recovered, while this behavior persisted for the female mice, suggesting a sex difference for the depressive phenotype time course. We also observed that nerve injury did not induce any changes in sucrose preference as both SNI and sham mice exhibited similar preference scores for sucrose across all time points. Lastly, there was a trend that indicated nerve injury increased latency to feed on the novelty suppression-feeding test,

however, this trend was only noticed in females at the 4-week time point, again suggesting a sex difference in the depressive phenotype. Overall, our experiments demonstrate that chronic neuropathic pain can induce sex specific changes in affect and thus demonstrates the importance of female inclusion in experiments.

Disclosures: V. Michailidis: None. **C. Cho:** None. **M. Sivaselvachandran:** None. **E. Acland:** None. **N. Lidhar:** None. **C. Chan:** None. **L.J. Martin:** None.

Poster

300. Pain Models: Behavior

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 300.21/Z14

Topic: D.03. Somatosensation: Pain

Title: A mechanistic study of cmt2b peripheral sensory neuropathy

Authors: *C. WU[1], K. J. SUNG[2], W. YANG[4], H. LIU[3], C. JOLIVALT[3], N. CALCUTT[3]
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Abstract: CMT2B, a rare but debilitating disease, features a prominent axonopathy - i.e. axonal dysfunction and degeneration - of peripheral sensory neurons. Patients lose pain sensation and frequently undergo amputation of the distal lower limbs. Genetic analyses have revealed missense autosomal dominant point-mutations in Rab7 (L129F, K157N, N161T/I, V162M). Currently, there are no disease-modifying treatments. We generated a knockin mouse model, the first ever rodent model for CMT2B. We have demonstrated in preliminary studies the mutant mice developed sensory deficits both functionally and structurally. The proposed study is to confirm and extend preliminary findings to explicate the mechanisms that underlie disease pathogenesis towards future discovery of treatment methods for CMT2B. The knockin mouse model of CMT2B that we have generated carries the Rab7V162M allele. The creation of the mouse is based on a well-characterized family of human CMT2B-Rab7V162M patients. Our preliminary results in the knockin Rab7V162M mutant mice demonstrate significant deficits in peripheral sensory function in comparison to wildtype littermates (+/+). The findings are consistent with an autosomal dominant effect. Furthermore, mice homozygous for the mutation (fln/fln) display more severe phenotypic manifestation than heterozygous littermates (+/fln), pointing to a possible gene-dosage effect. Consistent with findings in human CMT2B patients, mutant mice display no apparent deficits in learning and memory. Encouraged by these results, we propose to confirm and extend findings on the Rab7V162M knockin mouse, to demonstrate both its fidelity with respect to the human disease, and to decipher CMT2B disease mechanisms at the cellular and molecular level. Importantly, our preliminary studies and published work

shows that in mammalian cells CMT2B Rab7 mutations enhance activation of Rab7, resulting hyper-functional lysosomes and autophagy. Based on these studies, we will take advantage of the Rab7V162M knockin mouse to test the hypothesis that axonal dysfunction and degeneration in CMT2B is due to increased activation of Rab7 with consequent hyperactivity of the lysosome and autophagy pathways.

Disclosures: C. Wu: None. **K.J. Sung:** None. **W. Yang:** None. **H. Liu:** None. **C. Jolivalt:** None. **N. Calcutt:** None.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 301.01/Z15

Topic: D.03. Somatosensation: Pain

Support: National Natural Science Foundation of China 81500942
Beijing Talents Fund 2015000021469G204

Title: Involvement of spinal Src homology-2 domain-containing protein tyrosine phosphatase-2 and brain-derived neurotrophic factor in neonatal incision-induced exacerbation of incisional pain in adult rats

Authors: *X. DING[1,2], W. YANG[3], X.-D. LIU[5], X. YANG[4], H.-M. WANG[3], J. TAI[6]
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Abstract: Neonatal surgical trauma leads to exacerbated pain hypersensitivity after adult incision. Previously, we and others have reported that spinal Src homology-2 domain-containing protein tyrosine phosphatase-2 (SHP2) and brain-derived neurotrophic factor (BDNF) contribute to neuropathic pain and inflammatory pain in adult rodents. In this work, we investigated mechanisms in the spinal dorsal horn underlying the exaggeration of incisional pain induced by neonatal hindpaw incision. (1) Neonatal incision elevates the phosphorylation and expression of SHP2 in synaptosomal fraction of the spinal dorsal horn in adult rats subjected to neonatal incision and adult incision (nIN-IN), and the upregulation of SHP2 is highly correlated with pain hypersensitivity. Blockade of SHP2 phosphorylation in the dorsal horn using a SHP2 protein tyrosine phosphatase inhibitor NSC-87877, or knockdown of SHP2 by intrathecal delivery of small interfering RNA (siRNA), attenuates exacerbated pain hypersensitivity in nIN-IN rats.

Furthermore, the concentration of spinal phosphatidylinositol 3-kinase (PI3K) is significantly increased, which is highly correlated with pain behaviors in nIN-IN rats. Intrathecal application of PI3K inhibitors, LY294002 or wortmannin, alleviates exacerbated pain hypersensitivity in nIN-IN rats. Additionally, intrathecal administration of NSC-87877 or SHP2 siRNA attenuates the upregulation of PI3K. However, the phosphorylation of SHP2 and the expression of PI3K in the dorsal root near the dorsal surface of the spinal cord are not changed at the same time points used in detections of the spinal cord. (2) Spinal BDNF is significantly upregulated in nIN-IN rats. Coincidently, blockade of spinal BDNF alleviates pain hypersensitivity in nIN-IN rats, while spinal administration of exogenous BDNF in adult rats with only neonatal incision mimics exacerbated pain hypersensitivity, which have been found in nIN-IN rats. Finally, intrathecal application of minocycline to inhibit microglial reactivity attenuates the upregulation of BDNF and alleviates pain hypersensitivity in nIN-IN rats. Altogether, we provide solid evidence that spinal SHP2 and BDNF contribute to neonatal incision-induced exacerbation of incisional pain following adult incision.

Disclosures: X. Ding: None. **W. Yang:** None. **X. Liu:** None. **X. Yang:** None. **H. Wang:** None. **J. Tai:** None.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 301.02/Z16

Topic: D.03. Somatosensation: Pain

Title: Electrophysiological characterisation of nociceptive lamina I spinoparabrachial neurons in the anesthetized mouse

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Abstract: Recent behavioural and ex vivo electrophysiological experiments using wild type and KO mice have highlighted the role of lamina I projection neurons (PN) for the generation of pain sensation in pathological conditions. However, data on the in vivo properties of lamina I PN of the *mus* gender are markedly limited. The aim was to establish the physiological properties of lamina I spinoparabrachial neurons in naïve mice, and to evaluate the effect of “pharmacological disinhibition” on neuronal responses to light touch. Experiments were conducted in ventilated, isoflurane anesthetized, Swiss mice. Electrical activity was recorded using a tungsten microelectrode. Lamina I PN were searched for using antidromic stimulations from the parabrachial region. Mechanical and thermal stimuli consisted of brush, Von Frey hair (VF), pinch with haemostat clamp, and water jet (10 ml). Responses to electrical stimuli (ES) were generated using needles inserted in the receptive field. After the initial characterisation,

responses to brush and VF were reassessed before and after application of vehicle or a mix of bicuculline + strychnine (BS) on the spinal cord. Responses were measured as peak firing frequency over 0.1 s and number of action potentials (AP) over 5 s. Electrolytic lesion was performed to locate the recording site. Seventy one lamina I units satisfying classical PN criteria were characterized, with conduction velocities of 4.7 (3.0-6.5) $m.s^{-1}$ (data given as median (25^{th}-75^{th} percentiles)). Fifty seven units were classified as polymodal PN, and 14 as modality specific/preferential PN (2 heat, 2 mechanical, 10 cool/cold). Five, 14, 11, 9, 8 and 10 polymodal PN had mechanical thresholds corresponding to brush, VF 25, 50, 100, 200 mN and pinch, respectively. Polymodal PN responded to pinch with 96 (53-169) AP at 70 (45-105) Hz, and to WJ 50 °C with 163 (20-230) AP at 120 (55-170) Hz. Cool/cold PN responded to WJ 0 °C with 127 (110-156) AP at 105 (47-152) Hz. The maximum number of C fibre-induced AP in response to ES was 3 (1-5) AP. Upon repeated ES at 1 Hz, 12/27 PN did not show wind up. Increased response to brush was observed in 1/13 (+3 AP, +60 Hz) and 24/47 (+11 (6-22) AP, +85 (40-130) Hz) PN after vehicle and BS application, respectively. Increased responses to VF paralleled enhanced response to brush after BS application. Lamina I spinoparabrachial PN constitute a highly heterogeneous population, with about 70 % being nociceptive specific, and 50 % showing appearance/increase of responses to light touch upon local disinhibition. The specific physiological properties of the subgroup of lamina I PN responsible for abnormal pain in pathological conditions require further investigation.

Disclosures: J. Allard: None.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: D.03. Somatosensation: Pain

Support: Rita Allen Foundation
American Pain Society
Trustee and Proctor Scholar Program at CCHMC
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Title: Reduced muscle growth hormone levels regulate peripheral sensitization after incision through macrophage-dependent sequestering

Authors: *A. J. DOURSON[1], C. E. MCCROSSAN[1], Z. K. FORD[1], M. C. HOFFMAN[1], M. P. JANKOWSKI[1,2]
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Abstract: Growth hormone (GH) is a well-known regulator of growth and homeostasis. Reports have also shown that in addition to growth problems, children with deficits in GH have a resting pain in their limbs. Furthermore, exogenous GH treatment may relieve pain in subsets of patients with fibromyalgia and in children with cutaneous ulcers. However, the role of GH in nociceptive processing is largely unknown. Our recent preclinical data showed that low dose GH pre-treatment could significantly block inflammation induced afferent sensitization and pain-related behaviors in neonatal mice. We therefore sought to determine if similar results could be obtained in other models of pain and whether the effects of GH were localized to the site of injury. We used a rodent surgical pain model and found that GH was significantly reduced in the muscles after neonatal incision. A single, local, and low dose injection of GH to the incision site at the time of injury could block spontaneous and evoked pain-related behaviors 24 hours after injury. Using a neonatal *ex vivo* hind paw muscle/tibial nerve/dorsal root ganglion (DRG)/spinal cord recording preparation, we found that group III/IV primary afferent sensitization after incision was also blocked with local GH treatment. Upregulation of specific sensory transducing receptors in the DRGs after injury was additionally inhibited by local GH injection. Reduced GH levels after incision appeared to be due to infiltrating macrophages sequestering GH at the incision site. Macrophage-specific growth hormone receptor knockout mice (MacGHrKOs) showed blunted pain-related behaviors and no upregulation of incision-induced receptor expression in DRGs after injury. These mice also did not show any reduction in muscle GH after incision. Decrease in muscle GH levels appeared to mediate its effects on pain-related behaviors through a loss of neuronal microRNA-133a (miR-133a) mediated inhibition of serum response factor (SRF) regulated transcription. This data suggested that GH may provide a tonic inhibition of afferent sensitization that is removed upon peripheral injury. This hypothesis is currently being tested using afferent specific GH receptor knockout mice (Advillin-Cre x GHrfl/fl). Results may thus provide novel therapeutic targets for treating neonatal pain.

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Poster

301. Pain Models: Physiology

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Program #/Poster #: 301.04/Z18

Topic: D.03. Somatosensation: Pain

Support: NIH Grant DE018450
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Title: Alterations in cerebellar neuropeptide expression and astrocyte activation in a repetitive acidic saline exposure jaw pain model

Authors: *J. MORRIS-WIMAN[1], C. G. WIDMER[2]
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Abstract: Several imaging studies provide evidence that the cerebellum is activated with pain, but it remains unclear what role the cerebellum has during nociceptive processing. No studies have assessed cerebellar expression of pain-related neuropeptides or alterations in astrocyte activity. We have previously reported on a model for orofacial pain in which repetitive unilateral injections of acidic saline into masseter muscle elicited persistent bilateral pain that was associated with changes in chewing behavior and with significant increases in neuropeptide expression and astrocyte activation within trigeminal ganglia. Blocking ASIC3 channels prevented all pain-associated alterations. The objective of this study was to determine if similar changes in neuropeptide expression and astrocyte activation within the cerebellum occur with persistent pain in our model. **Methods**: Female CD-1 mice were repetitively injected with either neutral saline (pH 7, n=5), or acidic saline (pH 4, n=5) into the right masseter separated by five days. Five additional mice were injected with 10µl of APETx2 (3µM) into the right masseter just prior to a second acidic saline injection and 5 mice were used as unmanipulated controls. Seven days after the second injection, the mice were sacrificed, the cerebellum harvested, snap-frozen, and stored at -80° until cryosectioned. 12µm cryosections were immunostained for substance P (SP) and GFAP and images were acquired using a Zeiss MRm digital camera and Axiovision software. Images were histogram-matched and thresholded to produce binary images to eliminate bias. The total number of SP-positive Purkinje cells per folia length and the number of Purkinje cells associated with GFAP-immunostaining were counted for three sections, 150µm apart, for each animal. **Results**: No differences were detected among the groups in relative numbers of SP immunostained Purkinje cells. No significant differences were observed between control and neutral saline-injected groups in the percentage of SP-positive Purkinje cells co-localized with GFAP. However, a significant increase was observed between acidic saline-injected and neutral and control groups (91% acid, 52% control, 52% neutral). APETx2 did not prevent this increase. Additionally, SP-negative Purkinje cells were associated with GFAP immunostaining in the APETx2 group but not in other groups. **Conclusions**: The results of this study suggest that astrocyte activation occurs within the cerebellum in persistent pain and is associated with SP-positive Purkinje cells. Unlike in other pain processing regions of the CNS, astrocyte activation does not appear to be dependent on ASIC3.

Disclosures: J. Morris-Wiman: None. **C.G. Widmer:** None.

Poster

301. Pain Models: Physiology

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Title: Spinal lamina I projection neurons play distinct roles in nociception

Authors: *N. V. VOITENKO[1,4], K. AGASHKOV[2], V. KROTOV[3], M. KRASNIAKOVA[2], Y. ZABENKO[2], B. V. SAFRONOV[5], P. BELAN[3,4]
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Abstract: Spinal lamina I projection neurons (PNs) relay peripheral nociceptive inputs to the supraspinal pain processing centers. Yet, the principle of signal encoding by population of these neurons is poorly understood. Here we identified two groups of nociceptive-processing PNs with distinct input-output characteristics. The vast majority of neurons are excited only by a strong afferent stimulation, generate one-two spikes, and function as nociceptive input detectors. However, 85% of action potentials in the entire PN population originated from a small fraction of high-output neurons (16%). These receive a large number of direct C-fiber inputs, generate intrinsic bursts and efficiently integrate network activity via NMDA-receptor-dependent mechanisms and plasticity. The high-output PNs gradually encode the intensity of peripheral nociceptive input to the number of generated spikes. Thus, two groups of PNs, detectors and intensity encoders, play principally different roles in nociception.

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Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 301.06/AA2

Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS045594
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Title: Evidence of direct interactions between somatic sensory afferents and pre-ganglionic sympathetic neurons and their modification by peripheral nerve injury

Authors: *W. XIE, J. A. STRONG, J.-M. ZHANG
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Abstract: We previously reported that sympathetic innervation helps maintain immune homeostasis and that surgical sympathectomy reduces pain by suppressing inflammation in axotomized or inflamed DRGs. In this study, we investigated anatomical and functional interactions between the sympathetic and somatosensory systems in the spinal cord. Retrograde tracing with Dextran-Texas red injected into the transected L5 spinal nerve (spinal nerve ligation, "SNL" neuropathic pain model) revealed sensory fiber projections to the intermediolateral dorsal horn and the central canal that associated closely with clustered Choline Acetyltransferase (ChAT)-ir pre-ganglionic sympathetic neurons (PreGNs). Immunohistochemical studies demonstrated that the sensory fibers interacting with PreGNs included CGRP-ir sensory neurons. In other experiments, AAV8 expressing green fluorescent protein (GFP) was injected into both L5 spinal nerves to preferentially label larger diameter sensory neurons. SNL was performed on one side 2 weeks later. GFP positive fibers projected to the intermediolateral dorsal horn and formed close interactions with PreGNs in spinal cord samples obtained 3 weeks after SNL. These projections appeared to be more extensive on the ipsilateral side of the spinal cord. In vivo recordings were performed on microfilaments teased out from the postganglionic sympathetic chain at the level between L5 and L4 DRGs, after cutting the grey rami that bring postganglionic sympathetic axons into the L4 and L5 spinal nerves. In anesthetized rats, electrical stimulation of the sciatic nerve at C-fiber strength consistently evoked action potentials both monosynaptically (presumed PreGNs) and polysynaptically from the sympathetic chain fibers. These responses remained when the L4 and L5 ventral roots distal to the recording site were cut just prior to recording, indicating the evoked activities were triggered by primary sensory inputs. In recordings made 7, 28, or 56 days after spared nerve injury (model of neuropathic pain), both A- and C-fiber strength stimuli evoked responses in the sympathetic chain; the number of fibers that could be activated (both monosynaptically and polysynaptically) increased, and spontaneous

activity increased. This is to our knowledge the first report of direct activation of the sympathetic neurons by somatic sensory inputs, which may contribute to previously described spinal-level sympathetic reflexes. We suggest that abnormal activities originating from injured peripheral nerve or DRG neurons drive sympathetic activity, which in turn enhances pain by regulating inflammatory responses in the peripheral nervous system.

Disclosures: W. Xie: None. **J.A. Strong:** None. **J. Zhang:** None.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 301.07/AA3

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant Number 18K16462
Dokkyo Med Univ Endowment Fund

Title: Different effects of deletion of the serine racemase gene on nociceptive behavior among different models of neuropathic and inflammatory pain

Authors: *E. KATO, T. FUKUSHIMA, M. MAEKAWA, Y. HORI
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Abstract: Peripheral nerve injury and tissue inflammation often induce abnormal pain. The activation of *N*-methyl-D-aspartate (NMDA) receptors mediates the development and maintenance of this abnormal pain. D-serine co-localizes with NMDA receptors and acts as an endogenous co-agonist of the NMDA receptor at the glycine binding site. D-serine is synthesized from L-serine by serine racemase (SR), an enzyme that is abundant in the central nervous system. How alterations in SR activity are involved in the modulation of neuropathic and inflammatory pain behavior remains unclear. In the present investigation, we compared pain behaviors in SR knockout (KO) mice and wild-type (WT) mice after subjected to a chronic constriction injury (CCI model of Bennett), partial sciatic nerve ligation (PSL model of Seltzer), spinal nerve ligation (SNL model of Chung), and an inflammatory pain induced by subcutaneous formalin.
Seven- to nine-week-old male WT and SR-KO mice were used for the experiments. Under halothane anesthesia, the mice were subjected to neuropathic surgery. Three types of nerve ligations were performed, as previously described by Bennett et al. (1988), Kim and Chung (1992), and Seltzer et al. (1990). The left sciatic nerve was tied loosely with four ligatures of chromic gut at the mid-thigh level (Bennett model), the left L5 and L6 spinal nerves were isolated and ligated tightly with a 4-0 silk thread (Chung model), and the dorsal one-third to one-half of the left sciatic nerve was tightly ligated (Seltzer model). Mechanical allodynia was

assessed by measuring the frequency of withdrawal responses using von Frey filaments both before and after ligation. To induce inflammatory pain, paraformaldehyde (50 μL, 25% in distilled water) was injected subcutaneously in the dorsal surface of the left hind paw. The mice were continuously observed for 60 min after the formalin injection, and the time of licking of the injected paw was measured during the observation period.
Behavioral observations showed the following results: 1) The formalin-induced licking response was prolonged during the second phase in SR-KO mice, whereas the first phase was not affected. 2) Mechanical allodynia in the Seltzer model was quite similar between SR-KO mice and WT mice. 3) Mechanical allodynia in both the Chung and Bennett models was significantly enhanced in SR-KO mice compared with WT mice.
The present results may reflect the different involvements of NMDA receptors in different models of neuropathic and inflammatory pain. We are currently investigating how differently synaptic circuit activity in the spinal dorsal horn is affected by SR knockout in different pain models.

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Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

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Topic: D.03. Somatosensation: Pain

Support: CA200263
H.E.B. Professorship in Cancer Research

Title: TLR4 knockout rats show reduced signs of paclitaxel-related chemotherapy induced peripheral neuropathy

Authors: *P. M. DOUGHERTY, Y. LI
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Abstract: The contribution of the toll-like receptors (TLRs), TLR4 in particular, has been reported in the initiation and maintenance of paclitaxel-related chemotherapy-induced peripheral neuropathy. Furthermore, paclitaxel produces peripheral neuropathy by sensitizing transient receptor potential vanilloid subtype 1 (TRPV1) through Toll-like receptor 4 (TLR4) signaling. In current study, TLR4 knock-out rats have been used to further test the interaction of TLR4 and TRPV1 in paclitaxel-induced peripheral neuropathy. Western blot data shows that TLR4 and TRPV1 appear to physically interact, evidenced by their co-immunoprecipitation from L4-L5 DRG at 7 days after paclitaxel treatment using either as the anchoring epitope. TNFα levels of macrophage culture in response to paclitaxel or LPS were reduced in homozygote knock-out

compared to heterozygote and wild type rats which indicates that TLR4 is nonfunctional in homozygote knock-out animals. The behavior data show that paclitaxel-induced behavioral hypersensitivity is reduced in TLR4 knock-out rats. Calcium imaging in dissociated DRG neurons from homozygote knock-out rats and wild type rats with vehicle or paclitaxel treatment was used to assess whether TLR4 functionally enhances TRPV1 signaling. DRG neurons from paclitaxel-treated TLR4 knock-out rats were observed to show relatively weak (340/380 ratio) and slow response to capsaicin compared with DRG neurons from paclitaxel-treated TLR4 wild type rats. In summary, TLR4 is one of major players in paclitaxel-induced peripheral neuropathy by inducing sensitization of TRPV1.

Disclosures: P.M. Dougherty: None. **Y. Li:** None.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 301.09/AA5

Topic: D.03. Somatosensation: Pain

Support: R01 DE027233/NIH
CTSA/IIMS Pilot Award

Title: Contribution of peripheral brain-derived neurotrophic factor (bdnf) signaling in oral cancer pain

Authors: *D. ARRIS, M. GRAYSON, V. VALENZUELA, S. RUPAREL
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Abstract: Background: Pain is the primary presenting symptom of patients with head and neck carcinoma (HNC) and one of the most common persisting complaints, contributing to a tremendous reduction in quality of life. Many patients subsequently require opiates and tolerance develops rapidly. Developing a therapy that blocks cancer pain is of critical importance; however; little is known about the mechanisms by which HNC cells evoke pain. The current study seeks to decipher a novel peripheral role of brain-derived neurotrophic factor (BDNF) signaling in oral cancer pain. **Methods:** We use an *in vivo* tongue cancer pain model in male mice to study the role of BDNF in oral cancer pain by injecting either human Oral Squamous Cell Carcinoma (OSCC) or normal oral keratinocyte cells in the tongue. Upon cell inoculation, OSCC cells produce a localized tumor that mimics patient-reported pain-like symptoms in mice. Using this *in vivo* model, we performed human BDNF ELISA as well as immunohistochemical analysis of BDNF and TrkB (BDNF receptor) expression in tongue tissue of tumor-bearing and normal animals. Additionally, we also determined the effect of systemic and local administration of a TrkB antagonist in reversing pain-like behavior in the orthotopic model. **Results:** BDNF

signaling is significantly increased in HNC tumors, contributing to epithelial to mesenchymal transition, preventing apoptosis, and inducing chemo-resistance. Consistent with clinical findings, our data demonstrated that BDNF levels are up-regulated in oral tumors of a mouse orthotopic cancer pain model compared to normal animals**.** Moreover, our data show that BDNF is expressed specifically on the invasive front of tumor cells and BDNF positive cells were in close proximity to sensory fibers within the tumor. Antagonizing the TrkB receptor systemically and locally in the tongue significantly reverses pain-like behaviors *in vivo***.** This is a novel finding and, to our knowledge, the first demonstration of a peripheral role for BDNF signaling in HNC pain. **Conclusions:** Our data supports a novel role of BDNF signaling in mediating oral cancer pain. Targeting BDNF may prove an effective approach for treating cancer-induced pain, tumor progression as well as chemotherapy resistance. We are currently identifying different types of sensory fibers in the tongue that may be regulated by BDNF release from OSCC cells, using a novel electrophysiological method allowing for single-fiber recordings of normal tongue and tumor-bearing tongue in mice.

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Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 301.10/AA6

Topic: D.03. Somatosensation: Pain

Support: 5R01NS038253-18

Title: Modeling Nav1.7 channelopathies using CRISPR/Cas9

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Abstract: Pain is a critical adaptive sensation required for protection against danger and which facilitates healing after injury. However, when this system functions abnormally, either as a consequence of congenital or acquired abnormalities, pathological pain is generated. Mutations in ion channels expressed by sensory neurons have a major impact on pain sensibility. Among them, SCN9A which encodes Nav1.7 has been extensively studied because it is the most abundant voltage-gated sodium channel in these “pain” sensory neurons. Gain-of-function

mutations in Nav1.7 lead to inherited pain disorders including inherited erythromelalgia(IEM) and paroxysmal extreme pain disorder(PEPD), whereas loss-of-function mutations cause congenital insensitivity to pain(CIP). Most studies investigating the pathophysiology of Nav1.7 mutations do this by overexpressing human channels heterologously in non-neuronal cells or in rodent sensory neurons *in vitro*, which limits translational implications. We have successfully exploited CRISPR/Cas9 genome editing to introduce gain-of-function (GOF) and loss-of-function(LOF) point mutations in the SCN9A gene to generate IEM, PEPD, and CIP models *in vitro*(primary mouse and human induced sensory neurons) and *in vivo*(mutant mice) and have made multiple mutant lines. Nav1.7 GOF mutations in human iPSC induced sensory neurons dramatically increased spontaneous firing and burst firing rate in a temperature dependent manner as measured using multi-electrode arrays(MEA). Female mice carrying a Nav1.7 GOF mutation related to IEM in humans had difficulty nursing pups due to the pain and swelling of teats when lactating. For Nav1.7 LOF mutation studies, we have performed MEA and whole-cell patch clamp recording and observed less spontaneous firing (MEA), less Nav1.7 currents and an increased threshold to generate action potentials. We also observed a high mortality in pups carrying Nav1.7 LOF mutations, similar to that observed in global Nav1.7 knockout mice. These genetically engineered murine and human pain models not only enable us to mimic key features of the clinical presentation of the genetic pain disorder, but also provide a powerful tool to investigate pathophysiological mechanisms of the pain phenotype and to screen for novel therapeutics for these channelopathies.

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Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 301.11/AA7

Topic: D.03. Somatosensation: Pain

Support: NIH SC3 Grant 1SC3GM118218-01A1

Title: The effect of an insect pyrokinin on nociceptive sensitization of the defensive strike response in larval Manduca sexta

Authors: *M. FUSE, A. D. RICE
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Abstract: The opioid epidemic has necessitated a re-evaluation of the use of opioids in treating chronic pain. An insect-specific pyrokinin peptide (PK) defined by its conserved C-terminal FXPRLa amino acid sequence was previously suggested to act in an antinociceptive manner via opioid receptors, using both the hot-plate and tail immersion tests (Rykaczewska-Czerwinska et al., 2001). Given that this peptide does not appear to be structurally similar to opioids, this could be an alternative to opioid use in pain regulation, but may also be the endogenous "opioid-like" compound in insects. The defensive strike response in the hornworm, *Manduca sexta*, has been used to study pain-like responses, where nociceptive sensitization occurs after application of single noxious stimulus such as a pinch. Following a pinch, the force required to elicit a defensive strike response is attenuated, indicative of a state of hyperalgesia. The goal of this research was to determine whether the insect PK had antinociceptive effects in *M. sexta*, and whether this activity occurred via opioid receptors. Larvae were tested for baseline threshold to strike, then injected with naloxone, an opioid-receptor inhibitor, along with PK, and as with PK alone, the pinch threshold was significantly elevated. This suggested that naloxone could not counter the effects of PK. However, injection of naloxone alone significantly reduced the baseline threshold, suggesting that an opioid-like effect might be countering the mildly noxious effects of injection. Feeding naloxone did not reduce the baseline threshold, and a subsequent pinch still sensitized the larvae. Finally, multiple injections limited the efficacy of PK, but the effects of early naloxone injection could not fully block these effects. Taken together, these data suggest that the injection may be a mild stimulus to trigger an upregulation of endogenous opioid-like peptides, the effect of which is to maintain the high baseline threshold when no major aggravations exist. In contrast, the pinch appears sufficiently noxious to inhibit the analgesic effects of injection, lowering the opioid/PK levels, and allowing larvae to become sensitized.

Disclosures: M. Fuse: None. **A.D. Rice:** None.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

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Support: NIH GM115384
NIH NS100065
NSF-CRCNS IIS-130764
China Scholarship Council (201606370208)
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Title: A cortical gain control mechanism for pain

Authors: *J. WANG[1], J. A. DALE[2], H. ZHOU[3], Q. ZHANG[4], E. MARTINEZ[2], Z. W. CHEN, 10024[2]
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Abstract: Acute pain induces salient neural and behavioral responses that protect us from injury and harm. Chronic pain, however, is known to disrupt normal nociceptive processing. The prefrontal cortex (PFC) has been shown to exert critical top-down regulation of sensory inputs. Unfortunately, how individual neurons in the PFC respond to acute nociceptive inputs *in vivo* remains little-known. We recorded neurons from the prelimbic region of the PFC (PL-PFC) in freely behaving rats. We found that a significant number of PFC neurons increased their firing rates after noxious stimulations. Chronic pain, however, suppressed prefrontal activity by decreasing both basal spontaneous and pain-evoked firing rates. Importantly, we identified a linear correlation between basal and evoked firing rates of PFC neurons. As a result, even a small decrease in basal firing leads to a nearly two-fold reduction in the pain-evoked response in the chronic pain state. In contrast, enhancing basal PFC activity with low frequency optogenetic stimulation could scale up prefrontal outputs to inhibit pain. These results define a mechanism whereby PFC neurons can function as gain controllers for pain, and hence scaling up prefrontal outputs is a novel neuromodulation strategy to inhibit pain.

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Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 301.13/AA9

Topic: D.03. Somatosensation: Pain

Title: Ex-vivo human models of inflammatory and neuropathic pain states for enabling translational research and drug discovery

Authors: *A. GHETTI, Y. MIRON, A. TON, T. INDERSMITTEN, N. NGUYEN, P. RATCHADA, A. ALAMILLO, K. SWEAT, I. TAPIA, G. PAGE, P. E. MILLER
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Abstract: The incomplete understanding of chronic neuropathic and inflammatory pain mechanisms poses a major challenge for the development of new, non-addictive pain medications. In addition, cross-species differences in pharmacological responses and analgesic effects lead to poor translation of preclinical animal models to clinical studies in humans. We have previously shown that human sensory neurons, isolated from organ donors, can be

maintained in culture for several days (1); cells remain phenotypically stable for up to 14 days in culture and can be used to assess pharmacological responses by employing imaging- or electrophysiology-based methods. Here we present a novel preclinical discovery strategy, which utilizes human sensory neurons to establish cellular models of pathological states. These models recapitulate key features of inflammation-related and neuropathy-related pain. To generate these different pathological states *in vitro,* we incubated human sensory neurons with pro-inflammatory agents (PGE_2 and bradykinin) or with Oxaliplatin, a chemotherapy drug associated with peripheral neuropathy. Treatment with PGE_2 and bradykinin for 2 to 72 hrs. induced changes in neuronal excitability and in the nociceptive profile of human sensory neurons: sensory neurons had increased excitability, heightened responsiveness to TRPV1 agonists and increased expression of TTX-resistant voltage gated sodium channels. These changes are consistent with phenotypes of inflammatory pain observed in the clinic. Incubation with oxaliplatin for 24 hrs. resulted in cell hyperexcitability and enhanced response to cold buffer. These changes are consistent with cold allodynia frequently reported by cancer patients undergoing oxaliplatin treatment. Furthermore, we demonstrate that these cell-based models can be used to differentiate the preferential effects of pain drugs on diverse pain states and can be used to rank drug candidates based on potential analgesic efficacy and to predict the most appropriate pain indication for clinical trial development. (1) Davidson et al. Pain, 155(9):1861-1870 (2014)

Disclosures: **A. Ghetti:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **Y. Miron:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **A. Ton:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **T. Indersmitten:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **N. Nguyen:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **P. Ratchada:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **A. Alamillo:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **K. Sweat:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **I. Tapia:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **G. Page:** A. Employment/Salary (full or part-time):; AnaBios Corporation. **P.E. Miller:** A. Employment/Salary (full or part-time):; AnaBios Corporation.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01NS099245

Title: Neural oscillations and biomarkers of chronic pain in the rat

Authors: *A. KELLER, C. RAVER, D. SEMINOWICZ, A. FURMAN
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Abstract: Chronic pain is a debilitating, multidimensional disease that affects millions of individuals. A significant barrier to improved treatment of is that pain presentation is highly variable and, therefore, difficult to diagnose. Identifying biomarkers of chronic pain represents one promising avenue for addressing this obstacle. We used electrocortigraphy (ECoG) to record brain activity from female rats before and after constriction of the infraorbital nerve (CCI-ION), a validated animal model of chronic pain, to test the hypothesis that there exist neural oscillation patterns that are predictive of chronic pain. We recorded brain activity and behavioral metrics of pain at multiple time points, spanning from 7 days before to 21 days after injury. To ensure that recording are obtained during reproducible behavioral states, we recorded while the rats performed a stereotyped behavior, facial grooming. Our preliminary results indicate that CCI-ION is associated with decreases in the power of 4-7 Hz (theta) range oscillations, and that these changes emerge shortly after CCI-ION and persist for as long as three weeks after the injury. These results provide novel evidence that theta oscillations may serve as a reliable biomarker for chronic pain.

Disclosures: A. Keller: None. **C. Raver:** None. **D. Seminowicz:** None. **A. Furman:** None.

Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 301.15/AA11

Topic: D.03. Somatosensation: Pain

Support: Tarleton State University Internal Funds

Title: Cannabis for chronic pain results in decreased alpha frequency activity in the left frontal lobe measured by electroencephalogram

Authors: *K. P. SEYMOUR[1], T. W. BROWN, 76402[2], C. M. BOTELLO, 76402[2], A. L. HARRIS BOZER[3]
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Abstract: Chronic pain effects over 100 million Americans. Some individuals suffering from chronic pain may utilize cannabis for analgesia. Increasing marijuana legality in the United States calls for an investigation of the neurophysiological effects of cannabis for pain. While there is an abundance of studies on the efficacy of cannabis as an analgesic, there is less information on the interaction between cannabis and pain on the brain. Previous research has indicated that marijuana use is related to a decrease in alpha frequency band activity. In a

previous study, we found that chronic pain results in a widespread inhibition of activity in the alpha frequency band. We hypothesized that pain and marijuana will create a combinatorial decrease of alpha frequency band activity in the frontal lobe. Participants (aged 18-30, right-handed, 3 males) were placed into groups based on report of current pain for more than 6 months (chronic pain) and presence of cannabis use resulting in four groups (pain/cannabis, pain/no cannabis, no pain/cannabis, and no pain/no cannabis). Five minutes of electroencephalogram activity (20 active electrodes) was recorded using iMotions software and B-Alert EEG hardware (referenced to mastoids). Data were exported from iMotions into Matlab for filtering (.02-50Hz), channel distributions, and artifact rejection. Data were imported into Notepad++ and Cartool to apply Fast Fourier Transform (delta 0-3 Hz, theta 4-7 Hz, alpha 8-12 Hz, beta 13-30 Hz, gamma 31-50 Hz). Microsoft Excel was used to compute prefrontal asymmetry as the natural log of right side alpha (F4)- natural log of left side alpha (F3). SPSS was used to run ANOVA with group by alpha power (8-12 Hz). Cannabis and pain produce a decrease in alpha frequency activity in the left frontal lobe (confirmatory analysis), p=.04. An exploratory analysis (ANOVA) indicated that there was a significant interaction effect between pain and cannabis on prefrontal asymmetry (p=.03). There was a left hemisphere lateralization in the cannabis/no pain and pain/no cannabis groups. We conclude that pain and cannabis result in meaningful changes in brain activity in the left lobe that should be taken into account when making decisions about cannabis for analgesia.

Disclosures: K.P. Seymour: None. **T.W. Brown:** None. **C.M. Botello:** None. **A.L. Harris Bozer:** None.

Poster

301. Pain Models: Physiology

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Program #/Poster #: 301.16/BB1

Topic: D.03. Somatosensation: Pain

Support: Tarleton State University Internal Funds

Title: EEG alpha power decreases during approach of pain for reward in participants with chronic pain

Authors: *C. M. BOTELLO[1], T. W. BROWN[2], A. L. HARRIS BOZER[2]
[2]Psychological Sci., [1]Tarleton State Univ., Stephenville, TX

Abstract: Pain does not occur in a homeostatic vacuum and chronic pain sufferers do not have the choice to avoid or relieve pain. Approach-avoidance in the context of pain is a decision-making conflict consisting of approaching pain to achieve a reward or satiate a drive. This research was designed to elucidate the neural mechanisms that accompany approach-avoidance behaviors among chronic pain sufferers. We hypothesized (1) a chronic pain group would avoid

pain stimuli more than a painless control group and (2) a pain group would demonstrate increased prefrontal asymmetry, driven by increased left hemisphere activity related to avoidance. Participants included 31 right-handed people aged 19-55 (4 males) that reported current pain for more than 6 months (chronic pain) or reported being pain free controls. iMotions software recorded electroencephalogram activity from B-alert hardware containing 20 active electrodes (referenced to mastoid leads) attached to the scalp during a hypothetical approach-avoidance task. Participants chose to approach varying levels of pain (low-moderate-high) to receive varying levels of a monetary reward (low-moderate-high). MatLab was used for post-processing (filters at .02-50Hz with manual artifact rejections). Fast Fourier Transforms were calculated in Cartool (delta 0-3Hz; theta 4-7Hz; alpha 8-12Hz; beta 13-30Hz; gamma 31-50Hz). Prefrontal asymmetry was calculated in Microsoft Excel as the natural log of right side alpha (F4)- natural log of left side alpha (F3). SPSS was used to compute independent samples t-tests. The pain group avoided pain stimuli significantly less than controls, $p<.05$. The pain group did not demonstrate increased prefrontal asymmetry ($p>.05$), but had significantly less alpha frequency activity in 5 electrodes (F4, C3, Cz, C4, P3 & PoZ) during high threat trials, $p<.05$. High threat trials altered decision-making during the pain approach-avoidance task. This was powered by a widespread decrease in alpha band cortical activity, rather than the hypothesized hemispheric lateralization. High-threat level approach-avoidance stimuli produced a more salient threat to homeostasis. The broader impact of this research lies the development of a body of literature to continue exploring pain as a multidimensional, complex disruption of homeostasis.

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Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 301.17/BB2

Topic: D.03. Somatosensation: Pain

Support: NSF-CRCNS Grant IIS-130764
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Title: Ensembles of change-point detectors for real-time acute pain detections

Authors: *Z. XIAO[1], S. HU[3], Q. ZHANG[1], J. WANG[2], Z. CHEN[1]
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Abstract: Brain-machine interfaces (BMIs) have been widely used to study basic and translational neuroscience questions. In real-time closed-loop neuroscience applications, many

practical issues arise, such as trial-by-trial variability, and spike sorting noise or multi-unit activity. In this paper, we propose a new framework for change-point detection based on ensembles of in-dependent detectors in the context of BMI application for detecting acute pain signals. Motivated from unsupervised ensemble learning, our proposed “ensembles of change-point detectors” (ECPDs) integrate multiple decisions from independent detectors, which maybe derived based on data recorded from different trials, or data recorded from different brain regions, or data of different modalities. By integrating more information, the ECPDs are aimed to improve the detection accuracy (in terms of true positive and true negative rates) and to achieve an optimal trade-off of sensitivity and specificity. We validate our method using computer simulations and experimental recordings from freely behaving rats. Our results have shown superior and robust performance of ECPDS in detecting the onset of acute pain signals based on neuronal population spike activity from single or multiple brain regions.

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Poster

301. Pain Models: Physiology

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 301.18/BB3

Topic: D.03. Somatosensation: Pain

Support: ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan)

Title: The relationship between experimental thermal pain and autonomic nervous response in the parameters including pulse oximeter

Authors: M. MIYAMAE[1], T. SOSHI[2], Y. TSUGITA[2], R. URABE[1], Y. MINEGISHI[1], K. NAKAI[1], *A. NAKAE[2], T. YANAGIDA[2]
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Abstract: Background: Pain is a kind of biological defense reaction wherein the autonomic nervous system plays an important role. Autonomic reactions are monitored easily using pulse oximeter. We conducted the study to observe autonomic reaction to long-lasting thermal stimuli and investigated the possibility of using pulse oximeter as a tool for objective pain evaluation. Methods: After receiving the approval of the ethical committee of Osaka University, 12 females and 12 males who were recruited through the university intranet participated in this study. After the written informed consent, 59-second experimental heat stimulation at 48℃ with 60 seconds rest was presented to the left forearm using Pathway (Medoc, Israel) which was repeated 5 times, monitoring pulse oximetry. Subjective pain intensity was continuously evaluated using visual

analogue scale(VAS). Relationship between pulse rate(PR), pulse wave amplitude(Amp) extracted from the pulse oximeter, and subjective pain intensity were analyzed by paired t-test using JMP 12.0.1. Results & Discussion: Both male and female groups showed maximum pain intensity 9 seconds after reaching 48℃ and these changes lasted until the stimulation ended ($p<0.05$). PR was significantly higher after stimulation in both groups($p<0.05$). In both groups, Amp reached the lowest value when pain intensity hit the maximum. After reaching the lowest value, the Amp gradually increased($p<0.05$) and returned to the baseline despite the high pain. Amp showed a rebound increase after the stimulation ended. These rebound change patterns were significantly different between female and male groups. PR and Amp changed maximally in response to painful stimuli of the highest pain intensity. However, while VAS was consistently high during stimulation, PR and Amp returned towards baseline($p<0.05$). Conclusions: PR and Amp significantly changed after painful thermal stimulation. However, even though participants felt the same intensity of pain for over 60 seconds, these changes reversed significantly. By monitoring physiological parameters using pulse oximeter, the existence of pain may be detected. To evaluate pain objectively, another parameter should be added to perform precise objective pain evaluation.

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Poster

301. Pain Models: Physiology

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Topic: F.01. Neuroethology

Support: JSPS KAKENHI 16K09001
JSPS KAKENHI 125460729
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JSPS KAKENHI 16H05233
JSPS KAKENHI 22390063
JSPS KAKENHI 20022040

Title: Protein distributionand functional characterization of CASK-interacting protein 1 (Caskin1) in mice

Authors: *T. KATANO[1], K. TAKAO[2], M. ABE[3], M. YAMAZAKI[4], M. WATANABE[5], T. MIYAKAWA[6], K. SAKIMURA[7], S. ITO[1]
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Abstract: Calcium/calmodulin-dependent serine protein kinase (CASK)-interacting protein1 (Caskin1) is originally identified as a direct binding partner of the synaptic adaptor protein CASK. Furthermore, it forms homo-multimers and binds to not only CASK but also other functional molecules in vitro. In our previously study, we identified Caskin1 as an increased protein in the spinal dorsal horn in the chronic pain condition. It seems likely that Caskin1 has neural functions, such as pain transmission in vivo, however the function of it in vivo remains unclear. To clarify the protein distribution and neural function of Caskin1 in vivo, we generated anti-Caskin1 antibodies and Caskin1 knockout (Caskin1-KO) mice. Caskin1 was broadly distributed in all the spinal cord and brain areas. Caskin1-KO mice exhibited high sensitivity to noxious stimulation, such as heat and electro stimulations. In addition, several behavioral abnormalities were also demonstrated in Caskin1-KO mice by a behavioral test battery. These results suggest that Caskin1 plays multiple neuronal functions in the central nerve system.

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Poster

302. Inflammatory Pain

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Program #/Poster #: 302.01/BB5

Topic: D.03. Somatosensation: Pain

Support: VA grant 1 / I01RX001475
NIH grant NS094438

Title: Neuropeptide regulation of adaptive immunity in the tibia fracture model of complex regional pain syndrome

Authors: *W. LI[1,2], T.-Z. GUO[3], X. SHI[1,2], F. BIRKLEIN[4], T. SCHLERETH[4,5], W. S. KINGERY[3], J. D. CLARK[1,2]
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Abstract: Background: Both dysfunctional neuropeptide signaling and immune system activation are characteristic of complex regional pain syndrome (CRPS). Unknown is whether substance P (SP) or calcitonin gene related peptide (CGRP) support autoantibody production

and, consequently, nociceptive sensitization.
Methods: These experiments involved the use of a well-characterized tibia fracture model of CRPS. Mice deficient in SP expression ($Tac1^{-/-}$) and CGRP signaling ($RAMP1^{-/-}$) were used to probe the neuropeptide dependence of post-fracture sensitization and antibody production. The deposition of IgM in spinal cord, sciatic nerves and skin was followed using Western blotting, as was expression of the CRPS-related autoantigen cytokeratin 16 (Krt16). Passive serum transfer to B-cell deficient muMT mice was used to assess the production of functional autoantibodies in CRPS model mice. The use of immunohistochemistry allowed us to assess neuropeptide-containing fiber distribution and Langerhans cell abundance in mouse and human CRPS patient skin, while Langerhans cell deficient mice were used to assess the functional contributions of these cells.
Results: Functional SP and CGRP signaling were required both for the full development of nociceptive sensitization after fracture and the deposition of IgM in skin and neural tissues. Furthermore, the passive transfer of serum from wildtype but not neuropeptide deficient mice to fractured muMT mice caused enhanced allodynia and postural unweighting. Langerhans cells were increased in number in the skin of fracture mice and CRPS patients, and those increases in mice were reduced in neuropeptide signaling deficient animals. Unexpectedly, Langerhans cell deficient mice showed normal nociceptive sensitization after fracture. However, the increased expression of Krt16 after tibia fracture was not seen in neuropeptide deficient mice.
Conclusions: Collectively, these data support the hypothesis that neuropeptide signaling in the fracture limb of mice is required for autoantigenic IgM production and nociceptive sensitization. The mechanism may be related to neuropeptide-supported autoantigen expression.

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Poster

302. Inflammatory Pain

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Program #/Poster #: 302.02/BB6

Topic: D.03. Somatosensation: Pain

Support: NIH Grant AR047410

Title: Inhibition of nerve growth factor specific receptor, tropomyosin receptor kinase A, modulates glutaminase production in rat dorsal root ganglion during inflammation

Authors: *V. GUJAR, K. E. MILLER
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Abstract: Background: Apart from regulating the maturation of sensory developing neurons, nerve growth factor (NGF) also acts as a neurotrophin for a subset of nociceptive sensory neurons. It has been well established that, after NGF binds to its specific receptor tropomyosin receptor kinase A (TrkA), a signalling endosome is formed that is retrogradely transported via axons to the cell soma located in dorsal root ganglion (DRG). This complex is responsible for regulating the transcription of several important nociceptive genes. It is surprising, however, the role of NGF in modulating glutamate production during peripheral inflammation. Glutamate functions as the major excitatory neurotransmitter for CNS primary afferents and has a crucial role in sensitizing peripheral nociceptor terminals producing peripheral sensitization. Glutaminase (GLS) is the synthetic enzyme that converts glutamine to glutamate. GLS-immunoreactivity (-ir) is elevated in DRG neuronal cell bodies during chronic peripheral inflammation, but the mechanism for this GLS elevation is yet to be fully characterized. This study addresses the effect of TrkA inhibition on GLS expression in rat DRG during adjuvant induced arthritis (AIA) allowing us to understand the crosstalk between GLS production and the NGF-TrkA complex during peripheral inflammation. **Methods:** AIA was induced by injecting complete Freund's adjuvant in the right hind paw of 8-10 week old male Sprague Dawley rats (200-300 gm). Selective TrkA inhibitor (GW 441756, Tocris) dissolved in DMSO was injected in the same paw used for CFA treatment. L4 and L5 DRG were collected at different time points during inflammation. Immunohistochemistry, immunoblotting and quantitative real time PCR was performed for determining the expression of GLS. **Results:** We found that TrkA inhibition attenuated the GLS levels in DRG primary afferent neurons during acute phase of AIA and we observed reduced paw swelling in animals treated with TrkA inhibitor as compared to CFA treated animals. **Conclusion:** We conclude that the mechanism of GLS expression in DRG neurons during peripheral inflammation involves the NGF-TrkA complex retrogradely transported from the periphery to DRG.

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Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 302.03/BB7

Topic: D.03. Somatosensation: Pain

Support: NRJ Foundation 2015 Scientific price
ESPCI
CNRS
INSERM

Title: Imaging large scale brain networks alterations in arthritic rats using functional ultrasound imaging

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Abstract: Chronic pain (CP) diseases affect ~30% of the European population, however effective treatments are often missing. Only 50% of patients receive appropriate alleviation, due to a lack of treatment specificity and efficacy, as a result of a current poor understanding of the underlying mechanisms. Neural plasticity both in the peripheral and central nervous systems was already reported to be a key element in pain maintenance.
Over the last three years, through the collaboration with the team of Mickael Tanter, who developed the Functional Ultrasound (fUS) imaging technique[1], our team had the unique opportunity to be at the centre of new technological achievements. For instance, we showed that this highly resolved technique can image functional connectivity (FC) in the adult rat brain[2]. Also, using contrast agents, we performed fUS imaging through the intact skull[3] and went beyond doing super-resolution[4] in the living rat brain.
In the present project, we used this neuroimaging approach for the study of brain networks alterations in two animal models of peripheral inflammation, through the study of FC. FC defines a neural network through the emphasis of brain areas which haemodynamic fluctuations are temporally correlated. Using fUS, we show that FC is altered in several cortical and sub-cortical networks, in rats suffering from long-term inflammatory pain. However, this is not observed when pain lasted only two days, suggesting that these changes require long-lasting pain. Interestingly, analysis of the degree of pain does not show any significant segregation, suggesting that such networks alterations are observed even when CP is of mild amplitude. These results are in agreement with observations performed in CP patients, where alteration of the default-mode network was consistently observed across pathologies, while distinct intra-cortical alterations of FC were observed in some CP pathologies[5]. Besides, we observed that alterations in some networks are significantly associated with behavioural aspects of long-term inflammatory pain, suggesting a close link between alterations of these networks and the clinical manifestation of inflammatory pain.
The next step of our work is to analyse FC in awake, freely moving animals, suffering from either inflammatory or neuropathic pain. We expect to better understand the neurobiological nature of such brain plasticity and the functional effects of current beneficial treatments.
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[2] Osmanski, 2014, doi:10.1038/ncomms6023.
[3] Errico, 2016, doi: 10.1016/j.neuroimage.2015.09.037.
[4] Errico, 2015, doi:10.1038/nature16066.
[5] Baliki, 2011, doi:10.1371/journal.pone.0026010.

Disclosures: L. Rahal: None. **M. Thibaut:** None. **M. Tanter:** None. **S. Pezet:** None.

Poster

302. Inflammatory Pain

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Program #/Poster #: 302.04/BB8

Topic: D.03. Somatosensation: Pain

Support: Grant-in-Aid for Young Scientists (B)
Research Grant, Kitasato University

Title: Nerve growth factor and pain-related neuropeptide up-regulated by macrophage-derived inflammatory cytokines in degenerated human intervertebral discs

Authors: *M. MIYAGI, K. UCHIDA, S. TAKANO, M. NAKAWAKI, J. AIKAWA, H. SEKIGUCHI, G. INOUE, T. NAKAZAWA, T. IMURA, W. SAITO, E. SHIRASAWA, M. TAKASO
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Abstract: Introduction: The expression of various pain-related molecules including inflammatory cytokines, nerve growth factor (NGF), and pain-related neuropeptide in degenerated or injured Intervertebral disc (IVD) and sensory nervous system was associated with discogenic low back pain (LBP). We previously reported that macrophages in the IVD in injured mice produced inflammatory cytokines, but not growth factors. The aim of the current study was to evaluate the regulation and interaction of pain-related molecules by macrophages in human degenerated IVDs. **Methods:** Degenerated IVD samples were harvested from 11 patients including 8 with lumbar spinal stenosis and 3 with adult spinal deformity during spinal interbody fusion surgery. Harvested IVD-derived mononuclear cells were obtained and CD14 positive (+) and CD14 negative (-) cells were separated using CD14 antibody and streptavidin-labeled magnetic beads. Inflammatory cytokines including tumor necrosis factor alpha (TNF-alpha), Interleukin 1 beta (IL-1beta), NGF and calcitonin gene-related peptide (CGRP) in the CD14(+) or CD14(-) cells were determined using real-time polymerase chain reaction (RT-PCR). We compared expression levels of each molecular between CD14(+)and CD14(-) cells. To evaluate factors controlling the regulation of pain-related molecules, cultured CD14(-) cells from IVDs were stimulated with TNF-alpha and IL-1beta and the levels of NGF and CGRP were determined using RT-PCR. **Results:** The levels of TNF-alpha and IL-1 betain CD14(+) cells were significantly increased compared with those in CD14(-) cells ($p<0.05$). However, the levels of NGF and CGRP were not significantly different between CD14(+) and CD14(-) cells ($p>0.05$). NGF and CGRP levels increased significantly following TNF-alpha and IL-1beta stimulation ($p<0.05$). **Discussion:** In the present study, CD14(+) macrophages produced more TNF-alpha and IL-1 beta compared with CD14(-) cells in human degenerated IVDs similar to the findings in the present animal model study.. In addition, CD14(+) macrophage-derived inflammatory

cytokines promote the up-regulation of NGF and CGRP. These findings indicated that NGF and pain-related neuropeptide were stimulated by macrophage-derived inflammatory cytokines and were associated with the pathomechanism of chronic discogenic LBP in humans. <!--EndFragment-->

Disclosures: M. Miyagi: None. **K. Uchida:** None. **S. Takano:** None. **M. Nakawaki:** None. **J. Aikawa:** None. **H. Sekiguchi:** None. **G. Inoue:** None. **T. Nakazawa:** None. **T. Imura:** None. **W. Saito:** None. **E. Shirasawa:** None. **M. Takaso:** None.

Poster

302. Inflammatory Pain

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C.R. is supported by a FAPESP fellowship grant #2017/04644-0.

Title: Serotonin attenuates endotoxin-induced nociception by inhibiting IKKα/β in the dorsal root ganglia and GSK3α/β, CREB, and IKKα/β in the spinal cord dorsal horn

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Abstract: Serotonin (5-HT) is a neurotransmitter that plays an important role in endogenous analgesia, but its involvement in the nociceptive signaling during systemic inflammation (SI) remains unclear. Our hypothesis was that intracerebroventricular (icv) administration of 5-HT attenuates nociceptive responses by reducing pro-nociceptive and pro-inflammatory signaling pathways in the lumbar dorsal root ganglia (DRG) and in the spinal cord dorsal horn (DH) during SI. Thus, we administrated 5-HT in the 3rd ventricle of male adult *Wistar* rats and assessed for 120 min the thermal latency and the paw withdrawal threshold during endotoxin-induced SI. Endotoxin (LPS) caused thermal hyperalgesia at 30, 45, and 60 min, and mechanical allodynia at 15 and 30 min after administration. Moreover, 5-HT icv administration attenuated all the nociceptive responses during SI. Furthermore, we investigated whether the nociceptive signaling was altered in the DRG and DH at 45 and 120 min after endotoxin administration, which represented the phases of hyperalgesia and resolution, respectively. Interestingly, SI activated the inhibitor of κB (IκB) kinases type α and β (IKKα/β) within the DRG and DH whereas the cAMP-response element binding protein (CREB) was activated only in the DH. Central 5-HT

administration reduced these responses, activated CREB in the DRG and inhibited the glycogen synthase kinase-3 types α and β (GSK3α/β) in the DH during SI. Moreover, we observed no change in cyclooxygenase-2 (COX-2) relative expression in any of the groups. Interestingly, all significant alterations were observed in the period of hyperalgesia (45 min) only, indicating that these molecules probably contribute to the nociceptive responses. In summary, we suggest that 5-HT administration within the brain induces analgesia during SI, probably by modulation of crucial signaling pathways in the DRG (CREB and IKKα/β) and DH (GSK3α/β, CREB, and IKKα/β).

Disclosures: C.M. Mota: None. **C. Rodrigues-Santos:** None. **C.R.A. Leite-Panissi:** None. **L.G.S. Branco:** None.

Poster

302. Inflammatory Pain

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Support: NRF-2017R1D1A1B03028839
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Title: An intra-articular injection of PAT4, a peptide antagonist of TLR4, attenuates monoiodoacetate- induced osteoarthritis pain in the knee joint of rats

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Abstract: Osteoarthritis (OA) frequently develops in the population over 65 years of age with the loss of cartilage and subsequent structural changes of subchondral bones by the progression of aging. Because OA-triggered pain is tightly related with TLR4 signaling cascades, TLR4 is a reasonable target in developing therapeutics for OA pain. Here, we revealed that PAT4, a peptide antagonist of TLR4, debilitated long-termly monoiodoacetate (MIA)-induced OA pain in rats by decreasing the expression of proinflammatory mediators in knee joints and the microglial activation in spinal cords. First of all, we established the MIA-induced OA pain model by an intra-articular injection of MIA (2 mg/20 μl) into a left knee. In this MIA-administrated rats, TLR4 was highly expressed in chondrocytes and synoviocytes of knee joints. A single intra-

articular injection of PAT4 (25 nmol/rat) molecules targeting TLR4 at day 7 after MIA injection attenuated dramatically pain behavior for ~3 weeks in von Frey filaments by reducing the cartilage loss in knee joints and microglial activation in dorsal horn of spinal cords. Likewise, the level of inflammatory cytokines including TNF-alpha, IL-1beta and IL-6 was decreased by ~50% compared with the control in quantitative RT-PCR and ELISA when PAT4 was delivered to MIA-induced rats. Interestingly, the duration of PAT4 in weakening OA pain remained longer than that of chemical antagonists of TLR4 such as C34 and M62812 lasting for ~7 days. Taken together, PAT4 reduced powerfully the strength of OA pain promoted by MIA in rats by blocking TLR4 and its corresponding reactions and could be a prospective medicine for the patients of OA pain.

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Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

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Title: Pain in experimental autoimmune encephalomyelitis is mediated through neuronal interleukin-1 receptor signaling

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Abstract: The occurrence of chronic pain increases by up to 50% in patients suffering from autoimmune inflammatory diseases, such as multiple sclerosis (MS), suggesting the existence of an intricate connection between the development of chronic pain and the immune system. Here, we investigated whether the proinflammatory cytokine interleukin-1β (IL-1β), produced during MS relapses and the induction of its animal model experimental autoimmune encephalomyelitis (EAE), could be responsible for pain modulation mechanisms. Our histological analysis identified a laminae I and II projecting dorsal root ganglion (DRG) neuronal subpopulation that highly expresses the type 1 interleukin-1 receptor 1 (IL-1R1). We found that these neurons also

express the transient receptor potential vanilloid subfamily member 1 (TRPV1) and the neuropeptide somatostatin (Sst), but neither calcitonin gene-related peptide (CGRP) nor tyrosine hydroxylase (TH), and do not bind the isolectin B4 (IB4). Since IL-1R1-expressing neurons co-express TRPV1, we generated a new conditional knockout mouse in which IL-1R1 is selectively deleted in $TRPV1^+$ nociceptors (*Trpv1*-cre::$Il1r1^{flox/flox}$ or *Il1r1* cKO mice), and assessed in these mice the clinical severity of EAE and EAE-induced mechanical allodynia using the von Frey test. Conditional knockout of the *Il1r1* gene from $TRPV1^+$ neurons affected neither the onset nor severity of EAE, but prevented the development of allodynia. Because peripheral neuropathic pain may also contribute to the development of EAE, we performed a unilateral chronic constriction injury prior to EAE immunization and observed a significant increase in disease severity in those mice. Taken together, our results show that inflammation mediated by IL-1β during EAE can cause pain via the activation of neuronal IL-1R1, thus establishing the potential benefit of anti-IL-1β therapies for pain management in MS.

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Poster

302. Inflammatory Pain

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Support: Neurosurgery Pain Research Institute

Title: Alterations in pain behavior and physiology in a mouse model of palmoplantar keratoderma

Authors: *R. WEINBERG[1], Z. PANG[1], B. PAN[2], L. QU[1], S. YOUNG[4], M. POLYDEFKIS[3], M. CATERINA[1]
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Abstract: Palmopantar Keratodermas (PPKs) are a group of rare hereditary or acquired skin disorders characterized by a thickening of the epidermis on the palms of the hands and soles of the feet. Some PPK patients experience intense pain that can severely impact quality of life yet there are no established pharmacologic treatments for PPK-associated pain, in part because the mechanisms underlying such pain have been largely unexplored. Many patients with Mal de Meleda (MdM), a diffuse PPK caused by a mutation in the gene encoding secreted mammalian Ly6/urokinase plasminogen activator receptor-related protein (SLURP) 1, exhibit pain at the lesion sites. The aim of our investigation was to characterize pain behavior and neurophysiology of peripheral sensory neurons in a mouse model of MdM. We characterized nociceptive pathway

structure and function in SLURP2X KO mice, which recapitulate many histological features of human MdM. Behavioral assays, histological analyses, and qPCR arrays were performed on SLURP2X KO mice and wild-type littermate controls. In vitro patch clamp electrophysiology and spinal cord c-fos staining was utilized on hindpaw-innervating DRG neurons to assess sensory functional changes. We observed enhanced behavioral withdrawal responses to thermal, mechanical and irritant chemical stimuli in SLURP2X KO mice. We also observed histological and molecular changes in the skin and DRG of these animals, including altered epidermal innervation, immune cell infiltration, and molecular markers of pain. In addition, DRG neurons isolated from SLURP2X KO mice exhibited higher incidence of spontaneous firing and hyperexcitability in our electrophysiology experiments.Taken together, these data demonstrate a robust pain phenotype in SLURP2X KO mice, analogous to that in human MdM patients. In addition, our data suggest that these changes may be attributable to changes in DRG neuron anatomical, molecular, and physiological phenotypes, potentially assisting in the generation of more targeted analgesic therapies for these patients.

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Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

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Topic: D.03. Somatosensation: Pain

Support: the Scientific Research Foundation for Experts Recruitment by Shanghai University of Medicine &Health Sciences

Title: The role of inflamm-aging in the hyperalgesic priming state of aged mice

Authors: *H.-J. WANG[1], C. ZHAO[2], C.-F. ZOU[3], C.-Y. SHI[1], Y.-L. SUN[1]
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Abstract: Introduction: Several studies have showed that the feelings of aged people would become dull. However, they are prone to develop chronic pain in the conditions of diseases. Such characters of pain in aging were similar to hyperalgesic priming model, an animal model for studying the transition of acute to chronic pain. However, the mechanisms of chronic pain in

aging were not clarified yet. It is reported that the aged immune cells, including T cells, microglia and macrophages, would release more proinflammatory factors, which keep the aged body in proinflammatory status. This is called inflamm-aging. Here, we tested the hypothesis that aged mice were in hyperalgesic priming state and inflamm-aging may contribute to the development of chronic pain in the aged mice. **Methods:** Male mice older than 12 months were used as aged mice. Male mice which were 8 weeks old were used as young mice for control. For ongoing inflammatory pain model, 10ul CFA was injected intraplantarly into the hind paws. The hyperalgesic priming model was induced by carrageenan as described before. Both mechanical and thermal pain thresholds were determined at different timepoints after the pain models were produced. Mechanical pain thresholds were measured with von Frey test. Thermal pain thresholds were determined with Hargreaves' test. On 0, 2, 7 and 21 days after carrageenan priming, lumbar DRGs were isolated. CD3 and CD4 or CD8 were co-stained to show the subgroups of T cells. Moreover, Iba-1 was used as a marker of microglia to evaluate the changes of microglia activation in the aged and young mice. **Results:** Similar to what has been observed in clinic, the baselines of mechanical and thermal pain thresholds were significantly higher in the aged mice than those in the young mice, showing that the feelings became dull in the aged mice. In CFA-induced inflammatory pain model, the pain were resolved within 7 days in young mice, however, it is prolonged to more than 2 weeks in the aged mice. Similar to our previous work, the PGE_2 induced hyperalgesia lasted about 3 days in young primed mice. While in aged mice, it prolonged to about 5 days. These results suggested that the aged mice were in primed states, prone to get chronic pain in the condition of inflammation. IHC results showed that 7 days after carrageenan primed, there were more CD3+/CD8+, but not CD3+/CD4+ T cells were filtered into DRGs. Moreover, in the DRGs of aged mice, the activation of microglia was significantly higher than those in the young mice. These results indicated that the aged immune cells were involved in the primed state of aged mice. **Conclusion:** The aged immune cells were involved in primed state in aged mice.

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Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS045594
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Title: Differential regulation of the glucocorticoid receptor in rat models of inflammatory pain

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Abstract: Anti-inflammatory corticosteroids are a common treatment for different conditions involving chronic pain and inflammation. Clinically used steroids target the glucocorticoid receptor (GR) for its anti-inflammatory effects. We previously reported decreased GR immunoreactivity signal in dorsal root ganglia (DRG) after local inflammation. In the current study, we aimed to determine if similar changes in GR signal also exist in a skin inflammation model, the Complete Freund's Adjuvant (CFA) model, in which the terminals of the sensory neurons rather than the somata are inflamed. Immunohistochemical techniques were used to determine the expression pattern of the GR in the inflamed hindpaw and the associated DRGs. Behavioral signs of pain were confirmed by the presence of static, dynamic, and cold allodynia, and guarding behavior for 14 days (longest time tested). Moreover, paw swelling was confirmed with approximately two-fold increase in the paw cross-sectional area, which lasted at least 14 days. The immunohistochemical staining revealed that GR is widely expressed in the normal DRG and skin tissues. Paw injection with CFA caused upregulation of the GR in the skin tissue on post-injection day one, mostly detected in the dermis area. However, paw inflammation significantly reduced the GR signal in the DRG one day after the injection. Results from this study indicate that there are distinctive patterns of GR activation under different pain conditions, which may have a significant impact on the use of steroids as treatment in these conditions. It will be of interest to determine whether these changes in GR signal levels are transient or long-lasting.

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Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

Support: Grant-in-Aid for Scientific Research (C) (No. 16K09006)

Title: Cardiac sympathetic nerve activity changes induced by mechanical pressure stimulation of a calf are augmented by acute muscle inflammation in isoflurane-anesthetized rats

Authors: *N. WATANABE, H. HOTTA
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Abstract: Background and Aim
Muscle inflammation alters nervous system function such as increasing the resting discharge of

primary afferents in affected tissues and lowering mechanical threshold of withdrawal response. In contrast, an impact of muscle inflammation on autonomic nervous function remains to be studied. Recently, we reported that mechanical pressure stimulation of a calf altered cardiac sympathetic nerve activity (CSNA) and heart rate (HR), depending on the tonus level of CSNA; the stimulation induced tachycardia when the tonus was low and bradycardia was elicited when the tonus is high. We aimed to investigate the influence of acute muscle inflammation on CSNA and HR responses to calf pressure stimulation.

Methods

Experiments were performed on 5 Wistar male rats under isoflurane anesthesia. A catheter was implanted into the carotid artery for measuring arterial pressure and into the jugular vein for administering drugs. HR was calculated from arterial pressure waveforms. Mass discharges of inferior cardiac sympathetic nerve were recorded using bipolar hook electrodes. Rats were paralyzed using gallamine, administered after the sufficient depth of anesthesia was confirmed. A probe of 6 mm in diameter with a flat contact area was used and mechanical pressure stimulation was applied to the center of a calf over the skin with a constant force (10 N/cm^2 for 30 sec). To induce inflammation, 3% λ-carrageenan was injected in one side of calf muscles on the day before the experiment. Saline was injected in the contralateral calf as control.

Results

Mechanical pressure stimulation was applied to inflamed (27 trials in total) or non-inflamed (27 trials in total) calf. The stimulation increased or decreased CSNA and HR. As observed previously in naïve rats, changes in CSNA and HR were negatively correlated with pre-stimulus CSNA levels. Such a correlation was observed in responses of both non-inflamed and inflamed calf stimulation ($r < -0.64$, $p < 0.001$). The magnitudes of CSNA and HR changes were significantly larger in inflamed calf stimulation than those in non-inflamed calf ($p < 0.02$). To clarify sympathetic regulation of HR, the data of CSNA and HR changes were plotted, showing positive correlations between those parameters ($r > 0.77$, $p < 0.001$). The slopes of the correlation were identical between inflamed and non-inflamed calves, and naïve and carrageenan-injected rats.

Conclusion

The present study showed that mechanical pressure stimulation applied to acutely-inflamed muscles augmented CSNA and HR changes. Our results indicate that such an augmentation may be due to functional alterations of afferent pathways rather than a change in sympathetic regulation of HR.

Disclosures: N. Watanabe: None. **H. Hotta:** None.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

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Program #/Poster #: 302.12/BB16

Topic: D.03. Somatosensation: Pain

Title: Pain control by two types of dental laser irradiation using an animal pain model induced by experimental tooth movement

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Abstract: The analgesic effect of CO_2 laser irradiation on the experimental tooth movement-related pain was reported last year. Diode laser is also widely used in dentistry for many purpose including pain control, however, diode laser has higher tissue permeability compared with CO_2 laser. Therefore, the effect of diode laser irradiation on orthodontic pain was examined in this study. General anesthetized rats were applied continuous orthodontic force by Ni-Ti closed coil spring to only the right maxillary first molar. On the following day, rats were general anesthetized and pair of electrodes was inserted bilateral anterior digastric muscle to record EMG activity and the maxillary first molar gingiva to electric stimulation. Passing current (200 μs) was applied to the right then the left maxillary first molar region to determine jaw-opening reflex (JOR) threshold. After measuring JOR threshold, CO_2 or diode laser irradiation (0.5 W;distance CO_2 20 cm diode 3.2 cm ;time 30 s) was applied the right side maxillary first molar region then JOR threshold was determined again for subsequent 60 min with 30 min interval (D1 group). CO_2 or diode laser irradiation (30 s) was also applied to the right maxillary first molar region immediately after orthodontic force application in other animals, and JOR excitability was evaluated on next day (PI-D group). To confirm effect of laser irradiation on JOR excitability, another set of animals received only laser irradiation (30 or 600 s, without orthodontic treatment) to the right maxillary first molar region before JOR excitability evaluation (control group). Since JOR threshold was variable across animals, the right side threshold was standardized with that of left side in each animal. Either laser irradiation did not alter JOR threshold between right and left stimulations in the control group. Application of orthodontic force in the D1 group significantly ($P < 0.05$) decreased right side JOR threshold compared with that on the left side. CO_2 laser irradiation (30 and 600 s) in D1 group significantly ($P < 0.05$) increased right side JOR threshold (30 and 600 s @ 30 min and 60 min). However, diode laser irradiation (30 and 600 s) in group D1 did not alter the JOR threshold on the right side. Interestingly, in the PI-D group, the right side JOR threshold was also significantly increased ($P < 0.05$) by both laser irradiation. Taken together, CO_2 and diode laser irradiations are able to prevent orthodontic pain. Moreover, CO_2 laser irradiation is applicable to analgesic purpose for orthodontic pain.

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Poster

302. Inflammatory Pain

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Program #/Poster #: 302.13/BB17

Topic: D.03. Somatosensation: Pain

Title: *In vivo* tracing of single neuron activity with Ca^{2+} imaging of primary somatosensory cortex in mouse models of postoperative pain and inflammatory pain

Authors: *T. OKADA, Y. TACHIBANA, Y. NOMURA, N. OBATA, S. MIZOBUCHI, H. WAKE
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Abstract: Recently, prolonged postoperative pain and neuropathic pain are major problems with increased numbers of surgical operation. Previous studies using chronic pain models have shown that the activation of glial cells followed by the release of neurotrophic factor resulted in increased neuronal excitability in the spinal cord. In addition, accumulated evidence suggests that plastic changes of neuronal circuits in the primary somatosensory cortex (S1) are essential for the formation of chronic pain. However, little is known about how individual cells in neuronal population in S1 fire differently during the formation and maintenance of chronic pain. In this research, we used two mice models of pain to study the characteristics of individual neuronal activity patterns in the acute pain phase of S1: one which had the incision of hind paw as a model of postoperative pain, the other which received the injection of Complete Freund's adjuvant (CFA) into hind paw as a model of inflammatory pain. Firstly, behavior response to mechanical and thermal stimulation were evaluated before and after the operation of hind paw. The paw withdrawal threshold significant decreased in the affected hind paw of postoperative pain model and inflammatory pain model. Secondly, we used *in vivo* two-photon calcium imaging to trace the single cell activity during the formation of pain. The spontaneous neuronal activity in S1 was measured by fluorescent signal from GCaMP6f expressing in layer II/III pyramidal neurons of S1. The single cell activities were then traced before and after operation and their dynamics changes were analyzed mathematically. Consequently, the activity synchronization among cells increased with both models in acute pain phase and the period was more extended in a model of inflammatory pain. Furthermore, amplitude of Ca^{2+} traces in S1 was tend to increase with inflammatory pain model in acute pain phase, but the increase was not found with postoperative pain model. This result indicates that the intensity of pain with inflammatory pain model is higher than postoperative pain model and the pain lasts longer. This research will be able to clarify the mechanism of transition from acute pain to chronic pain, and in future, it is necessary to examine not only the spontaneous activity but also the change of neural activity against hind paw stimulation in S1.

Disclosures: T. Okada: None. **Y. Tachibana:** None. **Y. Nomura:** None. **N. Obata:** None. **S. Mizobuchi:** None. **H. Wake:** None.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 302.14/CC1

Topic: D.03. Somatosensation: Pain

Support: AT008742

Title: Experimental inflammation and inflammatory pain reduced by ketogenic diet

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Abstract: Ketogenic diets are very low carbohydrate, high fat, moderate protein diets used traditionally have been used to treat medication-resistant epilepsy. Growing evidence suggests that one of its mechanism of action is reducing inflammation. Here, we examined the diet's effects on experimental inflammatory pain in a rodent model. Adult (10-16 month old) male Sprague-Dawley rats were placed on ketogenic diet (~6:1 fats:(carbohydrates + proteins)) or maintained on control diet. At 2-4 weeks on diets, complete Freund's adjuvant (CFA, 100 μl) was injected in one hindpaw to induce inflammation; the contralateral paw was used as the control. Tactile sensitivity (von Frey) and spontaneous pain behavior (blind video scoring) were measured before and after CFA treatment. Ketogenic diet feeding did not affect baseline tactile sensitivity or body weight, and spontaneous pain behaviors (hindpaw licking, lifting or favoring) were essentially absent. Post-CFA, tactile hypersensitivity (allodynia) was clearly present in all animals (tested at 4 and 48 h post-CFA), but significantly less in the ketogenic diet-fed group at 4 h post-CFA. Spontaneous pain behavior involving the injected hindpaw was present in all animals (tested at 24 h post-CFA), with a strong trend to less in the ketogenic diet-fed group. Injected hindpaw swelling, assessed by weight, was significantly reduced by ketogenic diet feeding (uninjected paws were unaffected by diet). Our data suggest that ketogenic diets might be useful treatments for inflammatory conditions and inflammatory pain.

Disclosures: D.N. Ruskin: None. **L.S. Wyss:** None. **S.A. Masino:** None.

Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

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Title: The expression of aspartate aminotransferase and glutaminase in rat dorsal root ganglion treated with peripheral glutaminase inhibitor during adjuvant induced arthritis

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Abstract: Introduction: Glutamate is a major excitatory neurotransmitter and plays a crucial role in pain pathways. Therefore, it is important to know the precise sequence of expression of enzymes leading to biosynthesis of neurotransmitter glutamate. Intense noxious stimuli or tissue damage causes glutamate to be released from peripheral and central afferent nerve terminals and augmented release occurs during acute and chronic inflammation. Glutamate is synthesized by phosphate-activated glutaminase (GLS) and aspartate aminotransferase (AST) by two main pathways. First, glutamate is produced in mitochondria by glutaminase (GLS) through the glutamine-glutamate cycle and is transferred to the cytoplasm. Second, glutamate is transaminated by AST in mitochondria (mAST), producing alpha-ketoglutarate and aspartate, both of which are then transported out of mitochondria and utilized by cytosolic AST (cAST) to reform glutamate and oxaloacetate. Although cAST can provide a net synthesis of glutamate, its precise functional role in sensory neurons during inflammation remains to be established. For example, the role of cAST in production of glutamate in dorsal root ganglion neurons during adjuvant-induced arthritis (AIA) in rat has not been evaluated. Methods: AIA was induced by injecting complete Freund's adjuvant (CFA) into the right hind paw of anesthetized, 8-10 week old male Sprague Dawley rats (200-300gm). 6-Diazo-5-oxo-L-norleucine (DON) (glutaminase inhibitor) was pre- and co-administered to/with CFA in the same paw. L4 and L5 DRG were collected from naive and AIA animals at 24, 48 and 96 hours of inflammation. Messenger RNA and protein expression of cAST and GLS in dorsal root ganglion (DRG) was determined by quantitative PCR and immunoblot techniques. Result and Conclusion: Our findings show an early and prolonged alteration (24-96hr) in the expression of cAST and GLS in the DRG during AIA. DON treatment mitigated some of the inflammation induced changes. Alterations in GLS and AST appear to contribute to DRG neurotransmitter changes in response to peripheral inflammation.

Disclosures: R. Pande: None. **K.E. Miller:** None.

Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

Support: R01 1AA025967
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P50 AA022534

Title: Characterizing the pathological effects of prenatal alcohol exposure on spinal neuroimmune mechanisms that result in neuropathic touch sensitivity

Authors: *J. SANCHEZ, J. E. SANCHEZ, S. DAVIES, D. D. SAVAGE, E. D. MILLIGAN
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Abstract: A hallmark of peripheral neuropathic pain is increased sensitivity to light touch (allodynia). Glial cells (astrocytes and microglia) contribute to allodynia. Additionally, peripheral leukocytes may infiltrate the spinal cord through the adhesive actions of the β-2-Integrin, lymphocyte function-associated antigen (LFA)-1 (a.k.a. CD11a), in response to proinflammatory cytokines such as interleukin-1β (IL-1β). Recently, we demonstrated that prenatal alcohol exposure (PAE) increased susceptibility to allodynia following minor nerve injury in adult rats. Additionally, studies demonstrate elevated expression of LFA-1 in spinal cords of PAE rats compared to Saccharin (Sac) controls. Furthermore, *in vitro* studies have demonstrated that an anti-inflammatory environment can be induced by preventing LFA-1 activated conformational changes. Here, we examined whether: (1) spinal application of an LFA-1 antagonist suppresses glial activation, elevates anti-inflammatory interleukin-10 (IL-10), and reduces IL-1β to reverse PAE induced allodynia, (2) and whether spinal IL-1β is necessary for its induction. To do this, male (4 mo) PAE or Sac exposed rat offspring were used. Hindpaw response-thresholds to light mechanical touch were assessed prior to and after minor sciatic nerve injury (1-suture chronic constriction injury; CCI) or sham surgery. On Day 28, intrathecal (peri-spinal; i.t.) injection of BIRT-377 (LFA-1 antagonist) or vehicle was administered followed by daily reassessment of allodynia for 4 days (peak drug efficacy), at which time, spinal cords were processed for immunohistochemical detection of glial activation and cytokine markers. Separate groups of PAE rats were assessed prior to and up to Day 10 after CCI. At this time, i.t. IL-1 receptor antagonist (IL-1RA) or vehicle was administered followed by re-assessment of allodynia. Results show that in PAE rats with allodynia, BIRT-377 reversed allodynia and reduced spinal astrocyte, microglial, IL-1β, and CD11a immunoreactivity to basal levels. Sac rats

with minor CCI and vehicle injection displayed elevated expression of glial activation, IL-1β, and CD11a despite the absence of allodynia. IL-10 expression was blunted in PAE rats following CCI given vehicle injection. Furthermore, astrocyte activation was greatest in PAE rats compared to Sac rats following minor CCI. I.t. IL-1RA produced robust reversal of allodynia. These data suggest that in offspring with PAE, minor injury creates pathological susceptibility to neuropathy (allodynia) that is mediated by blunted spinal IL-10 responses in combination with increased IL-1β expression and altered astrocytic function.

Disclosures: J. Sanchez: None. **J.E. Sanchez:** None. **S. Davies:** None. **D.D. Savage:** None. **E.D. Milligan:** None.

Poster

302. Inflammatory Pain

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Title: Neuronal FcγRI contributes to antigen-induced inflammatory pain in the rat

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Abstract: Pain is a major symptom in certain immune-related disorders that were characterizedwith an elevated level of serum or diseased tissue IgG immune complex (IgG-IC). FcγR type I (FcγRI) is the high-affinity activating receptor of IgG-IC and critically involved in a number of inflammatory and immune diseases. Our previous studies demonstrated that a subpopulation of nociceptive dorsal root ganglion (DRG) neurons express FcγRI and can be directly activated by IgG-IC evoking an increased intracellular calcium level and neuronal excitability. This mechanism may be involved in the development of pain in multiple immune diseases such as rheumatoid arthritis. We hypothesize that IgG-IC directly activates nociceptive neurons innervating the joint by neuronal FcγRI to produce pain and inflammation in the rat model of rheumatoid arthritis. We generate FcγRIα^{loxP} transgenic rat line in which syntropy loxP

sequence were inserted the exon both ends of genome FcγRIα gene and pirt^{Cre} transgenic rat line which the Cre protein was expressed under the control of the pirt promoter, which expressed in the primary nociceptive neurons. The FcγRIα^{loxP} rat was crossed with pirt^{Cre} rat to generate the pirt-control conditional FcγRIα knockout transgenic rat line (Pirt-FcγRIα$^{-/-}$ rat). We found that the mechanical and thermal hyperalgesia induced by intracutaneous injection of IgG-IC (antigen: oval albumin, OVA, antibody: rat anti-OVA IgG) were significantly alleviated in Pirt-FcγRIα$^{-/-}$ rats as compared to the wildtype. We next produced a rat model of antigen-induced arthritis (AIA) using OVA as antigen, and found that both the pain-related behaviors and joint inflammation induced by AIA were significantly reduced in the Pirt-FcγRIα$^{-/-}$ rats as compared to the wildtype. Our results suggest that FcγRI expressed in the peripheral nociceptive neurons innervating the joint can be directly activated by IgG-IC and play an important role in the development of inflammatory pain in antigen-induced arthritis.

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Poster

302. Inflammatory Pain

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Program #/Poster #: 302.18/CC5

Topic: D.03. Somatosensation: Pain

Support: LABORATOIRES THEA
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Title: Increased corneal sensitivity and corneal nerve fiber activity is associated with peripheral and central neuroinflammation in a novel mouse model of dry eye disease

Authors: *D. FAKIH[1,2], Z. ZHAO[3], P. NICOLLE[3,4,5,6], F. JOUBERT[3], E. REBOUSSIN[3], A. LABBE[3,4,5,6], C. BAUDOIN[3,4,5,6], S. MELIK PARSADANINANTZ[3], A. RÉAUX LE GOAZIGO[3]
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Abstract: Dry eye disease (DED) which affects more than 10% of the population worldwide is a multifactorial disease associated with an inflammation of the ocular surface and ocular pain

symptoms. Despite the high prevalence of DED, the underpinning mechanisms of this ocular surface disease are not fully understood.
The aim of this study was to characterize by molecular, cellular, behavioral and electrophysiological analyses a novel preclinical mouse model of DED obtained by an unilateral excision of the extraorbital lachrymal gland (ELG) and Harderian gland (HG). A sham animal group was also constituted.
Experiments were performed at Day (D) 7, D14 and D21 post excision. Corneal inflammation, tear production, as well as the peripheral (trigeminal ganglion (TG)) and central (sensory trigeminal complex) neuroinflammatory mechanisms were evaluated. Corneal nerve fiber activity was evaluated by an electrophysiological approach in an *ex vivo* eye preparation by recording the multi-unit extracellular spontaneous activity of the entire ciliary nerve with a suction electrode.
The unilateral excision of the ELG and HG rapidly and drastically reduced the production of tears, which was associated with strong corneal inflammation. Behavioral studies revealed that DED animal developed a mechanical corneal hypersensitivity measured with von Frey filaments. Additionally, a significant increase of the spontaneous ciliary nerve fiber activity was observed in DED animals at D7, D14 and D21 compared to sham animals. At D21 post excision, RT-qPCR analysis revealed a significant increase of oxidative markers (iNOS2 and NOX4) and pro-inflammatory markers (IL-6 and IL-1β) in the TG.
Immunohistochemistry experiments also showed an increase of Iba1, GFAP and activating transcription factor-3 (ATF-3) staining in the ipsilateral TG compared to sham animals. At D21, pro-inflammatory cytokines (IL-6, TNFα, IL-1β and CCL2), oxidative stress markers (iNOS2), neuronal markers (ATF3 and FOS) and microglia marker (CD68 and ITGAM) expressions were up regulated in the trigeminal sensory complex in the DED group compared to sham. In this central structure, an increase of GFAP immunoreactivity was also noted in DED animals.
In conclusion, we reported a novel and highly relevant preclinical model of DED in mice. This model is characterized by a spread of the corneal inflammation via the TG to the sensory trigeminal complex.
These peripheral and central neuroinflammatory mechanisms are associated with a corneal hypersensitivity and a significant increase in spontaneous corneal nerve fiber activity, all these mechanisms might explain the ocular pain observed in some patients suffering from DED.

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Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

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Title: Chronic stress induces nociceptive hypersensitivity in rats via down-regulation of KCC2

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Abstract: Chronic stress can induce physiological and psychological changes that contribute to stress-induced nociceptive hypersensitivity. In humans, exposure to chronic stress reduces pain threshold, resulting in hypersensitivity. It is known that stress exacerbates the etiology of various pathologies such as fibromyalgia, irritable bowel syndrome and headache. However, the mechanisms by which they are related are unknown. Previous studies have reported that microglia-derived brain-derived neurotropic factor (BDNF) leads to the reduction of K^+-Cl^- co-transporter 2 (KCC2) expression in neuropathic and inflammatory pain models. However, the role of KCC2 in functional pain is unknown. The purpose of this research was to study whether chronic restraint stress induced nociceptive hypersensitivity by increasing BDNF, which then promotes down-regulation of KCC2 protein expression at the spinal cord. Chronic restraint stress (2 h daily for 28 days) produced tactile allodynia and thermal hyperalgesia in both hind paws from day 21 to 28. Moreover, chronic restraint stress enhanced BDNF tissue levels in the dorsal portion of the spinal cord from day 21 and 28 and decreased KCC2 and phospho-Ser940 KCC2 protein expression in the dorsal portion of the spinal cord from day 7 to 28. KCC2 was absent in DRG. Intrathecal injection of the KCC2 activator CLP 257 (100-300 μg), but not vehicle, reduced in a dose-dependent manner chronic stress-induced tactile allodynia. Furthermore, intrathecal injection of the KCC2 inhibitors DIOA (0.02-20 μg) or VU0463271 (0.02-20 μg), but not vehicle, produced tactile allodynia in a dose-dependent manner in naïve rats. Results suggest that chronic restraint stress induces nociceptive hypersensitivity by increasing BDNF, which then leads to down-regulation of KCC2 expression at the spinal cord.

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Poster

302. Inflammatory Pain

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Title: GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain

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Abstract: The pain resolution mechanism is not completely understood. In this study, we showed that the G-protein coupled receptor 37(GPR37) expressed macrophages but not microglia and contributed to resolution in the inflammatory pain. Neuroprotectin D1 (NPD1) that is the Docosahexaenoic acid metabolite, and Prosaposin relative peptide (TX14) elicited intracellular Ca2+ increase and phagocytosis in Gpr37 expressed macrophage. Hind-paw injection of zymosan particles not only induces inflammatory pain and infiltration of neutrophils and macrophages, but also causes GPR37 upregulation in macrophages, phagocytosis of zymosan particles and neutrophils by macrophages in inflamed paws, and resolution of inflammatory pain in wild-type mice. Mice lacking *Gpr37* display deficits in macrophage phagocytic activities and delayed resolution of inflammatory pain. *Gpr37*-deficient macrophages also exhibit dysregulations of pro-inflammatory and anti-inflammatory cytokines. Macrophage depletion delayed the resolution of inflammatory pain. Adoptive transfer of wild-type but not *Gpr37*-deficient macrophages promotes the resolution of inflammatory pain. Overall result suggests that GPR37 has a role in the resolution of inflammatory pain by regulation of phagocytosis and the cytokine in the macrophage.

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Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

Support: Nora Eccles Treadwell Foundation
Department of Anesthesiology, University of Utah School of medicine

Title: Blockade of Toll-like receptor 2 partially suppresses mycoplasma superantigen triggered arthritis pain in a mouse mode of autoimmune disease

Authors: *J. ZHANG[1], X. LU[1], C. J. MEANEY[2], X. WANG[2], R. HUGHEN[1], A. R. LIGHT[1], H.-H. MU[2]
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Abstract: Rheumatoid arthritis (RA) is an autoimmune disease that commonly affects joints and other tissues such as lung, heart, skin and nerves, causing swelling, fatigue and chronic pain. Although the genetic factors and environmental conditions have been widely studied, the cause of RA is not fully understood, and a cure is not yet available. To understand the mechanism of this disease, we recently modified the experimental collagen-induced arthritis (CIA) model by treating animals with a unique superantigen (M. arthritidis mitogen, MAM) from *Mycoplasma arthritidis*. We previously observed that MAM induced early onset of chronic arthritis with enhanced arthritis severity, predominantly by stimulating Th17 responses through TLR2 and TLR4. The current study evaluated pain phenotypes associated with MAM-triggered arthritis, and tested the idea of intervening the onset of the arthritis by interfering with innate immunity. Male B10RIII mice of 8-12 weeks old were separated into 3 groups. Mice in CIA group were treated intradermally at the base of the tail with 2 doses (250 μg) of bovine CII mix emulsified in CFA on Days 0 and 7. Mice in MAM group, however, were given 2 sub-optimal CII dose (150 μg) in CFA on days 0 and 7, followed by intraperitoneal (i.p.) injections of 25 ng MAM on days 14 and 21. Mice in TLR2 group received same pathogenic treatment as MAM group, plus 2 i.p. injections of 100μl αTLR2 antibody on days -2 and 0. Spontaneous and reflexive nocifensive behaviors, including guarding score, *von Frey* responses, inverted screen, hot plate, balance bar, and vertical behaviors were examined from day -1 twice a week for the first 4 weeks and once a week thereafter for 6 weeks. Immunohistochemistry was used to evaluate chemokines in dorsal root ganglia (DRG). We found that in CIA group, pain phenotypes started after day 49. For example, guarding score, an index for spontaneous pain, increased on Day 49 and quickly reached a peak on day 56, and maintained a high level after that. Compared to CIA group, MAM induced earlier onset of pain phenotypes, which started on day 21 and peaked on day 25. Peak value of guarding score (6.0±1.9, n=8) increased by 3 times compared to CIA group (2.1±0.9, n=8). In TLR2 group, although onset time of pain remained unchanged (started on day 18 and peaked on day 25), peak guarding score (2.7±1.2, n=8) significantly dropped to the level of CIA group. In line with this, amount of chemokines CCL2, CCL5 and CXCL12 in DRG also significantly dropped in αTLR2 antibody treated mice. Our results confirmed that MAM acts as a trigger for CIA in mice. Furthermore, it is suggested that TLR2 and other components in innate immune pathway are critical in the control of onset and/or severity of RA.

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Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

Title: Endogenous peripheral pain regulatory systems in orofacial pain patients

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Abstract: Persistent pain after root canal treatment is as high as 10-12% of all patients. Interestingly, ~40% of patients with apical periodontitis experience no pain (asymptomatic patients) despite similar radiographic presentation as symptomatic patients. Therefore, mechanisms mediating inhibition of nociception in asymptomatic patients may reveal novel factors or pathways that can be activated and therefore therapeutic in symptomatic patients. We hypothesize that soluble factors released from asymptomatic and symptomatic inflamed human apical tissues differentially regulate mouse TG nociceptor activities. We developed a clinically translational model where patients with either Symptomatic Apical Periodontitis (SAP) or Asymptomatic Apical Periodontitis (AAP) are phenotyped for pain followed by endodontic microsurgery to collect surgical biopsies and superfused to collect conditioned media (CM). Data were abalyzed using *Student's t-test* with $p<0.05$. We have found that 1.) Application of CM from periapical lesions from asymptomatic patients does not evoke calcitonin gene-related peptide (CGRP) release from cultured mouse TG neurons whereas CM from periapical lesions from symptomatic patients does. 2.) CM from periapical lesions from asymptomatic patients desensitizes capsaicin (CAP)-evoked calcitonin CGRP release and CAP-induced nocifensive behavior in mouse vibrissal pad whereas CM from periapical lesions from symptomatic patients show no such effect. 3.) Biopsies from patients without pain had ~2.5-fold greater levels of β-endorphin compared to patients in pain. 4.) Experiments using flow cytometric analyses and immuno-histochemistry revealed that periapical lesions contain large populations (~80%) of CD45+ leukocytes including CD11b+ macrophages, CD3+ T cells as well as CD19+ B cells and ~40% of all CD45+ leukocytes also express β-endorphin; 5.) Lastly, we also demonstrate that μ-opioid receptor (MOR) co-localizes with peripheral afferent sensory neurons in human periapical lesions. Taken together, these studies are consistent with a possible peripheral opioid-mediated regulation of pain in patients with asymptomatic periapical lesions but do not establish causality. Future studies will determine whether there are functional opioid- and non-opioid systems controlling peripheral neuronal activities in AAP patients.

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Poster

302. Inflammatory Pain

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Topic: D.03. Somatosensation: Pain

Support: HR16-003

Title: Epigenetic regulation of glutaminase expression in tnbs-induced colitis model of neuro-inflammatory pain

Authors: *S. DAS, K. E. MILLER
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Abstract: Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's diseases (CD) is chronic inflammation of the gastrointestinal tract leading chronic visceral discomfort pain. Many influences, including different biochemical and molecular mechanisms, genetic predisposition, and epigenetic factors, contribute to inflammatory chronic pain in IBD. Current pain management for visceral pain is very limited and is poorly understood. We have shown that glutamatergic sensory neurons play a central role in visceral neuro-inflammation and Glutaminase (GLS) expression, the enzyme that converts glutamine to glutamate, the excitatory neurotransmitter in sensory neurons, is upregulated. In this study, we explore different epigenetic factors controlling the regulation of GLS gene expression and how different epigenetic factors may modulate this chronic neuro-inflammatory pain.
Methods: Eight to ten-weeks old Sprague-Dawley rats were intra-rectally infused with trinitrobenzene-sulfonic acid to induce inflammatory colitis. The MeCP2 (Methyl CpG-binding protein-2) and GLS transcript and protein expression was studied in colon and L6/S1 DRGs in the absence or presence of GLS inhibitor, 6-diazo-5-oxo-L norleucine (DON) and/or Azacytidine (Aza, 50nM), DNA methyltransferase inhibitor. In *in vitro* studies, IEC-18 cells were used to study the effect of Aza on MeCP2 and GLS expression. Bisulphite conversion experiments and other epigenetic techniques were used to study DNA methylation of CpG islands of GLS promoter using methylation-specific PCR.
Results: There are two CpG islands in GLS promoter region. Our methylation-specific PCR studies targeted a sequence in the first CpG island (before TSS) and show increase in CpG DNA methylation in TNBS-induced colitis inflammation. This methylation was reduced in rats pretreated with DON, while in controls, there was no change. In IEC-18 studies, Aza treatment (25-50nM) reduced the GLS transcripts after 24 hours of treatment. Under these conditions, IEC-18 cells did express MeCP2-e2 but not MeCP2-e1.

Conclusion: Neuro-inflammation in TNBS-induced colitis induces different epigenetic factors that contribute to modification of GLS expression. We are investigating different epigenetic factors involved in modulation of pain in glutamatergic sensory neurons in DRG and colon. These epigenetic controls may be developed as crucial biomarkers for the pathogenesis, diagnosis and treatment of ulcerative colitis.

Disclosures: S. Das: None. **K.E. Miller:** None.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 302.24/CC11

Topic: D.03. Somatosensation: Pain

Support: Rosetrees Trust Grant A1296

Title: Investigating the expression and function of galanin in colonic sensory neurones

Authors: *T. S. TAYLOR, J. R. F. HOCKLEY, E. S. SMITH
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Chronic visceral pain and visceral hypersensitivity to normal bowel movements are associated with gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). The neuropeptide galanin has been previously identified to modulate neuronal excitability in areas of the central and peripheral nervous system, but its role in afferent sensitivity in the distal colon has not been fully investigated.
A comprehensive single-cell RNA sequencing of colonic sensory neurons shows galanin is expressed in subpopulations of neurones with a likely nociceptive phenotype. Here, we have further investigated the expression and function of galanin in colonic sensory pathways in mice using retrograde labeled dorsal root ganglia (DRG) and electrophysiological recordings of lumbar splanchnic nerve activity using an ex vivo colon preparation.
Immunohistochemistry analysis of retrograde labelled DRG neurones demonstrates that galanin is expressed in a significant proportion of colonic sensory neurones in both the thoracolumbar and lumbosacral pathway (lumbar splanchnic and pelvic nerves respectively) and that galanin is coexpressed with the neuropeptide CGRP and Gfrα3, a marker of high-threshold stretches sensitive afferent fibres. In addition, we investigated how galanin modulates lumbar splanchnic nerve activity in response to noxious mechanical stimuli using in C57BL/6 mice. We observed that galanin attenuated peak firing in response to noxious mechanical stimulation and reduced basal firing. Effects of galanin receptor specific agonists and antagonists have also been investigated to determine which galanin receptor mediates the inhibitory effects observed.
In summary, we show that galanin may function in an auto-inhibitory role to attenuate afferent

firing in the lumbar splanchnic nerve in response to noxious mechanical stimulation and therefore contribute to the regulation of visceral pain.

Disclosures: T.S. Taylor: None. **J.R.F. Hockley:** None. **E.S. Smith:** None.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 302.25/CC12

Topic: D.03. Somatosensation: Pain

Support: Arthritis Research UK RG20930
Rosetrees Postdoctoral Grant
Gates Cambridge Trust scholarship
BBSRC Doctoral Training programme

Title: Role of transient receptor potential (TRP) channels in acute inflammatory knee pain

Authors: *S. CHAKRABARTI, L. A. PATTISON, G. CALLEJO, K. SINGHAL, J. R. F. HOCKLEY, E. S. J. SMITH
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Abstract: Inflammatory joint pain is ongoing, diffuse and reduces the quality of human life. To determine how changes in joint neuron function during inflammation contribute to inflammatory knee pain, we conducted intra-articular injection of complete Freund's adjuvant (CFA) into the knee joint of mice. Subsequent to this inflammatory insult, mice displayed a decreased ability to perform natural digging behavior. To understand the neural basis of this symptom, we performed retrograde tracing of knee-innervating dorsal root ganglion neurons (knee neurons) and recorded their electrical and chemical sensitivity in culture using whole-cell patch clamp. We found that after inflammation, knee neurons show a decreased threshold of action potential firing and an increased sensitivity to capsaicin, an agonist of the transient receptor potential vanilloid 1 (TRPV1) ion channel. We further showed increased expression of TRPV1 in knee neurons from the CFA-injected side using immunohistochemistry. Nerve growth factor (NGF) signaling is a minor contributor to the increase in TRPV1 expression because there was a small increase in expression of TRPV1 with the NGF receptor, tropomyosin receptor kinase A (TrkA) following CFA injection. We also assessed the role of other TRP channels in inflammatory joint pain, but no change in cinnamaldehyde (TRPA1 agonist) or menthol (TRPM8 agonist) sensitivity was observed in knee neurons. Taken together, our data suggest that following CFA-induced knee inflammation there is a recruitment of TRPV1 sensitive knee neurons, which, combined with a lowered action potential threshold, likely contribute to the decreased digging behavior observed.

Disclosures: S. Chakrabarti: None. **L.A. Pattison:** None. **G. Callejo:** None. **K. Singhal:** None. **J.R.F. Hockley:** None. **E.S.J. Smith:** None.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 302.26/CC13

Topic: D.03. Somatosensation: Pain

Support: DPI MH 103908
W.M. Keck Foundation I160621
Brain Research Foundation SIA

Title: General anesthesia activates a central circuit that functions to suppress pain

Authors: *T. HUA[1,2], K. SAKURAI[3], Y. CHEN[1,2], S. ZHAO[1], B.-X. HAN[1], F. WANG[2]
[2]Dept. of Neurobio., [1]Duke Univ., Durham, NC; [3]Tohoku Univ., Sendai, Japan

Abstract: One of the key functions of general anesthesia (GA) is analgesia, or pain relieving. We hypothesized that the GA-induced analgesic process is an "active" pain-suppression process rather than a passive consequence of GA-induced loss of conscious perceptions. Specifically, we hypothesize that there are neurons in the brain that are activated by GA and certain GA-activated neurons function to actively inhibit pain perception. Indeed, using the immediate early gene Fos as a marker for highly activated neurons, we discovered a subset of neurons in the mouse central amygdala (CeA) that become strongly Fos+ under GA (here after referred to as CeA_{GA}). Neurochemical characterization revealed that CeA_{GA} neurons are all GABAergic neurons. Using our recently developed CANE (Capturing Activated Neuronal Ensembles) technology that is ideal to capture and manipulate Fos+ neurons in mice, we are able to label CeA_{GA} neurons and express the optogenetic activator channelrhodopsin in these cells. We showed that optogenetic activation of CeA_{GA} neurons do not induce any fear related responses, which is a function generally associated with CeA. Importantly, activating CeA_{GA} significantly reduced sensory responses to mechanical, heat, cold, and chemical stimuli, also drastically abolished pain-induced self-recuperative behaviors such as wiping and licking of injured regions. Further, the pain-suppressing effects extend to both acute and chronic pain models. Finally, CeA_{GA} neurons project to numerous brain regions implicated in pain processing. Taken together, our study revealed a central pain-suppression circuit that is activated by GA, and is a previously unappreciated key neural substrate for the analgesic effect of GA.

Disclosures: T. Hua: None. **K. Sakurai:** None. **Y. Chen:** None. **S. Zhao:** None. **B. Han:** None. **F. Wang:** None.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 302.27/CC14

Topic: D.03. Somatosensation: Pain

Title: Paclitaxel chemotherapy induced neuropathic pain: Mechanism and neurocircuitry of adult rat brain

Authors: *P. P. KULKARNI[1], X. CAI[2], T. POTTALA[1], K. CRUITE[1], T. KNOX[1], S. NODINE[1], A. G. HOHMANN[3], C. FERRIS[1]
[1]Psychology, Northeastern Univ. Dept. of Psychology, Boston, MA; [2]Ctr. For Translational Neuroimaging, Northeastern Univ., Boston, MA; [3]Indiana Univ., Bloomington, IN

Abstract: Cancer is the second leading cause of death in the US accounting for over 600,000 deaths annually. The most common treatment for inoperable cancer is chemotherapy. Though chemotherapy can improve prognosis, side effects range from cognitive impairment to neuropathic pain. Between 30 and 50 percent of the patients undergoing chemotherapy experience some level of peripheral neuropathy (CIPN) that can continue after cessation of treatment. CIPN putatively results from the reorganization of neural circuits associated with pain perception and manifests as numbness, weakness, and prolonged pain in the extremities. These chemo-induced changes in brain structure and function are not well understood. In this study we characterized the anatomical and behavioral effects of the chemotherapeutic drug Paclitaxel in adult male Sprague-Dawley rats. Rats were given four injections of Paclitaxel at one day intervals followed by a behavioral test for cold allodynia and in vivo magnetic resonance imaging to assess changes in gray matter microarchitecture and functional connectivity. Following exposure to paclitaxel rat showed increased sensitivity to temperature or cold allodynia by a shorter latency to withdraw their paw when in response to a cold stimulus. Diffusion weighted imaging with computational analyses of indices of anisotropy showed putative changes in gray matter microarchitecture that included the basal ganglia, limbic ctx, amygdala and ventral hippocampus. Resting state functional connectivity showed an overall increase on connectivity or hyper-connectivity in many brain regions. The ventral posteriolateral thalamus, a key node in pain transmission to the sensory ctx, shows connectivity to immediate thalamic areas and the sensory ctx with vehicle treatment but loses connectivity to the ctx following paclitaxel treatment. The median raphe a key node in pain perception and integration shows hyper-connectivity to multiple brain areas following paclitaxel treatment. The dorsal medial striatum involved in habit formation and motivation shows an interesting anticorrelation (negative connectivity) with paclitaxel to brainstem and cerebellar regions suggesting a online/offline relationship between the brain might be compensating for neuropathic pain by disconnecting the striatum from the brainstem pain areas and the cerebellum. Together these

finding suggest paclitaxel induces reorganization of neural circuitry related to controlling pain, learning, and memory.

Disclosures: P.P. Kulkarni: None. **X. Cai:** None. **T. Pottala:** None. **K. Cruite:** None. **T. Knox:** None. **S. Nodine:** None. **A.G. Hohmann:** None. **C. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Animal Imaging Research. Holden MA.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 302.28/CC15

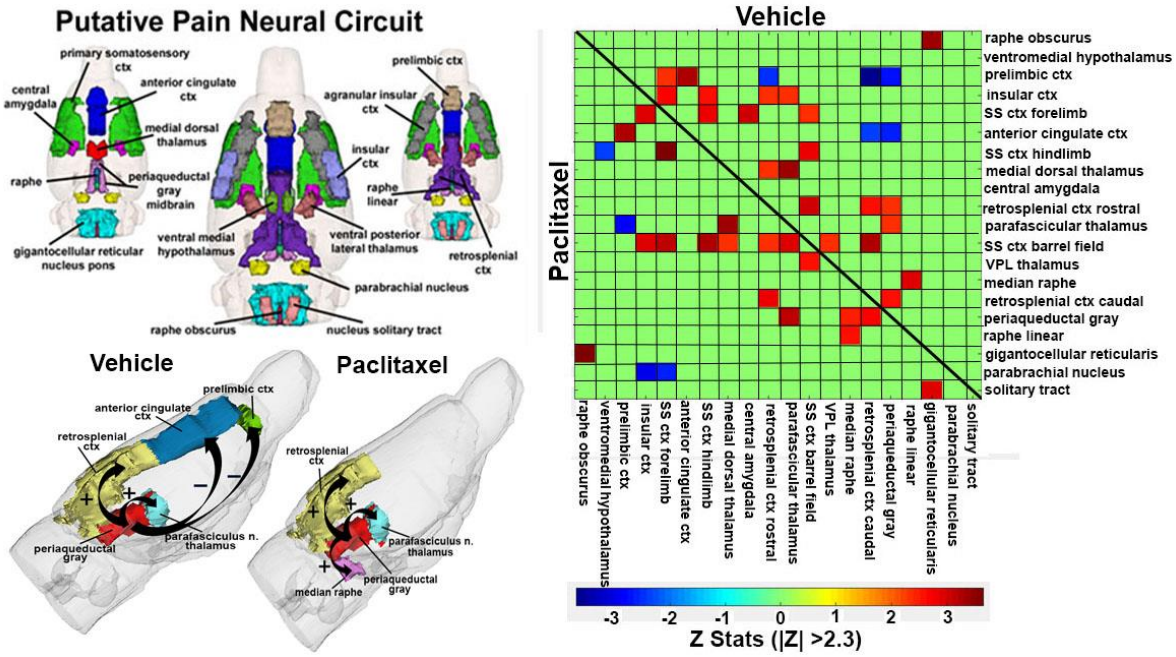
Topic: D.03. Somatosensation: Pain

Title: Altered gray matter microarchitecture following early adolescent chemotherapeutic treatment

Authors: *S. IRIAH[1], T. KNOX[1], I. KEHOE[1], K. CRUITE[1], O. OMETORUWA[1], R. SLIVICKI[2], I. ALKISLAR[1], D. PANOZ-BROWN[2], I. SOMETH[2], T. MORRISON[1], A. G. HOHMANN[2], P. KULKARNI[1], C. FERRIS[3]
[1]Psychology, Northeastern Univ., Boston, MA; [2]Indiana Univ., Indiana, IN; [3]Psychology, Northeastern, Boston, MA

Abstract: Chemotherapy is an indispensable treatment option for many common cancers and is used in neoadjuvant, adjuvant, and metastatic settings. Despite its usefulness, the systemic nature of chemotherapy carries implications for healthy dividing cells, and ultimately overall patient health. The effects of chemotherapy on the CNS are often subtle and may persist well after the end of treatment. There is limited research on the effects of chemotherapy in the pediatric population, specifically chemotherapy-induced changes in brain function and sensory processing. In this study we characterized the anatomical and behavioral effects of the chemotherapeutic drug paclitaxel in prepubescent (30-35 days of age) male Sprague-Dawley rats. Rats were given four injections of paclitaxel (2 mg/kg i.p.) at one day intervals followed by a behavioral test for cold allodynia and in vivo magnetic resonance imaging to assess changes in gray matter microarchitecture and functional connectivity. Behavior testing revealed no difference in chemotherapy-treated animals, when testing for withdrawal latencies on a cold plate assay for neuropathic pain. Diffusion weighted imaging (DWI) showed alterations in gray matter microarchitecture in the primary olfactory system, deep cerebellar nuclei and interestingly, the midbrain dopaminergic neurons. Areas comprising the pain neural circuitry were unaffected. Changes in resting state functional connectivity were modest. These data are in in stark contrast to paclitaxel treatment in adult rats that show robust cold allodynia , alterations in pain neural circuitry (see adjacent poster) as well as reductions in both hippocampal neurogenesis and

reversal learning deficits. Ongoing studies are exploring changes in learning and memory, functional connectivity and immunohistochemical biomarkers of inflammation following chemotherapy treatment in prepubescent rats.



Disclosures: S. Iriah: None. **T. Knox:** None. **I. Kehoe:** None. **K. Cruite:** None. **O. Ometoruwa:** None. **R. Slivicki:** None. **I. Alkislar:** None. **D. Panoz-Brown:** None. **I. Someth:** None. **T. Morrison:** None. **A.G. Hohmann:** None. **P. Kulkarni:** None. **C. Ferris:** None.

Poster

302. Inflammatory Pain

Location: SDCC Halls B-H

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Program #/Poster #: 302.29/CC16

Topic: D.03. Somatosensation: Pain

Support: FAPEMIG RED-00006-14

Title: Effect of the Pha1b toxin on spinal cord glia in CFA-induced inflammatory pain

Authors: *H. TENZA FERRER[1], J. DA SILVA[2], L. A. V. MAGNO[1], M. V. GOMEZ[1,2]
[1]Univ. Federal De Minas Gerais, Belo Horizonte, Brazil; [2]Inst. de Ensino e Pesquisa da Santa Casa de Belo Horizonte, Belo Horizonte, Brazil

Abstract: Phα1β (or Tx3-6) is a toxin obtained from the venom of the Brazilian spider *Phoneutria nigriventer*. We have previously showed that this toxin blocks different types of neuronal voltage sensitive calcium channels with preference for N-type, which is directly involved with pain. Although different animal pain models including inflammatory pain were attenuated by acute or chronic administration of Phα1β, it is still unclear the anti-inflammatory mechanisms of this toxin. An intraplantar CFA injection into the hind paw induce an inflammation in the site of the injection, and this conducts to a behavior change in the animal as a mechanical hyperalgesia. The peripheral inflammation in the CFA model also produce a cellular response observed in the dorsal horn of the spinal cord such as glial activation. For example, Ikeda *et al.* (2012) showed that glial activation is observed in the rat spinal cord following peripheral inflammatory pain with CFA, which result in pain behaviour. In the present study, we sought to determine whether anti-inflammatory effects of Phα1β involve glia recruitment or activation in the rat spinal cord. To conduct this, we produced the peripheral inflammatory model injecting a single unilateral injection of CFA into the hind paw. Two days after CFA or vehicle injection, animals were intrathecally injected with Phα1β and, two hours later, we observed antinociceptive effects through an analgesimeter test. Then, we intracardially perfused the animals and performed spinal cord confocal microscopy for Iba1 and GFAP. As expected, our inflammatory model increased the astrocytes and microglia activation and proliferation in the spinal cord two days post CFA injection. The activation was studied through fluorescence intensity and morphology of the cells and the proliferation was conducted by manual counting of cells and BrdU immunofluorescence. Our observations show that the toxin-treated animals displayed reduced astrocytes activation and increased local proliferation of these cells, but no alteration in microglia proliferation. These results suggest that anti-inflammatory effects of Phα1β are related to astrocyte inhibition in the spinal cord.

Disclosures: H. Tenza Ferrer: None. **J. da Silva:** None. **L.A.V. Magno:** None. **M.V. Gomez:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.01/DD1

Topic: D.03. Somatosensation: Pain

Support: Chinese FRFCU 2016QN81017
Chinese NSF 61673346
Chinese NSF 81600982
Chinese NSF 81527901

Title: Pain modulation by delivering gaba$_a$agents across the blood-brain barrier through focused ultrasound

Authors: *K. WANG[1,2], T. HE[1], W. XIONG[1,2], X. YU[1,3], C.-H. TSAI[4], X. LI[3], H.-L. LIU[1,4], H.-Y. LAI[1,2]
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Abstract: The pain processing is associated with an extensive cortical network, and the primary somatosensory cortex (S1) is the kernel to modulate the pain sensation. Multiple $GABA_A$ agents have been used in the pain modulation, however, these agents may produce poor modulated effect or side effect because the molecule size of these agents could not cross the blood brain barrier (BBB) locally. Focus ultrasound (FUS) combined with microbubble could temporally disrupt the BBB to induce $GABA_A$ agents delivery. In the present study, we proposed that FUS-induced BBB opening combined with picrotoxin (PTX, a $GABA_A$ receptor antagonist), and muscimol (MUS, a $GABA_A$ receptor agonist) could modulate the pain perception with dosages. We presented FUS at the rat's left primary somatosensory cortex forelimb region (S1FL, 1 mm posterior and 4 mm lateral to the bregma) followed by intravenous administration of PTX (0.2, 0.4 or 1 mg/kg), and MUS (0.2, 0.4 or 1 mg/kg). Behavioral tests were evaluated by mechanical nociceptive threshold (MNT) testing before and after FUS exposure and immunohistochemistry staining was performed after electrical stimulation in forepaw. As compared with the non-FUS side, the paw withdrawal threshold decreased in the PTX group and increased in the MUS group in the FUS side with 3-h post-FUS ($p<0.05$). Moreover,the variation of paw withdrawal threshold was dosage-dependent. Immunohistochemistry staining showed that PTX and MUS respectively excited and inhibited the expression of c-Fos in left S1FL (FUS exposure site) as compared with right S1FL, corresponding with the results of behavioral tests. In addition, the statistical results displayed that most c-Fos expression localized in the layer II/III and IV of S1FL.These results may suggest a further potential to specifically modulate pain sensation by targeting on the layer II/III and IV in S1FL.

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Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.02/DD2

Topic: D.03. Somatosensation: Pain

Title: The effect of electroacupuncture on cord dorsum potentials produced by sural nerve stimulation in the diabetic rat

Authors: *S. QUIROZ-GONZÁLEZ[1], G. VERÓNICA BEATRIZ[1], Y. GARCIA-PICENO[1], R. LÓPEZ-GÓMEZ[1], B. SEGURA-ALEGRÍA[2], I. JIMÉNEZ-ESTRADA[3]
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Abstract: In this study, the effect of low and high frequency electroacupuncture (EA) on the negative components of the spinal cord dorsum potentials (CDPs) generated by the electrical stimulation of the sural nerve was analyzed in diabetic rats induced by streptozotocin (STZ). Two groups of Wistar rats (120-150 gr) were used: one received STZ (60mg/kgi.p.) and the other, the STZ vehicle solution. The animals were anesthetized with ketamine (100 mg / kg) and Xilasine (2 mg/kg) and underwent a laminectomy to expose the L4, L5, L6, S1 spinal segments. To record the CDPs, a "ball" electrode was placed on the back of the spinal cord and the sural nerve (SU) was stimulated with "hook" electrodes (single current pulses. 0.05 ms, 3.5 and 20 times threshold, xU). EA stimulation was applied at 2 and 100 Hz at the acupoints Zuzanli (ST36) and Sanjinjiao (SP6) during 30min. One week after STZ injection, treated animals (n = 9) had an increase in blood glucose (from 110 ± 15 to 421 ± 23.6 mg / dl), which was maintained until the week 5. On the other hand, animals with vehicle (n = 7) had no increase in blood glucose. Body weight also decreased in treated animals (19.5 ± 4.2%). At week 5 a facilitation was observed in the N2 (33 ± 7.1%; n = 9) and N3 (40 ± 8.5%; n = 9) components in the CDPs recorded in diabetic animals, but there was a depression in amplitude of the N1 component (20.5 ± 6.5%; n = 9) in comparation with control animals. Both, facilitation and depression of the negative CDPs were reduced by 2 and 100Hz of EA stimulation (N1; 34 ± 8.8%, N2; 22 ± 6.1%, N3; 43 ± 8.5%). Our results indicate that EA partially reverse the alterations provoked in the negative components of the CDPs in animals under experimental diabetes.

Disclosures: S. Quiroz-González: None. **G. Verónica Beatriz:** None. **Y. Garcia-Piceno:** None. **R. López-Gómez:** None. **B. Segura-Alegría:** None. **I. Jiménez-Estrada:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.03/DD3

Topic: D.03. Somatosensation: Pain

Support: GACR 18-09853S
GACR P304/12/G069

LQ1604 BIOCEV-FAR
GAUK 734218
RVO67985823
TE 01020028

Title: Alterations of spinal inhibitory and excitatory nociceptive transmission in VGAT-ChR2-eYFP mice in different pain models

Authors: *P. ADAMEK[1,2], M. HELES[1,2], J. PALECEK[1]
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Abstract: Disbalance between inhibitory and excitatory neurotransmission in the spinal cord may be one of the underlying mechanisms of different pain syndromes. Our goal was to describe and compare changes in excitatory and inhibitory transmission in the superficial laminae (I, II_o) excitatory dorsal horn neurons in a model of paclitaxel-induced neuropathy, chronic constriction injury of the sciatic nerve (CCI), and peripheral inflammation in adult male mice. Blue light (470 nm) optogenetic stimulation of inhibitory dorsal horn neurons evoked IPSC (le-IPSC) currents in combination with whole-cell patch clamp recordings of spontaneous excitatory and inhibitory postsynaptic currents (sEPSC, sIPSC) from excitatory neurons in spinal cord slices from VGAT-ChR2-eYFP mice were used. Inhibitory interneurons with channelrhodopsin-2 (ChR2) expression were characterized by le-IPSC response with long plateau phase that was missing in the excitatory neurons. Only excitatory, non-ChR2 expressing neurons were analyzed in this study. Our results showed that all three pathological conditions: paclitaxel-induced neuropathy, CCI and also peripheral inflammation lead to significant reduction in the amplitudes of le-IPSC (65 %, 48 and 59 % of the control group). The ratio between the glycinergic and GABAergic component of the le-IPSC did not change substantially in comparison with controls. Frequencies of sIPSC were significantly reduced while sEPSC were increased under the pathological conditions. Mechanical sensitivity was significantly increased in all three models in behavioral tests. Our data suggest that different pathological conditions may induce similar changes in neurotransmission together with corresponding behavioral changes. A better understanding of the specific mechanism of the fragile balance between the excitatory and inhibitory neurotransmission under the pathological conditions may help to improve analgesic therapy in various pain states.

Disclosures: P. Adamek: None. **M. Heles:** None. **J. Palecek:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

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Program #/Poster #: 303.04/DD4

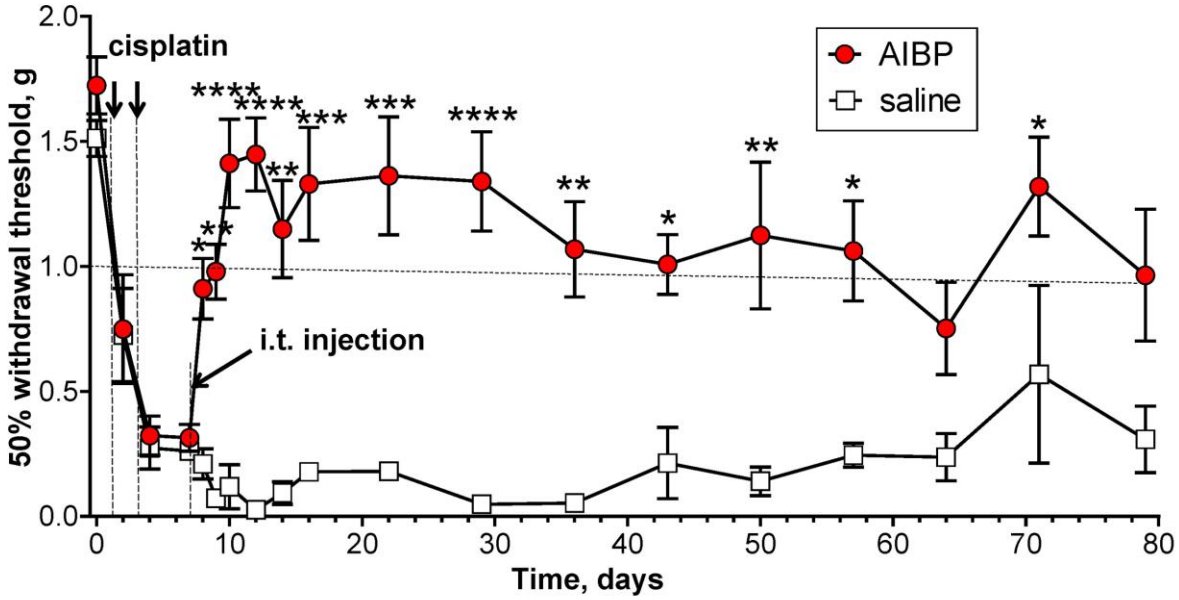
Topic: D.03. Somatosensation: Pain

Support: NS102432
NS099338
HL135737
HL136275
HL088093

Title: AIBP selectively regulates lipid rafts and inhibits neuroinflammation

Authors: ***Y. MILLER**, S.-H. CHOI, S. WOLLER, T. YAKSH
UC San Diego, La Jolla, CA

Abstract: Apolipoprotein A-I binding protein (AIBP) reduces lipid raft abundance by augmenting removal of excess of cholesterol from the plasma membrane. Here, we report that AIBP prevents and reverses processes associated with neuroinflammatory-mediated spinal nociceptive processing. The mechanism involves AIBP binding to Toll-like-receptor-4 (TLR4) and increased binding of AIBP to activated microglia, which mediates selective regulation of lipid rafts in inflammatory cells. AIBP-mediated lipid raft reductions downregulated LPS-induced TLR4 dimerization, inflammatory signaling and expression of cytokines in microglia. In mice, intrathecal injections of AIBP reduced spinal myeloid cell lipid rafts, TLR4 dimerization, neuroinflammation, and glial activation. Intrathecal AIBP reversed established allodynia in mice in which pain states were induced by the chemotherapeutic cisplatin (as shown in the figure below), intraplantar formalin, or intrathecal LPS, all pro-nociceptive interventions known to be regulated by TLR4 signaling. These findings demonstrate a novel mechanism by which AIBP regulates neuroinflammation and suggest the therapeutic potential for AIBP in treating preexisting pain states.



Disclosures: **Y. Miller:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **S. Choi:** None. **S. Woller:** None. **T. Yaksh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.05/DD5

Topic: D.03. Somatosensation: Pain

Support: NRF-2012R1A3A1050385
35B-2011-1-C00034

Title: Active turnover of synaptic protein NCAM1 regulates synaptic reorganization after peripheral nerve injury

Authors: ***H.-G. KO**[1], J.-H. CHOI[1], D. PARK[3], S. KANG[1], C.-S. LIM[1], S.-E. SIM[1], J.-I. KIM[1], S. KIM[1], S. YE[1], J. LEE[1], P. PARK[1], S. KIM[1], M. ISLAM[1], H. KIM[2], C. TURCK[3], G. L. COLLINGRIDGE[4], M. ZHUO[5], B.-K. KAANG[1]
[2]Dept. of Dent. Anesthesiol. and Dent. Res. Institute, Sch. of Dent., [1]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Dept. of Translational Res. in Psychiatry, Max Planck Inst. of Psychiatry, Munich, Germany; [4]Mt. Sinai Hosp., Toronto, ON, Canada; [5]Dept Physiol., Univ. Toronto, Toronto, ON, Canada

Abstract: Peripheral nerve injury can induce pathological conditions that lead to persistent sensitized nociception. Although there is evidence that plastic changes in the cortex contribute to this process, the underlying molecular mechanisms are unclear. Here, we find that activation of the anterior cingulate cortex (ACC) induced by peripheral nerve injury increases the turnover of specific synaptic proteins in a persistent manner. We demonstrate that neural cell adhesion molecule 1 (NCAM1) is one of the molecules involved and show that it mediates spine reorganization and contributes to the behavioral sensitization. We show striking parallels in the underlying mechanism with the maintenance of NMDA-receptor- and protein-synthesis-dependent long-term potentiation (LTP) in the ACC. Our results, therefore, demonstrate a synaptic mechanism for cortical reorganization and suggest potential avenues for neuropathic pain treatment.

Disclosures: **H. Ko:** None. **J. Choi:** None. **D. Park:** None. **S. Kang:** None. **C. Lim:** None. **S. Sim:** None. **J. Kim:** None. **S. Kim:** None. **S. Ye:** None. **J. Lee:** None. **P. Park:** None. **S. Kim:**

None. **M. Islam:** None. **H. Kim:** None. **C. Turck:** None. **G.L. Collingridge:** None. **M. Zhuo:** None. **B. Kaang:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.06/DD6

Topic: D.03. Somatosensation: Pain

Support: DE018661
DE023090

Title: Exploration of sensory integration for nociceptive and tactile inputs in primary somatosensory cortex of rats

Authors: *H. KANDA, J. G. GU
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Abstract: We have recently shown that Piezo2 channel is involved in mechano-transduction and serotonin is mechanical transmission in Merkel cells of whisker hair follicles (Ikeda et al, Cell 2014). Since tactile information from whisker hair follicle is relayed to the barrel cortex in primary somatosensory regions of the rat brain, we seek to further understand how tactile signals from a single whisker hair follicle are processed in the barrel cortex and whether the sensory process of tactile signals in the brain may be significantly affected by nociceptive inputs form the periphery. To address these questions, we performed *in vivo* whole-cell patch-clamp recordings from neurons in layer 2/3 of rat barrel cortex (C1 region) to examine excitatory postsynaptic currents (EPSCs) and action potential firing following mechanical stimulation of a whisker hair. Experiments were performed on adult Sprague-Dawley rats that were anesthetized with urethane. The region of recordings was is around 2.5 mm posterior and 5.5 mm lateral to the bregma, and at a depth between 200 and 500 μ m from the surface of the brain. Mechanical stimulation was applied by air puff (20 psi for 50 ms) to a C1 whisker hair. Under the voltage-clamp configuration, the air puff to whicker hair evoked excitatory postsynaptic currents (EPSCs) in recorded neurons. The latency of the first EPSC following the mechanical stimulation was about 22 ms. Around 10 EPCSs usually could be evoked by a single air-pull stimulus. Under the current-clamp configuration, an air-puff stimulus could evoke several excitatory postsynaptic potentials (EPSPs), and some of these EPSPs could reach the threshold to fire action potentials. The responses of layer 2/3 barrel cortical neurons to whisker stimulation at different frequency were also characterized. The development of this *in vivo* patch-clamp recording method should lend us an important tool to explore sensory integration for nociceptive and tactile inputs in primary somatosensory cortex of rats.

Disclosures: H. Kanda: None. **J.G. Gu:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.07/DD7

Topic: D.03. Somatosensation: Pain

Support: Dept. of Anesthesiology, UW Hospitals and Clinics

Title: The effect of baclofen on mechanical sensitivity following nerve injury

Authors: *R. C. LENNERTZ, III, M. BANKS
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Abstract: Baclofen is commonly used to treat muscle spasm. The pain relief associated with its use is often attributed to muscle relaxation. However, baclofen may have multiple mechanisms of action. There is evidence that cortical somatostatin-expressing (SOM) interneurons signal via GABA-B receptors and that SOM neuron activity in somatosensory cortex (S1) is diminished following nerve injury. Further, increasing SOM neuron activity in S1 normalized mechanical sensitivity following nerve injury. These studies suggest that a GABA-B agonist may alleviate mechanical sensitivity following nerve injury. We performed spared nerve injury (SNI) in 7-8 week old C57bl6 mice as a model of neuropathic pain, where the tibial nerve was ligated leaving the peroneal and sural branches of the sciatic nerve intact. We assessed paw withdrawal threshold (PWT) as a measure of mechanical sensitivity. We found SNI significantly lowered PWT in mice for at least 4 weeks, as previously described. Sham mice demonstrated lower PWT for about 1 week before returning to baseline. We performed intraperitoneal injections of baclofen (0.1-1 mg/kg) or vehicle in SNI and sham animals 7-10 days following nerve injury. The experimenter was blinded to the content of each injection. PWT was measured between 30-60 minutes following injection. We found no differences in paw withdrawal threshold in SNI or sham animals. The mice exhibited normal activity and no change in PWT in the contralateral paw at any baclofen concentration. There were no differences between male and female mice. It is possible that a higher concentration of baclofen would influence PWT. Baclofen also may activate GABA-B receptors on SOM neurons themselves or influence GABA-A receptor activity on pyramidal cells in a manner that does not increase PWT following nerve injury.

Disclosures: R.C. Lennertz: None. **M. Banks:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.08/DD8

Topic: D.03. Somatosensation: Pain

Support: ADA Grant 1-17-ICTS-062

Title: Probing the spinal mechanisms of pain in human diabetic neuropathy

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Abstract: Research objective and rationale Rodent models of painful diabetic neuropathy show evidence of disinhibition in the spinal cord dorsal horn. This disinhibition is accompanied by impaired Hoffman reflex rate dependent depression (HRDD). Spinal disinhibition and impaired HRDD are reversed by 5HT2A blockers including duloxetine. The translational potential of these studies is suggested by initial findings of impaired HRDD in painful neuropathy in patients with type 1 diabetes. Whether patients with type 2 diabetes and pain have reduced HRDD and whether spinal disinhibition is associated with impaired diffuse noxious inhibitory control (DNIC), potentially modifiable by drugs enhancing this pathway, are unknown. **Methods** 19 patients with diabetes (7 type 1 and 12 type 2) were assessed and stratified into 'pain' (n=8) or 'no pain' (n=11) groups according to average visual analogue scale pain rating. HRDD was determined by delivering a train of ten stimuli at 1Hz to the tibial nerve in the popliteal fossa. The respective responses were termed H1-H10. Stimulus intensity was set to evoke a response approximately 75% of maximum H-reflex on the rising section of the recruitment curve. HRDD was calculated as a ratio of H2, H3 etc to H1 as well as the mean of H2-H10 to H1. Conditioned Pain Modulation (CPM), to assess the efficiency of DNIC, was performed using immersion of the hand in painfully cold water (4°) as the conditioning stimulus. Test stimuli to determine pressure pain threshold were given using an algometer. Temporal summation was assessed using wind-up ratio (WUR); a comparative pain rating '0-100' of a single pinprick (256mN) to a series of 10 stimuli applied at 1 per second. **Results** Age, gender and clinical severity of neuropathy did not significantly differ between the two groups. Patients with painful diabetic neuropathy showed significant impairment of HRDD (Mean H2-H10: H1) when compared to the non-painful group ($p=0.008$). Significant impairments ($p<0.05$) were also seen when comparing the majority (7/9) of individual stimuli within the train. Efficiency of CPM and WUR were not significantly different between the two groups and showed no significant correlation with HRDD. **Conclusion** The results support the hypothesis that painful neuropathy

in patients with type1 and type 2 diabetes is associated with spinal disinhibition. Whilst anti-neuropathic pain agents targeting this mechanism may represent a therapeutic target in patients with impaired HRDD these preliminary data provide no evidence that impaired HRDD is linked to deficient DNIC.

Disclosures: A. Worthington: None. **N. Calcutt:** None. **R. Malik:** None. **A. Marshall:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.09/DD9

Topic: D.03. Somatosensation: Pain

Title: Comparing the firing patterns of superficial dorsal horn neurons evoked by robotically automated and human manual brushing

Authors: *D. C. LEE[1], J. E. LEE[3], K. LEE[4], Z. KAGAN[2], K. BRADLEY[2]
[1]Nevro, Santa Clarita, CA; [2]Nevro, Redwood City, CA; [3]ANC Robotics, Santa Clarita, CA; [4]Res., Nevro Corp, Mississauga, ON, Canada

Abstract: Background and Aims: Investigations into the response of spinal dorsal horn neurons to afferent inputs typically employ various types of mechanical stimulation to peripheral structures (e.g., a rodent paw). Most often, these stimuli are applied manually (i.e., by the experimenter) to a receptive field; manual application may contribute to inconsistent variation in the parameters of the stimulus: temporal timing, duration, location, etc. This may challenge the analysis and interpretation of the data. In this study, we compared the spinal dorsal horn neural response between custom robot-based brushing system and manual brushing.
Methods: A robot with four degrees of freedom (Dobot Magician, Shenzhen, PRC) was programmed to brush (Paint brush with 0.5 cm width) the hind paw of an anesthetized rat. Multichannel electrodes (NeuroNexus, Ann Arbor, MI) were placed in the ipsilateral superficial dorsal horn (SDH; lamina II-III within the spinal segment L4-6) to monitor single unit firings evoked by a similar brushing motion performed by the robot and from a trained examiner. The proximal and distal boundary of receptive field, identified manually by the examiner using Von Frey probes, was marked on the skin of the paw, and used as start and end points for brushing. The robot brushing was programed to brush in an arc motion at different depths (0.5, 1, 2 and 3mm), speeds (50, 100 and 200mm/s) and directions (proximal to distal vs. distal to proximal). Firing patterns evoked by robot and manual brushing were compared based on their firing rates, durations, and timing with respect to an event marker
Results: Qualitatively, automated brushing generated consistent and repeatable patterns of multiunit SDH activity, while manual brushing revealed a wider variability. Manual forward brushing was most similar to the automated brushing with depth=2mm, speed=100mm/s in terms

of firing rate and duration. Interestingly, it appeared that most recorded neurons, activated by manual brushing were also fired by automated brushing, but certain neurons were activated more by one brushing mode or the other. Using the robot, reverse brushing showed a disrupted firing pattern compared to forward brushing; this difference may have been due to topologic feature differences along the brushed surface of the paw.
Conclusion: Automated brushing appeared to demonstrate a more consistent pattern of response of SDH neurons to afferent input compared to manual brushing. Standardization of the sensory stimulus using this novel robot tool may allow for fewer trials of applied afferent input and greater sensitivity to detect subtle changes in response in sensory experiments.

Disclosures: D.C. Lee: A. Employment/Salary (full or part-time):; Nevro. **J.E. Lee:** None. **K. Lee:** F. Consulting Fees (e.g., advisory boards); Nevro. **Z. Kagan:** A. Employment/Salary (full or part-time):; Nevro. **K. Bradley:** A. Employment/Salary (full or part-time):; Nevro.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

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Topic: D.03. Somatosensation: Pain

Support: This research was supported by a grant the National Research Foundation of Korea grant funded by the Republic of Korean Government (NRF-2017R1A2A2A05001402).

Title: Cytochrome P450scc and P450c17 increase the production of D-serine in the development of neuropathic mechanical allodynia

Authors: S.-R. CHOI[1], H.-S. CHOI[1], H.-J. HAN[1], *J.-H. LEE[2,1]
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Abstract: We have recently shown that spinal D-serine plays an important role in the development of neuropathic pain. However, the modulatory mechanism of D-serine production following peripheral nerve injury is poorly understood. In the present study, we determined whether the levels of spinal D-serine and its synthesizing enzyme, serine racemase (Srr) are modulated by activities of neurosteroidogenic enzymes, P450 side-chain cleavage (P450scc) and P450c17 in the development of neuropathic pain. After chronic constriction injury (CCI) of the right sciatic nerve, mechanical allodynia test was performed in the ipsilateral hind paw. The expression levels of P450scc, P450c17 and Srr in the spinal cord were also evaluated using Western blot assay and immunihistochemistry. Sciatic nerve injury increased the expression of

P450scc and P450c17 in the spinal cord dorsal horn astrocytes. Intrathecal administration of the P450scc inhibitor, aminoglutethimide or the P450c17 inhibitor, ketoconazole on postoperative days 0 to 3 (during the induction phase of pain) significantly suppressed the development of mechanical allodynia in CCI mice. In addition, sciatic nerve injury increased the levels of D-serine and Srr expression, which was co-localized with P450scc or P450c17 in spinal astrocytes. Administration of aminoglutethimide or ketoconazole during the induction phase of neuropathic pain significantly attenuated the CCI-induced increase in D-serine production and Srr expression. Exogenous D-serine restored the development of mechanical allodynia, which was attenuated by administration of aminoglutethimide or ketoconazole. These results demonstrate that spinal P450scc and P450c17 increase D-serine production via modulation of Srr expression in spinal astrocytes contributing to the development of mechanical allodynia induced by peripheral nerve injury.

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Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

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Topic: D.03. Somatosensation: Pain

Support: NSC 100-2311-B-001 -002 -MY3
(MOST 105-2314-B-001 -003 -MY3

Title: Anterior nucleus of paraventricular thalamus (PVA) mediates mechanical hyperalgesia in neuropathic and inflammatory pain models

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Abstract: Pain-related diseases are the top leading causes of life disability. Identify brain regions involved in persistent neuronal changes will provide new insights for developing efficient chronic pain treatment. Here we showed that anterior nucleus of paraventricular thalamus (PVA) plays an essential role in the development of mechanical hyperalgesia in neuropathic and inflammatory pain models in mice. An increase of c-Fos and pERK staining, hyperexcitability and firing pattern switch of PVA neurons were detected in hyperalgesic mice. Direct activation of PVA neurons using optogenetics and pharmacological approaches were sufficient to induce persistent mechanical hyperalgesia in naïve animals. Conversely, inhibition of PVA neuronal

activity using DREADDs or inactivated PVA ERK at the critical time window blunted mechanical hyperalgesia in chronic pain models. At the circuitry level, PVA received innervation from the central nucleus of amygdala (CeA) a known pain-associated locus. Activation of the right CeA innervated PVA neurons with blue light was enough to induce persistent mechanical hyperalgesia. These findings support the idea that targeting PVA can be a potential therapeutic strategy for pain relief.

Disclosures: C. Chen: None. **Y. Chang:** None. **W. Chen:** None. **A.C.C. Shih:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

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Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant 17K09042
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Title: Effect of neuropathic pain on the optogenetically activated feedforward inhibition in the central amygdala of rats

Authors: *Y. TAKAHASHI, T. ONOZATO, Y. K. SUGIMURA, F. KATO
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Abstract: The majority of the nociceptive information arising from the spinal cord or the spinal nucleus of the trigeminal nerve targets the lateral parabrachial nucleus (LPB), from which monosynaptic excitatory projection to the central amygdala (CeA) initiates. In particular, a large portion of this projection terminates in the capsular part of the CeA (CeC)". This LPB-CeC synaptic transmission undergoes robust synaptic potentiation in various persistent pain models (Cheng et al. 2011; Han and Neugebauer 2004; Ikeda et al. 2007; Nakao et al. 2012; Neugebauer et al. 2004), thus making it a site for the pain-dependent changes in the nociception-emotion link. By applying the optogenetics, we have demonstrated for the first time that the activation of LPB-CeC fibers results in a large-amplitude bicuculline-sensitive IPSCs that follow the EPSC (Sugimura et al, J Neurophysiol, 2016). This evidence for the "feedforward inhibition" by excitatory inputs of LPB origin had been impossible to obtain because the past studies using electrical stimulation of LPB fibers used drugs that block GABA(A) receptors to avoid complications caused by probable direct stimulation of the CeA GABAergic neurons by the stimulation electrode. Taking this advantage of the optogenetic stimulation, we analyzed the effects of persistent pain on the "direct" LPB-CeC EPSC and the subsequent "feed forward" IPSC. We injected AAV for channelrhodopsin-2 expression into the right LPB of Wistar rats and

made L5 spinal nerve ligation (SNL). Light-evoked EPSCs and IPSCs were separately recorded in the same CeA neurons in acute brain slices. SNL resulted in side-specific mechanical allodynia and appearance of larger-amplitude EPSCs in the right CeC, which was accompanied by a significant increase in IPSC amplitude. However, despite the concurrent increase in EPSC and IPSC amplitudes, we failed to observe any significant correlation between the amplitudes of EPSCs and IPSCs in both sham-operated and neuropathic animals. It is supposed that the enhanced impact of the LPB inputs to the CeA circuit in persistent painful state would increase the LPB influence to the CeA network signaling, further leading to variable consequences of the chronic pain.

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Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

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Topic: D.03. Somatosensation: Pain

Support: Craig Neilsen Foundation
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Title: Facilitation of touch and tactile neuropathic pain sensations by corticospinal projections

Authors: *Y. LIU[1], A. LATREMOLIERE[2], X. LI[3], Z. ZHANG[1], M. CHEN[1], X. WANG[1], C. FANG[1], C. ALEXANDRE[4], K. H. WANG[3], C. WOOLF[1], Z. HE[1]
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Abstract: Although traditionally viewed only as a primary motor pathway, a subset of corticospinal neurons innervates the dorsal horn of the spinal cord, raising the possibility of a role in sensory processing. In support of this, we now show that either ablation of somatosensory corticospinal neurons (CSNs) or transection of their spinal-projecting axons in mice selectively impairs behavioral responses to light touch and greatly attenuates tactile allodynia in peripheral neuropathic pain models, without altering response to noxious stimuli. While tactile stimulation activates somatosensory CSNs, their corticospinal projections facilitate light touch-evoked activation ofcholecystokinin (CCK^+) interneurons in the deep dorsal horn. This CSN-meditated facilitation is also important for the indirect recruitment of nociceptive neurons in the superficial laminae for tactile pain sensation after peripheral nerve injury. In addition to revealing an

underappreciated descending pathway for cortical control over sensory perception, these results open up opportunities for designing new treatments for neuropathic pain.

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Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.14/DD14

Topic: D.03. Somatosensation: Pain

Support: NSF Graduate Research Fellowship Prograam

Title: Deconstructing the role of interneurons in spinal sensory processing

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Abstract: While chronic pain continues to affect 1 in 5 people globally, the neural mechanisms underlying its pathology and the therapies targeting its treatment, such as electrical stimulation, remain to be deconstructed. Certain cell types, such as parvalbumin-positive neurons, have been hypothesized to play a role in modulating or disrupting circuits in the presence of nerve injury or inflammation leading to pain. However, a main challenge in electrophysiological characterization of cell types in the spinal cord is the lack of cell specificity innate to electrical recording. Genetically modified calcium indicators (e.g. GCaMP6) have been used with great success in dissecting the role of specific neuronal populations in the brain. Recently, this technique was adapted for use in the spinal cord for *in vivo* imaging. Here, we utilize a "spinal window" technology to visualize, record, and disentangle the role of both heterogeneous and cell-type specific neuronal populations in the spinal cord to elucidate the organization and activity of interneurons in tactile perception and pain in both wild-type and transgenic mice. Enhanced identification of specific cell populations in awake, behaving animals not only enables us to explore the contribution of their activity in normal sensory processing, but further enables us to adapt this methodology to understand how these neurons are modulated under painful conditions. Such results may lead to a greater understanding of the mechanisms mediating pain therapy from pharmacological agents and electrical stimulation of the nervous system.

Disclosures: A. Allawala: None. **C.J. Black:** None. **C.Y. Saab:** A. Employment/Salary (full or part-time):; Rhode Island Hospital, Providence, RI USA. **D. Borton:** A. Employment/Salary (full or part-time):; Carney Institute for Brain Science, Providence, RI,USA, Department of Veterans

Affairs, Providence Medical Center, Center for Neurorestoration and Neurotechnology, Providence, RI USA..

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

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Topic: D.03. Somatosensation: Pain

Support: NRF-2017M3A9E4057926
NRF-2017M3C7A1025604
Society of Immune and Pain

Title: Bee venom acupuncture suppresses paclitaxel-induced mechanical hyperalgesia through spinal α2-adrenergic activity in rats

Authors: *J. LEE[1,2], W. KIM[1], G. CHUNG[1], H. YOON[2,1], S. KIM[1]
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Abstract: Paclitaxel, which is a chemotherapy drug for solid tumors, induces peripheral painful neuropathy. Bee venom acupuncture (BVA) has been reported to have potent analgesic effects. Its analgesic effects are known to be mediated by activation of spinal-adrenergic receptor. Here, we investigated the effect of BVA on paclitaxel induced mechanical hyperalgesia and spinal neuronal hyperexcitation. The role of spinal-adrenergic receptor subtypes in the BVA analgesia was also observed. Administration of paclitaxel (total 8 mg/kg, intraperitoneal) on four alternate days (days 0, 2, 4, and 6) induced significant mechanical hyperalgesic signs. This behavioral signs were quantified using a von Frey filament. BVA (1 mg/kg, ST36) relieved this mechanical hyperalgesia for at least two hours, and suppressed the spinal wide dynamic range neurons hyperexcitation evoked by press or pinch stimulation. Both melittin (0.5 mg/kg, ST36) and phospholipase A2 (0.12 mg/kg, ST36), major components of bee venom, were shown to play an important part in this the BVA analgesia, as they significantly attenuated the pain. Intrathecal pretreatment with the α2-adrenergic receptor antagonist (idazoxan, 50 μg) blocked the BVA analgesia, whereas the effect of BVA were not inhibited by α1-adrenergic receptor antagonist (prazosin, 30 μg). These results suggest that BVA has potent suppressive effects against paclitaxel-induced mechanical hyperalgesia, which were mediated by spinal α2-adrenergic receptor.
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Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

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Program #/Poster #: 303.16/DD16

Topic: D.03. Somatosensation: Pain

Support: NIH NIDCR R01 DE022746

Title: Dorsal hippocampal activation suppresses neuropathic pain behaviors: Chronic pain as extinction-resistant pain-related memory traces

Authors: *M. V. CENTENO[1], X. WEI[5], W. REN[2], D. PROCISSI[6], T. XU[7], R. JABAKHANJI[8], A. BORRUTO[3], M. MARTINA[10], J. M. RADULOVIC[4], D. SURMEIER[11], A. V. APKARIAN[9]
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Abstract: Accumulating evidence suggests the hippocampus being involved in, and modified with, chronic neuropathic pain. However, it is still not clear whether hippocampal activity has direct control over neuropathic behaviors. Here we show that activation of the dorsal, but not ventral, hippocampus, by glutamate microinjection or by chemogenetically increasing excitability (PSAM/PSEM), completely or partially reversed neuropathic behaviors: tactile allodynia and thermal hyperalgesia in the models of spared nerve injury and lumbar spinal nerve ligation. Using a new methodology (chemo-fMRI), where we combine awake resting state brain imaging with viral vector mediated chemogenetic activation (PSAM/PSEM), we could demonstrate that increased excitability of dorsal hippocampus neurons altered resting state functional connectivity within circuitry specifically related to the extent of diminution of neuropathic behavior (tactile allodynia). The identified circuitry most reliably (survived a validation procedure) identified dorsal hippocampal connections to the somatosensory cortex and the thalamus. Moreover, anterograde tracing indicated non-overlapping projections from dorsal and ventral hippocampus. Thus, the present study exhibits a novel causal role for the dorsal hippocampus, and mediating circuitry, controlling neuropathic pain-related behaviors. Altogether, these results imply downregulation of dorsal hippocampus circuitry in chronic neuropathic pain; the activation of which reverses pain behaviors either through disruption of accumulated memories and/or by enhancing extinction circuitry.

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Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

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Program #/Poster #: 303.17/DD17

Topic: D.03. Somatosensation: Pain

Support: NIH R01 NS095366
Wings for Life

Title: Collateral projections of lumbar spinoparabrachial neurons in mouse

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Abstract: Chronic pain is the most common cause of long-term disability and has profound effects on the overall quality of life for those afflicted. Pain is a multifaceted sensation consisting of sensory-discriminative and affective aspects, therefore, involving multiple signaling pathways and higher order structures. The anatomical correlate of the sensory-discriminative component of pain is the spinothalamic tract, where the affective component is thought to be primarily signaled via the spinoparabrachial pathway. The main spinal projection to the parabrachial nucleus (Pb) is from neurons in lamina I. Efferents from the Pb project onto emotional nodes of the brain, most notably to the lateral hypothalamus and amygdala, which enable sensory information from the periphery to be integrated towards an emotional response. Dysfunction within this circuit at any level along the neuraxis, particularly when chronic, can result in adverse emotional effects including anxiety and depression. In addition to the Pb, lamina I neurons send projections to several other pain-related regions. The degree to which common lamina I projection neurons share diverse targets varies by both species and spinal segment. The regions receiving collaterals, the extent of overlap, and spinal segmental differences have been well-studied in rat. Although transgenic mice are often used in pain studies, a systematic analysis of spino-Pb collateral projections is lacking in mouse. The goal of the present study was to determine the regions receiving collateral projections from lumbar spino-Pb neurons and to determine the proportions of common source neurons between the Pb and other structures involved in pain processing. Fluorogold and cholera toxin B were used for co-labeling experiments. One tracer was injected into the Pb and the other into hypothalamus, thalamus, periaqueductal gray, or caudal ventromedial medulla, unilaterally in mice. Labeled dorsal horn neurons and degree of co-labeling were quantified in sections taken from the lumbar spinal cord, focusing on lamina I. Anatomical evidence of collateral projections of lamina I spino-Pb neurons provides insights into

the divergence of affective pain information in mice, which may be important for the interpretation of data from mouse models of pain.

Disclosures: N.J. Stachowski: None. **L. Yao:** None. **M.R. Detloff:** None. **K.J. Dougherty:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.18/DD18

Topic: D.03. Somatosensation: Pain

Title: Time-course of the effect of continuous theta burst stimulation over primary somatosensory cortex on pain perception

Authors: *N. RAO[1], Y.-T. CHEN[3], S. LI[4], P. J. PARIKH[2]
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Abstract: Perception of pain involves information processing within a cortical network that includes primary somatosensory (S1), dorsolateral prefrontal, and primary motor (M1) cortices. Reducing the excitability of these areas using repetitive transcranial magnetic stimulation (rTMS) alleviates pain. Importantly, S1 is the final common gateway for ascending afferent pathway. However, it is not known how long the effect of rTMS over S1 lasts on pain perception. In this study, we investigated the time course of effect of continuous theta burst stimulation (cTBS; a form of rTMS) over S1 on pain perception threshold in healthy young adults. We assessed pain and sensory thresholds by delivering electrical pulse of 100 μs width over abductor pollicis brevis muscle. We also estimated tactile sensitivity using Semmes-Weinstein monofilaments over the thumb and index fingertips. The effects of cTBS over S1 on sensory threshold may result from the spread of current from S1 to M1 via reciprocal horizontal axonal connections. Therefore, we also investigated the effects of cTBS over S1 on corticospinal excitability (CSE) by delivering single pulse TMS over M1. Following initial sensory and CSE assessments, we delivered MRI-guided cTBS over S1. Subsequently, we performed sensory and CSE assessments immediately, 10 min, 20 min, 30 min, and 40 min post cTBS. In four healthy young adults, we found that cTBS over S1 increased electrical pain threshold and reduced tactile sensitivity with effects lasting for 40 min. However, cTBS over S1 failed to reduce electrical sensory threshold. Also, cTBS over S1 did not reduce CSE. Our preliminary findings suggest that a single application of cTBS over S1 can be used to alleviate pain for at least 40 min. These effects were not due to spread of stimulation current to M1 as we did not observe modulation of CSE following cTBS over S1. Future studies should investigate the effects of multiple sessions

of cTBS over S1 on pain threshold. Neuromodulation of S1 using cTBS may prove to be an effective intervention in alleviating pain in clinical populations.

Disclosures: N. Rao: None. **Y. Chen:** None. **S. Li:** None. **P.J. Parikh:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.19/EE1

Topic: D.03. Somatosensation: Pain

Support: MD Anderson Cancer Center internal funding
University of Texas System Rising STARs Award

Title: Microglial contributions to multidimensional behaviors in neuropathic pain

Authors: *M. J. LACAGNINA, P. M. GRACE
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Abstract: Background: Microglia, the resident immune cells of the central nervous system (CNS), constantly survey the tissue microenvironment and dynamically change their morphology and function in response to conditions of altered neural activity. Peripheral nerve injury results in profound activation of microglia in the spinal cord, and the resulting neuroinflammatory glial response contributes to the initiation and maintenance of neuropathic pain. However, it remains unclear if supraspinal microglial activation promotes the behavioral sequelae associated with chronic pain. Here we sought to determine if inhibiting microglial activation in the rodent brain would resolve pain-related behaviors across sensory and affective dimensions.
Methods: To model neuropathic pain, adult male Sprague Dawley rats received unilateral chronic constriction injury (CCI) of the sciatic nerve or sham control surgery. To selectively suppress the activation state of brain microglia, soluble CD200 chimera protein (CD200Fc), a CD200 receptor agonist, was intracerebroventricularly administered daily from days 22-28 following CCI, and multiple behavioral assays were performed during this timeframe. Sensory-discriminative behaviors were interrogated using two methods: mechanical allodynia was measured by von Frey filaments, and thermal hyperalgesia was measured by Hargreaves assay. Affective-motivational behaviors were also investigated by two approaches: novel juvenile social exploration was measured in a three-chamber interaction assay, and goal-directed motivation to acquire food rewards was measured using a progressive ratio operant task.
Results: In relation to sensory-discriminative processes, CD200Fc treatment attenuated mechanical allodynia induced by CCI, while having no effect on sham controls. However, CD200Fc resulted in no change in withdrawal threshold for thermal stimulation. For affective-motivational domains, CCI resulted in reduced social interaction that was reversed by CD200Fc

treatment. In contrast, acquisition of food pellets in the progressive ratio operant task was not significantly impaired following nerve injury or CD200Fc treatment during this post-injury time frame.
Conclusions: These data suggest that inhibition of microglial activity in the brain influences distinct sensory- and affect-related behavioral outcomes in neuropathic pain.

Disclosures: M.J. Lacagnina: None. **P.M. Grace:** None.

Poster

303. Somatosensation: Central Mechanisms of Neuropathic Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 303.20/EE2

Topic: D.03. Somatosensation: Pain

Support: NIH Grant GM107469-05
NIH Grant NS106469-01

Title: Generalization of sensory modalities in dorsal root ganglion neurons under neuropathic pain in awake mice

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Abstract: Peripheral sensory neurons are classified into modality-specific or polymodal on the basis of their responses to different sensory stimuli. So far, studies of the dorsal root ganglion (DRG) sensory neurons *in vivo* have been largely restricted to anesthesia preparation. Previous *in vivo* optical studies have suggested most of somatosensory neurons under anesthesia are modality-specific, while electrophysiological studies have suggested that most are polymodal. To reconcile the diverging views on the modalities of DRG sensory neurons and to better understand the function of DRG neurons in somatosensory perception and disorders, we developed a permanent DRG window allowing chronic visualization of the DRG at cellular and subcellular resolution over weeks in awake mice. Combined with genetically encoded fluorescent calcium indicator GCaMP mouse line, we first compared the activity profiles of sensory neurons in the fourth lumbar DRG in mice under awake versus under anesthesia when challenged with different sensory stimuli (punctate and dynamic mechanical, noxious heat and cold stimuli). In addition, we investigated how peripheral nerve injury affects the sensory modalities of DRG neurons. We found that the majority of stimuli-responsive DRG neurons are polymodal in normal awake mice. Though anesthesia silenced more than 75% of the responsive neurons, the majority of stimuli-responsive neurons are still polymodal. Peripheral nerve injury induced spontaneous excitation in 66.2% of DRG neurons compared with 10.2% of DRG neurons in sham-operated

mice, which was almost completely silenced by anesthesia. Modelity-specific population decreases progressively after peripheral nerve injury, from 13.6% (before injury) to 11.8% (2 days post injury) and 6.2% (4 days post injury), and polymodal population increases correspondingly. Together, our present study defines polymodality as a major feature of DRG sensory neurons in awake animals, and this feature is further potentiated after peripheral nerve injury.

Disclosures: L. Sun: None. **G. Yang:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.01/EE3

Topic: D.03. Somatosensation: Pain

Title: Adenylyl cyclase 1 (AC1) in anterior cinglutate cortex and spinal cord in contributed to the pain-related behavior of two fibromyalgia model rats

Authors: *Y. SAKURAI, R. TAMANO, S. YONEDA, T. TSUKAMOTO, M. OYAMA, Y. MASAGO, I. NANCHI, M. FUJITA, E. KASAI, T. OKUDA, T. ASAKI
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Abstract: Adenylyl cyclase 1 (AC1) is a calcium/calmodulin-stimulated enzyme that is predominantly expressed in the central nervous system. It couples NMDA receptor-induced cytosolic calcium elevation to cyclic adenosine monophosphate (cAMP) signaling pathways and has a crucial role in long-term potentiation (LTP) which may develop the pain in both the spinal cord and the anterior cingulate cortex (ACC). In addition, genetic deletion and pharmacological inhibition of AC1 reduced pain in inflammatory and neuropathic pain models. Fibromyalgia (FM) is a disorder characterized by widespread musculoskeletal pain complicated by psychiatric symptoms, such as anxiety and depression. Gabapentinoids, serotonin and noradrenaline reuptake inhibitors (SNRIs) and opioids are used for the pain relief, but these efficacies are not enough. Therefore, the more effective drugs are required for FM patients. In FM patients, the activation of ACC by pressure stimulation enhanced using by fMRI and NMDA receptor antagonist reduces the VAS scale. These studies indicate that AC1 might be involved in the pain of FM patients. In this study, we examined the contribution of AC1 to the pain of two experimental FM models: the acid-induced model and the reserpine model. The acid-induced model was generated by repeated acidic saline (pH 3.0) injection in gastrocnemius muscle and the reserpine model was generated by the repeated subcutaneous injection of reserpine (1 mg/kg), which depleted the monoamine. The both FM models showed the pressure hypersensitivity of bilateral gastrocnemius muscle, mechanical allodynia of bilateral hind paw, the anxiety-like behavior and depression-like behavior. In our pharmacological study, duloxetine

and morphine reduced both the pressure hypersensitivity and the mechanical allodynia, pregabalin reduced only the mechanical allodynia. To investigate the contribution of AC1 to the pain behaviors of FM models, we generated the AC1-deficient rats (AC1-KO). The AC1-KO rats demonstrated no pressure hypersensitivity, and the development of mechanical allodynia was partially improved both in the acid-induced and the reserpine model. In addition, intraperitoneal injection of NB001, an AC1 selective inhibitor, reduced the pressure hypersensitivity of the acid-induced model and the mechanical allodynia of both FM models. Both bilateral intra-ACC injection and intrathecal injection of NB001 and ST034307, another AC1 selective inhibitor, reduced the pressure hypersensitivity in acid-induced model. These results suggested that AC1 in ACC and spinal cord is therapeutic target of the pain in FM patients.

Disclosures: Y. Sakurai: None. **R. Tamano:** None. **S. Yoneda:** None. **T. Tsukamoto:** None. **M. Oyama:** None. **Y. Masago:** None. **I. Nanchi:** None. **M. Fujita:** None. **E. Kasai:** None. **T. Okuda:** None. **T. Asaki:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.02/EE4

Topic: D.03. Somatosensation: Pain

Support: NS019296
DE025137

Title: Compositional changes in gut microbiome of rats with stress-induced comorbid visceral pain

Authors: *J. ASGAR[1], J. YANG[1], R. TRAUB[1], J. RAVEL[2], W. GUO[1], S. ZOU[1], R. DUBNER[1], K. REN[1], F. WEI[1]
[1]Neural and Pain Sci., Univ. of Maryland Sch. of Dent., Baltimore, MD; [2]Inst. for Genome Sci., Baltimore, MD

Abstract: Recent clinical findings suggest that substantial overlap may exist between chronic pain conditions such as temporomandibular disorder (TMD), irritable bowel syndrome (IBS) and chronic lower back pain. Although the etiology is unclear, chronic overlapping pain conditions (COPCs) are highly prevalent in women and often impacted by psychological stress. Our previous study showed that in female rats with existing orofacial neuropathic pain, 3-day repeated forced swimming stress led to prolonged visceral hypersensitivity including referred hyperalgesia in the lower back area when compared with male animals. In rats with such comorbid pain, 5-HT3A receptor upregulation occurred in the lumbosacral spinal cord and dorsal root ganglia. Intrathecal injection of 5-HT3R antagonist could transiently attenuate stress-

induced lower back pain, suggesting 5-HT3R-mediated sensitization of primary afferents from the gut. However, the underlying gut mechanisms remain poorly understood. Based on recent literature, psychological stress can lead to gut microbial dysregulation in animal models; and gut microbial dysbiosis is a common finding among IBS patients. In the present study, we further examined microbiota composition in the gut of rats with orofacial pain before and after stress. We found that stress-induced depression-like behavior was positively correlated with the intensity of referred hyperalgesia. We also revealed extensive compositional changes in fecal microbiota of female rats with orofacial pain after stress by using 16S rRNA-based analysis. Compared with nerve injury or stress alone, rats with comorbid pain showed an increase in relative abundance of bacterial species from phylum Firmicutes, including families *Clostridiaceae*, *Ruminococcaceae*, *Eubacteriaceae*, and *Erysipelotrichaceae*, and a reduction in species from phyla Bacteroidetes, Actinobacteria, and Verrucomicrobia. These data are consistent with some clinical reports for IBS patients. Interestingly, we found an increase in relative abundance of genus *Alistipes* from phylum Bacteroidetes, which was reported in clinic to correlate with higher frequency of abdominal pain. Thus, this study for the first time explores dynamic changes in gut microbiota composition in female rats with comorbid visceral pain. Our results suggest that female rats with comorbid pain share multiple features of gut dysbiosis with IBS patients. Understanding gut mechanisms of stress-induced comorbid pain will promote novel therapeutic strategies for managing COPCs including IBS.

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Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.03/EE5

Topic: D.03. Somatosensation: Pain

Support: P20GM103643

Title: Exercise effects on osteoarthritis joint pain: Impact of sex and site in a rat model of osteoarthritis

Authors: *T. E. KING[1], S. SANNAJUST[2]
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Abstract: Osteoarthritis is a highly prevalent chronic joint disease with incidence predicted to rise due to the aging population and increased obesity. Exercise is commonly recommended for osteoarthritis patients. We examined whether exercise is equally effective in alleviating evoked and persistent ongoing pain in males and females and in load bearing compared to non-load

bearing joints. Adult male or female Sprague-Dawley rats received joint injection of monosodium iodoacetate (MIA) or saline into the knee joint or temporomandibular joint (TMJ). All knee joint MIA treated rats developed weight asymmetry with 7 days post-MIA and TMJ MIA treated rats developed tactile hypersensitivity within 7 days post-MIA. Futher, MIA into the knee-joint and the TMJ induced behavioral signs of ongoing pain, as measured by conditioned place preference to duloxetine, within 14 days of injection. Notably, female rats develop ongoing pain at a 5-fold lower concentration irrespective of whether MIA is injected into the knee joint or TMJ. All rats underwent treadmill exercise starting 10 days post-injection, a time-point that osteoarthritis pathology and pain are established. Treadmill exercise across 4-weeks effectively blocked pain behaviors in male and female rats with knee joint OA. In contrast, treadmill exercise did not produce full reversal of TMJ pain until after 9 weeks of exercise. These observations indicate that MIA-induced osteoarthritis induces evoked and ongoing pain in female rats at a 5-fold lower dose indicating that females are more susceptible to development of advanced osteoarthritis pain. This is consistent with clinical observations that osteoarthritis is more prevalent in women and that women report more severe pain. Treadmill exercise is equally effective in blocking osteoarthritis-induced knee joint pain in males and females. Finally, a longer period of exercise was necessary to block TMJ osteoarthritis suggesting a site dependent difference in the effects of exercise on joint pain. This research was supported by a COBRE award (P20GM103643) and UNECOM Peter Morgane fellowships to medical students.

Disclosures: T.E. King: None. **S. Sannajust:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.04/EE6

Topic: D.03. Somatosensation: Pain

Support: Supported by a MAPP Research Network grant (U01 DK082370) from NIDDK and NIH

Title: Ceftriaxone inhibits stress-induced hyperalgesia and alters cerebral micturition and nociceptive circuits in the rat: A multidisciplinary approach to the study of urologic chronic pelvic pain syndrome (MAPP) research network study

Authors: *D. P. HOLSCHNEIDER[1], Z. WANG[1], H. H. CHANG[2], R. ZHANG[2], J. MAO[2], Y. GUO[1], L. V. RODRIGUEZ[2]
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Abstract: BACKGROUND: Chronic emotional stress plays a role in the exacerbation and development of interstitial cystitis/bladder pain syndrome (IC/BPS), with neuroimaging in

patients suggesting a unique functional and structural reorganization of specific brain regions associated with the perception, processing and response to pain. Our prior findings in a rat model demonstrated that water avoidance stress (WAS) elicits a visceral hypersensitivity during bladder filling, as well as an increased engagement of portions of the supraspinal micturition circuit responsive to urgency, viscerosensory perception and its relay to motor regions coordinating imminent bladder contraction. Given the significant overlap of brain circuits involved in stress, anxiety, and micturition, and the documented role of glutamate in their regulation, the current study examined the effects of ceftriaxone (CEF)-dependent upregulation of the glutamate transport on the central amplification of stress-induced bladder hyperalgesia. METHODS: Adult, female Wistar-Kyoto rats were exposed to WAS (1 hr/d x 10 d) or sham paradigms following the daily administration of CEF or vehicle. On day 11, cystometrograms were obtained during titrated bladder dilation, with visceromotor responses (VMR) recorded simultaneously. Functional brain activation was assessed during passive bladder distension (20-cmH2O) following i.v. administration of [14C]-iodoantipyrine. Regional cerebral blood flow was quantified by autoradiography and analyzed in 3D reconstructed brains with statistical parametric mapping. RESULTS: WAS in rats, elicited visceral hypersensitivity during bladder filling as demonstrated by a decreased pressure threshold and visceromotor threshold triggering the voiding phase, as well as by increased VMR to bladder distension. Perfusion mapping revealed stress effects in brain regions noted to be responsive to passive bladder filling. Administration of CEF diminished visceral hypersensitivity and attenuated many of the stress-related functional brain changes within the supraspinal micturition circuit. A significant differential effect of CEF on the brains of stressed rats compared to controls was noted in posterior cingulate/anterior retrosplenial and primary somatosensory cortices. These regions contribute to nociceptive and to micturition circuits, show stress effects, and have been previously reported to demonstrated altered functionality in IC/BPS patients. CONCLUSION: Given the actions of CEF on the glutamate transporter, our results suggest the possibility of glutamatergic pharmacologic strategies in modulating stress-related bladder dysfunction.

Disclosures: D.P. Holschneider: None. **Z. Wang:** None. **H.H. Chang:** None. **R. Zhang:** None. **J. Mao:** None. **Y. Guo:** None. **L.V. Rodriguez:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.05/EE7

Topic: D.03. Somatosensation: Pain

Title: Evidence for role of KCC2 and NKCC1 in reserpine-induced nociceptive hypersensitivity

Authors: *E. J. RODRIGUEZ-PALMA, Y. E. DE LA LUZ-CUELLAR, V. GRANADOS-SOTO
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Abstract: Fibromyalgia is characterized by the presence of widespread musculoskeletal pain. This condition affects around 2.7% of population with a slight predominance in women. Despite the relevance of this disease, the current treatments are not effective in all patients. On the other hand, the gradient of chloride in neurons of the nervous system depends on NKCC1 and KCC2 co-transporters. Previous studies have reported that inflammatory and neuropathic pain enhances NKCC1 expression in dorsal root ganglion (DRG) neurons and decreases KCC2 expression in dorsal horn neurons. Changes in these co-transporters have been associated to inflammatory/neuropathic pain. However, the role of these co-transportes in functional pain has been less studied. The purpose of this study was to determine the participation of KCC2 and NKCC1 in the nociceptive hypersensitivity induced by reserpine in rats. Fibromyalgia-type nociception in female Wistar rats was induced by daily reserpine injections (1 mg/kg) during 3 days. Von Frey filaments were used to assess tactile allodynia. Randall-Selitto test was used to determine muscular hyperalgesia. Reserpine-injected rats were administered with bumetanide (10-100 μg, i.t.) and furosemide (10-300 μg, i.t.) (NKCC1 inhibitors), CLP 257 (50-300 μg, i.t., KCC2 activator) or vehicle (DMSO 100%). In addition, the effect of the highest dose of each drug was evaluated in naïve rats. Finally, rats were treated with a combination of bumetanide or furosemide and CLP-257. Reserpine induced widespread tactile allodynia and muscular hyperalgesia reaching the maximal effect at the 5th day post-administration. Intrathecal administration of bumetanide (10-100 μg) and furosemide (10-300 μg), but not vehicle, partially reversed tactile allodynia and muscular hyperalgesia. Furthermore, intrathecal administration of CLP-257 (50-300 μg) reversed tactile allodynia and muscular hyperalgesia in reserpine-treated animals. Drugs did not affect baseline withdrawal threshold and muscle pressure threshold in naïve rats. Co-administration of either bumetanide (50 μg) or furosemide (50 μg) and CLP-257 (50 μg) had an additive effect on tactile allodynia. Taken together, these results suggest that KCC2 and NKCC1 contribute to the hypersensitivity (tactile allodynia and muscular hyperalgesia) observed in a reserpine-induced model of fibromyalgia in rats.

Disclosures: E.J. Rodriguez-Palma: None. **Y.E. De La Luz-Cuellar:** None. **V. Granados-Soto:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.06/EE8

Topic: D.03. Somatosensation: Pain

Support: UQTR/CIUSS
NSERC
FRCQ
FRQS

Title: Inhibition of cerebral pain-related gamma oscillations by counter-stimulation and selective attention is abolished in patients with irritable bowel syndrome

Authors: *A. WAGENAAR-TISON[1,2], N. RUSTAMOV[1,2], E. DOYER[1,2], M. PICHÉ[1,2]
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Abstract: Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort and abnormal bowel function. Several studies indicate that chronic pain in IBS is associated with altered pain modulation mechanisms, including those producing hypoalgesia during counter-stimulation, which involves the application of two competing nociceptive stimuli. However, counter-stimulation hypoalgesia may be confounded with selective attention that also produces hypoalgesia. In this study, we examined hypoalgesia induced by counter-stimulation and by the manipulation of selective attention, in order to determine whether hypoalgesic mechanisms of either or both interventions are altered in patients with IBS.Participants took part to three counterbalanced experimental sessions. The first session involved a series of 80 painful electrical stimuli applied to the right ankle at an inter-stimulus interval of 5 seconds, with no intervention. The intensity of electrical stimulation was adjusted individually at 120 % of nociceptive flexion reflex (NFR) threshold and produced moderate pain. This control session allowed quantifying and controlling for temporal nonspecific effects. The second and third sessions included the same 80 stimuli distributed in four conditions, including baseline, non-painful cold stimulation on the left forearm, painful cold stimulation on the left forearm (counter-stimulation) and recovery. The only difference these two sessions was the focus of attention that was directed either to the electrical stimulation or the cold stimulation. Electroencephalography was measured to test the effects of counter-stimulation and selective attention on brain activity across groups.A robust difference was observed for the amplitude of evoked-potentials (peak-to-peak at Cz) between conditions across sessions and between groups ($p < 0.001$). Planned contrasts revealed that in comparison to the control session, brain activity was decreased by counter-stimulation in controls ($p < 0.001$) but not in patients with IBS ($p < 0.01$). Moreover, compared with the control session, selective attention decreased brain activity in controls ($p < 0.05$) while no effect was observed in patients with IBS ($p = 0.61$). Consistent with these results, pain-related gamma oscillations were decreased by counter-stimulation and selective attention in controls but not in patients with IBS. Together, these results indicate that Inhibition of pain-related brain activity by both counter-stimulation and selective attention are abolished in patients with IBS.

Disclosures: A. Wagenaar-Tison: None. **N. Rustamov:** None. **E. Doyer:** None. **M. Piché:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.07/EE9

Topic: D.03. Somatosensation: Pain

Title: The α_5-$GABA_A$ receptors contribute to nociception in a rat model of fibromyalgia

Authors: *Y. E. DE LA LUZ-CUELLAR[1], A. SALINAS-ABARCA[2], R. DELGADO-LEZAMA[2], V. GRANADOS-SOTO[2]
[1]Ctr. de Investigación Y de Estudios Avanzados, Ciudad de Mexico, Mexico; [2]Ctr. de Investigación y de Estudios Avanzados, Ciudad de México, Mexico

Abstract: Fibromyalgia is a chronic widespread musculoskeletal pain syndrome for which no alternative cause has been identified. Activation of $GABA_A$ receptors in primary afferent fibers induces a depolarization known as primary afferent depolarization. Evidence suggests that this inhibition is reduced or reversed in chronic pain states. There is evidence that extrasynaptic α_5 subunit-containing $GABA_A$ (α_5-$GABA_A$) receptors modulate excitability of sensory neurons. α_5-$GABA_A$ receptors are expressed in the dorsal root ganglion (DRG) and spinal cord in rodents, and play a role in neuropathic and inflammatory pain models. However, the role of α_5-$GABA_A$ receptors in functional pain has not been studied. The aim of this study was to investigate the role of spinal α_5-$GABA_A$ receptors in a reserpine-induced model of fibromyalgia in rats. Fibromyalgia-type nociception was induced by a reserpine injection (1 mg/kg) for three consecutive days. Tactile allodynia and muscular hyperalgesia were assessed with Von Frey filaments and the Randall-Selitto test, respectively. Reserpine-treated rats were intrathecally injected with the selective α_5-$GABA_A$ receptor inverse agonists L-655,708 (0.15-15 nmol) and TB21007 (1.5-150 nmol) or vehicle (DMSO 30%). To corroborate the participation of α_5-$GABA_A$ receptors, rats were treated with a siRNA against α_5-$GABA_A$ receptors during three days. The α_5-$GABA_A$ receptors protein expression in DRG and spinal cord was determined by western blot. In addition, activation of microglia and astrocytes at the spinal cord was assessed by immunohistochemistry.
Reserpine produced tactile allodynia and muscle hyperalgesia in both hind paws 7 days after its last injection in male and female rats. Intrathecal injection of L-655,708 and TB21007, but not vehicle, partially reversed reserpine-induced tactile allodynia and muscle hyperalgesia in a dose-dependent manner in female rats. The effects of these drugs were lower in male rats. Intrathecal injection of L-838,417 reversed the anti-allodynic effect of L-655,708. Furthermore, i.t. siRNA against α_5-$GABA_A$ receptors attenuated allodynia in reserpine-treated rats and induced tactile allodynia in naïve rats. Reserpine injection
increased the expression of α_5-$GABA_A$ receptor at the DRG and spinal cord. Moreover, reserpine enhanced OX-42 and GFAP immunoreactivity at the spinal cord.

Results suggest that spinal α_5-$GABA_A$ receptors contribute in a sex-dependent manner to the nociceptive hypersensitivity induced by reserpine in rats.

Disclosures: Y.E. De La Luz-Cuellar: None. **A. Salinas-Abarca:** None. **R. Delgado-Lezama:** None. **V. Granados-Soto:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.08/EE10

Topic: D.03. Somatosensation: Pain

Title: Sex differences in visceral hypersensitivity in the Dextran Sodium Sulfate model of colitis in mice

Authors: *S. MARTINEZ GONZALEZ[1], C. PICHARDO[2], Y. CARRASQUILLO[3]
[1]NIH, Gaithersburg, MD; [3]Natl. Ctr. for Complementary and Alternative Med., [2]NIH, Bethesda, MD

Abstract: Visceral pain is the main symptom of multiple abdominal conditions and it represents a frequent reason for patients to seek medical attention, with women disproportionately affected. Despite the female prevalence of visceral pain, pre-clinical studies, especially in rodents, are male dominated and only a few studies have looked at sex differences, particularly in pathological states. For this reason, it is important to systematically evaluate the potential for sex differences in rodent models of visceral pain. The present study measured visceral hypersensitivity in male and female mice using intracolonic capsaicin and the dextran-sodium sulfate (DSS) model of colitis. Our results demonstrate robust sex differences in capsaicin-induced visceral responses both at baseline and following DSS treatment, with female mice exhibiting significantly increased visceral nociceptive responses compared to males. Preliminary results further suggest that visceral hypersensitivity in females is indistinguishable across the different stages of the estrous cycle . Ongoing pathological studies of bowel tissues in DSS-treated male and female mice aim at determining whether differences in DSS-induced colonic pathology underlies the observed sex differences in visceral hypersensitivity. Given the established role of the central amygdala (CeA) in the modulation of persistent pathological pain, ongoing experiments also aim at investigating the contribution of specific CeA cell-types in the modulation of visceral hypersensitivity in the DSS model of colitis.

Disclosures: S. Martinez Gonzalez: A. Employment/Salary (full or part-time):; NCCIH NIH IRTA Post-doctoral fellow. **C. Pichardo:** A. Employment/Salary (full or part-time):; NIH Research Fellow. **Y. Carrasquillo:** A. Employment/Salary (full or part-time):; Principal Investigator NCCIH: PAIN Branch, NIH, Bethesda, MD.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.09/EE11

Topic: D.03. Somatosensation: Pain

Support: SLU Center for Neuroscience SCFN-SGP-01

Title: Somatosensory behavioral alterations in a rat low back pain model

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Abstract: Low back pain (LBP) is a leading cause for global disability. Although a substantial burden, relatively little attention is given to understand its underlying mechanisms. One preclinical model allows examination of LBP mechanisms after two nerve growth factor (NGF) injections into low back muscles of rats. NGF is a neurotrophin involved in pain transduction, critical to many pain states, and implicated in LBP. NGF induces persistent ipsilateral low back mechanical hyperalgesia (LBP) through day (D)14 in rats. The NGF-induced LBP model also had spinal cord changes consistent with central sensitization. Further work is required to reveal the neurobiological events underlying NGF-induced LBP and the somatosensory alterations that manifest from these changes. In LBP patients, somatosensory alterations occur at the low back and distant sites. These are hypothesized to result from sensitization in the central and peripheral nervous systems that manifest as enhanced responses to noxious (hyperalgesia) and non-noxious (allodynia) stimuli. The most consistent finding in LBP patients is a decreased threshold to a deep low back mechanical stimulus (mechanical hyperalgesia) with low back and distant hypersensitivity to cutaneous mechanical and thermal stimuli. Here, we examined the somatosensory alterations that occur during NGF-induced LBP. In addition to low back mechanical hyperalgesia, we examined hypersensitivity to cutaneous mechanical stimulation of the low back and hindpaw (distant) regions. Two injections of NGF (0.8μM/50μL; 5 days apart) or vehicle (50μL of phosphate-buffered saline) were given into the same site (left paraspinal muscles, L5 vertebral level) in male Sprague Dawley rats (215-225 g). For behavioral testing, rats were randomly selected into groups and acclimated to the testing environment and examiners prior to testing. Examiners were blinded to all groups. Behaviors were assessed at baseline (pre-1st injection) and post-1st injection on D2, D5 (pre-2nd injection), and post-2nd injection at D5 + 4 hours, D7, D10, and D14. Mechanical hypersensitivity was assessed superficially on the low back and hindpaw skin using von Frey filaments then assessed deep on the low back (algometer) as reported. NGF rats (n=4/group) had ipsilateral low back mechanical

hyperalgesia from D5 + 4 hours to D14 with increased responses to a low back cutaneous mechanical stimulus from D7 to D14 ($P<0.05$). There were no changes in hindpaw withdrawal threshold. Our results suggest the NGF model has additional somatosensory alterations that mimic clinical features of LBP. These findings support further examination of the NGF model to expand our understanding of LBP.

Disclosures: N.R. Reed: None. **M.K. Syrett:** None. **A. Frolov:** None. **W.R. Reed:** None. **J. Little:** None.

Poster

304. Visceral and Musculoskeletal Pain

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 304.10/EE12

Topic: D.03. Somatosensation: Pain

Support: F32DK104544 (KR)
R01DK083609 (PT)

Title: The role of transient receptor potential vanilloid 1 channel in chronic pelvic pain

Authors: *K. M. ROMAN[1], C. HALL[2], A. J. SCHAEFFER[2], P. THUMBIKAT[2]
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Abstract: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a multifaced disorder that encompasses several symptoms. Effective therapeutic treatments are scarce, due to a poorly defined etiology and pathogenesis of CP/CPPS. Although several studies suggest that the transient receptor potential vanilloid 1 (TRPV1) channel is involved in various pathways of chronic pain, the capsaicin receptor TRPV1 has not been implicated in chronic pelvic pain associated with CP/CPPS. Thus, we sought to determine the role of TRPV1 in CP/CPPS via a rodent model called experimental autoimmune prostatitis (EAP). C57BL/6J (B6; n=3) and TRPV1 knockout (TRPV1 KO; n=3) mice (5-7 weeks old) were administered a rat prostate antigen to induce EAP and then assessed for pelvic tactile allodynia at days 0 (baseline), 7, 14 and 20. Here, we showed that B6 mice with EAP developed markedly enhanced pelvic tactile allodynia at days 7, 14, and 20, compared to naive controls. Surprisingly, our data revealed that TRPV1 KO mice with EAP do not develop pelvic tactile allodynia between days 7 to 20 and demonstrated a similar tactile response observed in controls. The prostate, lumbosacral (L6-S4) regions of the dorsal root ganglia (DRG) and spinal cord were excised from mice at day 20. The prostates were processed and examined via blinded observers. Although we observed a slightly higher number of mast cells in the prostate of TRPV1 KO mice, the number of activated mast cells remained the same between TRPV1 mice with EAP and controls. However, B6 mice with EAP showed a significant increase in the number of activated mast cells, compared to controls.

Moreover, the DRG and spinal cord excised from TRPV1 KO mice with EAP showed no change in levels of ERK1/2 phosphorylation (p-ERK1/2). In contrast, we observed a significant increase of p-ERK1/2 in the DRG and spinal cord of B6 mice with EAP at day 20, compared to controls. In a separate experiment, B6 mice with or without EAP received intraurethral administration (10µl) of either a TRPV1 antagonist peptide (L-R_4W_2; 1µM) or saline after day 10 (every two days) and we investigated the development of pelvic tactile allodynia at days 20, 25, 30, and 35. Our data suggests that B6 mice with EAP that received saline developed pelvic tactile allodynia; yet, B6 mice with EAP that received the peptide treatment show blunted pelvic tactile allodynia. Together, our study demonstrates that TRPV1 is important to 1) establish pelvic tactile allodynia in our model, 2) required to induce mast cell activation in the prostate, 3) crucial for p-ERK1/2 expression in DRG and spinal cord regions relevant to the prostate, and 4) targeted delivery of a TRPV1 antagonist can alleviate chronic pelvic pain.

Disclosures: K.M. Roman: None. **C. Hall:** None. **A.J. Schaeffer:** None. **P. Thumbikat:** None.

Poster

304. Visceral and Musculoskeletal Pain

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Topic: D.03. Somatosensation: Pain

Support: P20GMI03643

Title: Separation of roles for nociceptor populations in cancer-induced ongoing and hindpaw movement evoked pain

Authors: *J. J. HAVELIN, T. E. KING
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Abstract: Patients that suffer from cancer-induced bone pain report two distinct pain. One is a constant ongoing pain that increases in severity over time as the disease worsens, and the second is pain that breaks through medication that is controlling the ongoing pain. Patients are treated with mu opioid receptor (MOR) agonists to manage background ongoing pain, whereas breakthrough pain episodes are often treated with rapid onset MOR agonists such as transmucosal fentanyl. The inability of MOR agonists to successfully treat breakthrough pain indicates that perhaps a unique subset of nociceptors are involved in transducing this pain, and they do not respond to MOR agonists. Utilizing the motivational aspects of pain relief and aversion to the induction of pain in a classical conditioned place preference/aversion (CPP and CPA) paradigm, we are following up on our initial observations that ongoing and breakthrough pain are mechanistically distinct. Female SAS fischer rats had MATB3 cells implanted into their tibia that has been previously shown to induce both ongoing and breakthrough pain. In our

experimental procedure relief of ongoing pain results in CPP whereas the induction of breakthrough pain causes CPA. Our preliminary data indicates the MOR agonist DAMGO treats ongoing pain and the delta opioid receptor (DOR) agonist Deltorphin II blocks movement induced breakthrough pain. We are further investigating the effects of these MOR and DOR agonists in a mouse model of cancer-induced bone pain caused by surgical implantation of the LLC cell line into the femur of C57BL6 mice. CPP/CPA experiments in the mouse are performed 10-12 days post-surgery which coincides with noticeable radiographic bone remodeling and increases in spontaneous and evoked behaviors of pain measured by limb use, flinching and tactile hypersensitivity measured with calibrated von frey filaments. Currently preliminary data in the mouse mimics that in the rat where DAMGO induces CPP to pain relief and Deltorphin II blocks hindpaw movement induced CPA. Using these two rodent models of cancer-induced bone pain, our preliminary data indicate that MOR agonists block ongoing pain but not breakthrough pain, consistent with clinical observations. In contrast, DOR agonists may block breakthrough pain but not ongoing pain. These results may highlight a distinct role for subsets of nociceptive neurons in the periphery involved in differentially transducing these two pain phenomena, and that this pharmacological approach is consistent between species. This work will also allow for further investigation into unique molecular targets for pain relief.

Disclosures: J.J. Havelin: None. **T.E. King:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 305.01/EE14

Topic: D.05. Olfaction and Taste

Support: JSPS
Marie Curie

Title: Functional analysis of top-down projections to the zebrafish olfactory bulb

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Abstract: Top-down inputs to primary sensory areas modulate sensory processing and play important roles in perception. The olfactory bulb (OB), the first processing station of the mammalian olfactory system receives dense top-down inputs from cortical and sub-cortical regions that modulate neuronal activity during behavioral tasks and different brain states. However, the functional relevance of these inputs for olfactory processing is unclear. To address

this question, we have developed viral and imaging techniques in adult zebrafish to map and functionally characterize top-down inputs to OB. In order to map top-down inputs to OB, we injected herpes simplex viruses (HSV) into the OB to retrogradely label populations of projection neurons from other brain areas. We found multiple areas in telencephalon that project to OB, including (1) the posterior zone of the dorsal telencephalic area (Dp), a homolog of olfactory cortex, (2) the ventral *area* of the subpallium (*Vv*), a homolog of septum and (3) the medial zone of the dorsal telencephalon (Dm-OB). Furthermore, we found that Dp and Vv areas receive direct input from mitral cells in OB, but Dm-OB area does not. To map the inputs to Dm-OB, we developed procedures for retrograde transsynaptic tracing using glycoprotein-deleted rabies virus in zebrafish. This approach revealed that Dm-OB receives prominent projections from Dp as well as other telencephalic areas that are thought to be related to memory and emotion. In order to functionally characterize top-down inputs to OB, we applied odour stimuli and simultaneously performed two-photon calcium imaging of neuronal populations in telencephalon. We found that while neurons in Dp and Vv responded to odours, neurons in Dm-OB did not. Ongoing experiments combine simultaneous in vivo imaging and behavioral approaches to examine the function of Dm-OB during spontaneous behaviors and in an olfactory learning paradigm.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

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Topic: D.05. Olfaction and Taste

Support: N.G. is an Intermediate Fellow of Wellcome-DBT India Alliance, IA/I/15/2/502091
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UGC Grant F.No. 6-11/2016 (IC)

Title: A computational model of across-individual stereotypy in the responses of mushroom body output neurons

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Abstract: In the insect olfactory system, sensory neurons on peripheral organs detect odors and carry this information to the antennal lobe. Odors generate stereotypic responses in projections neurons (PNs) of the antennal lobe across individuals. PNs then transmit olfactory information to Kenyon cells (KCs) in the mushroom body. Anatomical studies have shown that PN-KC connections are random and vary across individuals. Expectedly, KC responses are not

stereotyped. But mushroom body output neurons (MBONs), which receive input from KCs, showed partially stereotyped odor responses. We used a computational model to explore the mechanisms underlying stereotypy in MBONs. We modeled the olfactory network using integrate-and-fire neurons, whose parameters were constrained by experimental data. Fly olfactory system has approximately 200 PNs and 2000 KCs; we scaled down the network to 100 PNs and 1000 KCs to reduce the computing time while preserving the ratio of the two types of neurons. PN responses were generated by first setting the spiking rates of neurons, separately for each odor. The PN spikes were then distributed into five bins of 200ms each. For PN-KC synapses, we used a binary connection matrix such that each KC received inputs from approximately seven PNs, mimicking the experimental observed connection probabilities. Synaptic weights were assigned such that physiological levels of spiking activity were maintained in all neuron layers. While PN responses were kept similar for individuals (with some noise), PN-KC connectivity matrix was randomly generated. We analyzed the responses of a single MBON, connected to half the KCs, to different odors across individuals. KC responses produced by the model were sparse in both numbers (10% probability of spiking) and spiking rates (less than 4 spikes/s), while the MBON responded with dense spiking activity (about 60 spikes/s) for all odors. We quantified stereotypy as the accuracy in correctly recognizing the same odor across individuals. We found that the MBON response stereotypy was high (about 70%). Further, we found that the stereotypy depends on the firing rate of the PNs, the number of PNs connected to KCs, the number of KCs responding to the odors, the number of KCs connected to the MBON, noise level, and temporal patterns in the PN responses. A simplified theoretical model using binary neurons corroborated the findings from the simulations. Our results provide insights into how stereotypy can arise despite randomness in a neural network.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Program #/Poster #: 305.03/DP05/FF2

Topic: D.05. Olfaction and Taste

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Janelia Visiting Scientist Program (GSXEJ)

Title: Communication from learned to innate olfactory processing centers is required for memory retrieval in *Drosophila*

Authors: *G. JEFFERIS[1], M. DOLAN[2,1], G. BELLIART-GUERIN[3], A. BATES[1], P. HUOVIALA[1,4], F. LOVE[4], S. FRECHTER[1], Z. MITREVICA[4], R. ROBERTS[4], P. SCHLEGEL[4], Y. ASO[2], G. M. RUBIN[2], D. BOCK[2], M. COSTA[4], T. PREAT[3], P.-Y. PLACAIS[3]
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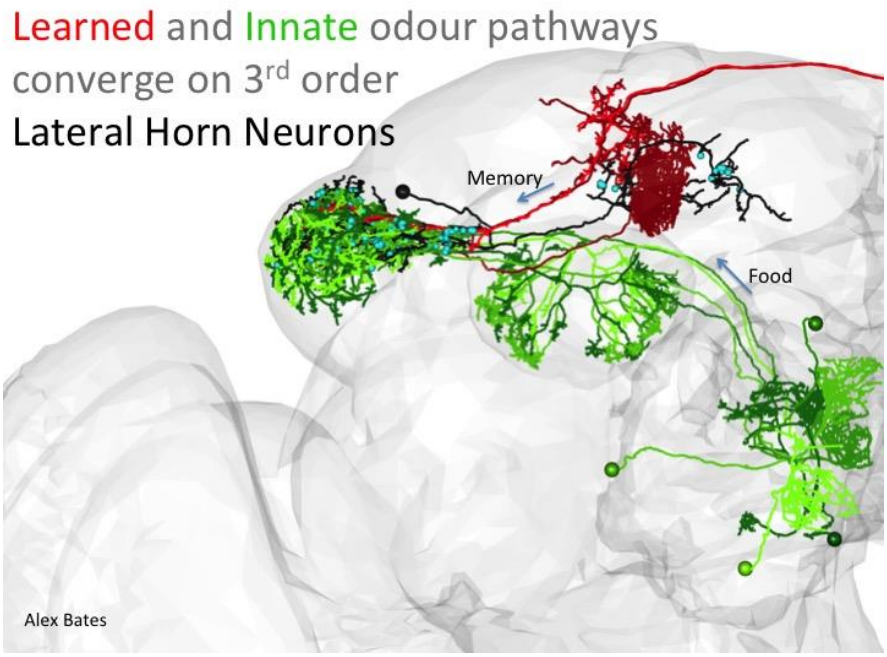
Abstract: Many sensory stimuli elicit behavioral responses in naive animals that can be modified or even reversed by learning. In the olfactory system of flies and mice, it is proposed that divergent pathways, targeting distinct higher centres, are specialised for learned and innate behaviour. However little is known about how they interact.
In *Drosophila*, the mushroom body (MB) is critical for associative learned behaviour while indirect evidence suggests that neurons of the Lateral Horn (LHNs) mediate naive odour responses. We now identify LHNs that receive input from an MB output neuron required for recall of aversive olfactory memories. Like the MB output neuron, PD2 LHNs are require for learned but not innate aversive odour behaviour and depress their response to the conditioned odour after training.
EM connectomics reveals that PD2 LHNs also receive direct input from second order projection neurons encoding food odours. PD2 neurons are essential for naive attraction to some of these odours. A single neuronal population therefore mediates both innate attraction and aversive memory retrieval.
Our results show that aversive memory recall depends on a conditioned reduction in drive to innately appetitive olfactory neurons. Furthermore they delineate a complete circuit, from sensory periphery to central integrator neurons, by which learned and unlearned information can interact.
We will discuss a number of apparent advantages of this circuit architecture.
Finally we will contrast this circuit with new and ongoing work to uncover the circuit basis of innate aversive olfactory behaviour. This demonstrates that a circuit with a peripheral labeled line organisation diverges massively at the level of third order lateral horn neurons. It also suggests possible opponent interactions between appetitive and aversive circuitry at the level of the lateral horn.



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Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

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Topic: D.05. Olfaction and Taste

Support: MCO training grant GM007598
NIH grant DC013329
NIH grant DC014453

Title: Integrating information from both nostrils - random or not?

Authors: *J. F. GRIMAUD, V. N. MURTHY
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Abstract: In most sensory systems, neuronal connections from the periphery to the brain occur in a spatially organized manner, giving rise to topographic maps. By contrast, in the olfactory system, the projections from peripheral regions to the olfactory cortex, as well as the local

cortical connections, appear to be spatially distributed and disordered, which has led to the postulate that these connections are random. Inter-hemispheric cortical projections that arise from the anterior olfactory nucleus and the anterior piriform cortex will, in principle, add even further disorder when integrating information from both nostrils. To gain insight into bilateral integration of information in cortical neurons, we developed a method for unilateral odor delivery in awake mice. We used this method to investigate responses of individual olfactory cortical neurons to 15 distinct monomolecular odors presented to one nostril or the other. We found that the odor tuning (responses to the 15 odors) of many neurons in three cortical regions (anterior olfactory nucleus, anterior and poster piriform cortex) were different when stimuli were presented to each of the two nostrils. However, a significant fraction of neurons in the anterior olfactory nucleus had highly correlated tuning curves to odors presented on the two sides. Our data support the general notion of disordered connectivity in the olfactory cortex, but also point to significant degree of non-random connectivity that could arise through experience-dependent synaptic plasticity. These and ongoing experiments will shed light on how the brain uses bilateral sensory information to make sense of the chemical world.

Disclosures: J.F. Grimaud: None. **V.N. Murthy:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

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Program #/Poster #: 305.05/FF4

Topic: D.05. Olfaction and Taste

Support: NIH National Institute on Deafness and Other Communication Disorders (NIDCD) 4R00DC014516-03

Title: Learned modulation of innate odor-driven behavior requires the orbitofrontal cortex

Authors: *K. MIYAMOTO, A. LIMARY, J. VICTORIANO, M. KATHROTIA, C. M. ROOT
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Abstract: Animals use a combination of innate and learned behaviors to survive. In the natural environment, animals are faced with choices that involve balancing risk and reward. Although behaviors such as feeding and mating are essential to species survival, they subject an animal to the risk of predation or other danger. Thus, innate drives must exist in a balance of risk and reward, which may be modulated by experience and internal need. We seek to elucidate the circuit mechanisms in the mouse brain involved in the executive override of innate odor-driven behaviors.
Our previous work has shown that the cortical amygdala, a third-order olfactory brain structure, mediates innate odor-driven responses. It is thought that prefrontal brain areas are control

complex behavioral planning and decision-making. Specifically, the orbitofrontal cortex (OFC) receives olfactory input from piriform cortex and has outputs to the innate pathways and reward circuitry, which make it a candidate for higher-order control of innate behaviors. We have tested the role of the OFC in modulation of behavioral response to fox odor.
We began by creating a behavioral paradigm that resembles a risk-reward tradeoff foraging task. Briefly, a water-restricted mouse is introduced into a chamber with two water ports that have either the aversive fox odor (TMT) or the attractive rose odor (2-phenylethanol). Innately, mice prefer the rose port to the fox port. However, decreasing the probability of water at the rose port causes mice to learn to prefer the fox port. This behavior persists even if water is unavailable from either port, reflecting a learned override of the innate response to the odors. We optogenetically silenced the OFC, and found that animals revert back to their preference for the rose odor port, whereas control animals exhibited the learned preference for the fox port. These findings reveal that the OFC is indeed required for the learned override of innate behavior. We next plan to record neural activity in the OFC as mice perform the learning task to reveal changes that occur in OFC to accommodate learning, and to map out the relevant downstream targets of OFC.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

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Program #/Poster #: 305.06/FF5

Topic: D.05. Olfaction and Taste

Support: DFG-SFB870

Title: Value-coding of dopamine neurons in olfactory processing

Authors: *K. P. SIJU[1], V. STIH[2], R. PORTUGUES[2], I. C. GRUNWALD KADOW[1]
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Abstract: Value-based decision-making is critical for animals to survive in their environment. Continuously changing environmental cues, internal state, and prior experience greatly influence and modulate decision-making. The neural basis of this behavior is not fully understood. Several recent studies in Drosophila showed that dopaminergic neurons (DANs) in the mushroom body (MB), a higher brain center, are important in assigning value to sensory cues and modulating instantaneous decision-making and fast adaptive behaviors. In the fly brain, DANs are found in two main clusters, PAM and PPL that are thought to encode attractive and aversive contexts,

respectively. Distinct types of DANs innervate the MB in a compartmentalized manner, where they synaptically interact with axons of the MB Kenyon cells and the dendrites of the MB output neurons (MBONs). In this study, we investigated how the population of DANs, rather than single neurons, innervating the MB represent value and how internal state and prior experience influence this representation. Using a systematic volumetric in vivo 2-Photon imaging technique, we characterized the representation of a number of odors in the context of feeding state across the entire DAN population. We developed an automated, unbiased segmentation and registration method to extract the response from each MB/DAN compartment. Our results reveal that in naïve flies, DANs show dynamic activity pattern and odors are represented differentially along the DAN compartments depending on the odor identity and valence. Interestingly, starvation changes this representation to a similar pattern irrespective of the odor valance. Furthermore, we show that, similar to the MBON response profile (Hige et al.,), DANs also show highly variable response profiles across different individuals. This individuality in response profile starts to disappear according to the feeding-state of the animals, and the resulting response profile becomes more similar across hungry animals. This suggests that similar physiological states are reflected in DAN odor representations indicating that state shapes individual experience. Building on these results and developed methods, we aim to elucidate how odor valence and internal state modulate DAN representations to guide perception of different individuals, and ultimately their decision-making and associated behavior.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Topic: D.05. Olfaction and Taste

Support: NIH Grant R01DC015139

Title: Inhibitory circuits that gate associative synaptic plasticity in olfactory cortex

Authors: *M. CANTO-BUSTOS, E. KAMBOUROGLOS, A. M. OSWALD
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Abstract: The piriform cortex plays a role in the combinatorial representation of odorant features from the olfactory bulb (OB) as well as associating odors with information coded from other cortical areas. OB afferents as well as intracortical inputs form synapses on the apical dendrites of pyramidal cells of piriform cortex. Long-term potentiation of the intracortical synapse is achieved by co-stimulation of the lateral olfactory tract (LOT) coming from the OB

and the intracortical fiber tracts in Layer 1B. It has been shown that this associative LTP is highly dependent of intrinsic inhibition. However, the inhibitory circuits that gate LTP has not been elucidated. In this study, we explored the inhibitory circuits that modulate associative LTP induction in anterior piriform cortex (APC) by using a combination of optogenetic tools and electrophysiological recordings. Three inhibitory interneuron classes were evaluated; somatostatin (SST) cells that inhibit pyramidal cell (PC) dendrites, parvalbumin cells (PV) that inhibit PC somas and vasoactive intestinal peptide cells (VIP) that are postulated to inhibit both SST and PV cells. Our results reveal three main findings. First, inactivation of SST cells but not PV cells promotes associative LTP induction. Second, VIP cells inhibit both SST and PV cells in olfactory cortex. Third, activation of VIP cells promotes associative LTP. These findings support a model in which VIP cells inhibit SST cells and thus, disinhibit PC dendrites to promote LTP induction. Interestingly, our preliminary results suggest an additional functional difference between L2 and L3 PCs. Associative LTP is gated by the VIP-SST disinhibitory circuit in L2 but not in L3 PCs. Our work proposes a disinhibitory circuit gates associative LTP in APC and also suggests different circuits are involved the modulation of synaptic plasticity in distinct layers of piriform cortex.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Topic: D.05. Olfaction and Taste

Support: NIH Grant U01NS094191
NIH Grant RO11DC016222

Title: Hierarchical and invariant representations of odor space in cortex

Authors: *S. PASHKOVSKI[1], G. IURILLI[2], D. CHICARRO[2], K. DRUMMEY[2], S. PANZERI[3], S. R. DATTTA[2]
[2]Neurobio., [1]Harvard Med. Sch., Boston, MA; [3]Ctr. for Neurosci. and Cognitive Systems, Italian Inst. of Technol., Rovereto, Italy

Abstract: In olfaction, molecular structure determines perception. Chemically-related odors evoke similar percepts within and across individuals, suggesting that the cortex harbors a conserved mapping from chemical to neural space. The specific organization of these representations will define olfactory acuity by setting the balance between odor discrimination and generalization. However, neural representations for odor chemical relationships have not yet been identified in cortex, and thus an understanding of how the olfactory system transforms

chemistry into perception has remained elusive. We hypothesized that chemical representations in cortex could be revealed and explored through a systematic interrogation of chemical space at multiple distance scales; we therefore took a chemoinformatics approach to systematically vary chemical odor distances, and then monitored odor responses in mouse piriform cortex (PCx) during wakefulness, the state most relevant to perception. Given the ability of animals to categorize odors at distinct scales without explicit training, we further hypothesized that the olfactory cortex would contain multiple parallel representations for chemical odor space. Volumetric 2-photon imaging was therefore used to assess neural activity in both the input-dominated PCx layer 2 (L2), as well as the more associational layer 3 (L3). This approach revealed that odor-evoked neural responses are systematically related to distances in odor chemical space in a manner that is preserved across individuals. These relationships are sculpted by the olfactory system to emphasize close similarities amongst a subset of odorants. PCx L2 and L3 differentially balance discrimination and generalization, suggesting they represent two fundamental levels of acuity for the olfactory system. We validated the observed chemical-neural relationships by predicting cortical responses based upon chemistry, and to predict perceptual responses based upon cortical activity. These data provide the first direct evidence for a systematic and invariant remapping of odor chemistry in cortex, demonstrate that the cortex organizes information about odor relationships in parallel at multiple scales, and identify a key neural substrate through which chemically-related odors can be linked to similar perceptual qualities both within and across individuals. <!--EndFragment-->

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Topic: D.05. Olfaction and Taste

Support: DC-015525

Title: Robust cortical sensory coding across distinct activity regimes

Authors: *K. A. BOLDING[1], K. M. FRANKS[2]
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Abstract: How does the olfactory system cope with internal dynamics that may degrade or otherwise alter odor representations? As odor information is transformed through successive feedforward projections from periphery to olfactory bulb (OB) and piriform cortex (PCx) it is subject to variable internal network dynamics and modulation. For example, cortical sensory

responses are thought to be “gated” during slow-wave sleep and enhanced during arousal or attentional states. However, PCx circuits are also equipped to recover reliable stimulus-specific odor representations from noisy or degraded input by signaling through extensive recurrent connections. Thus, it remains unclear whether the net effect of olfactory processing is to modify or preserve odor representations when network state varies. Here, recording in awake and anesthetized mice, we find odor representations are more robust to state in PCx than in OB, their immediate upstream input. Odor representations in OB were substantially degraded under anesthesia, but PCx odor representations were intact and could be accurately decoded within and across states. A small subset of OB responses were robust to state. Robust OB responses were not larger, but had shorter latencies than state-dependent responses, suggesting PCx could use a temporal filter to identify reliable odor information. Cortical responses that were robust to state emerged rapidly and from deep cortical layers, where recurrent input is predominant. We used a viral chemogenetic strategy to block neurotransmitter release from PCx principal cells and recorded population activity across states in this circuit lacking recurrent connectivity. Odor decoding was preserved within states, but similar representations could no longer be recovered from one state to the other. These data thus suggest a major role for PCx recurrent circuitry in retrieving stimulus-specific activity patterns from degraded input and maintaining reliable odor identity coding.

Disclosures: K.A. Bolding: None. **K.M. Franks:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 305.10/FF9

Topic: D.05. Olfaction and Taste

Support: HFSP CDA00029/2013
EC Marie Curie DopaPredict
KU Leuven C14/17/109

Title: Modulation of neural response in olfactory cortex by novelty and familiarity

Authors: *S. HAESLER[1], C. AYDIN[1], M. BROUX[1], S. LIBBRECHT[2], J. NOUTEL[1], J. ESQUIVELZETA RABELL[1]
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Abstract: When humans or animals detect novel stimuli in their environment, they respond with distinct orienting and exploratory behaviors. Detection of stimulus novelty is extremely fast - behavioral novelty responses can be observed already less than 100ms after stimulus presentation. In order to accomplish such rapid detection and motor response, the brain needs to

perform a remarkably efficient computation involving a memory-based classification of incoming sensory stimuli. To investigate the algorithm behind this classification, we use a spontaneous olfactory novelty detection task, which allows us to investigate how sensory representations of novel but not familiar stimuli are transformed into motor responses. The task involves a stimulus-driven, bottom-up attentional process that is intimately linked to olfactory sensory processing. Hence, we systematically characterize neural responses in olfactory cortical areas, specifically in the anterior olfactory nucleus (AON) and piriform cortex, using multielectrode recordings in awake, behaving animals. We evaluate how novelty and familiarity modulates olfactory responses. In our preliminary analysis, we find that neurons in the AON are less odor-selective than in the PCx and that they are stronger modulated by novelty. These differences between AON and PCx are consistent with their different inputs. The AON mainly receives input from fast-responsive tufted cells in the olfactory bulb, whereas the PCx mainly receives slower input from mitral cells, integrating the activity state of sister tufted and mitral cells. Neural responses to novel stimuli rapidly habituate in both AON and PCx during the task. However, since in the PCx, a similar number of neurons was excited and inhibited by odorants, response habituation almost cancels out at the population level. In the AON on the contrary, we find almost exclusively odor-excited neurons, thus rapid response habituation is prominent at the population level. These findings are consistent with a functional segregation of the main olfactory pathway at the level of the olfactory bulb. Additional experiments are needed to further address this hypothesis.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 305.11/FF10

Topic: D.09. Multisensory Integration

Support: NSF
Kavli Institute, UCSD

Title: Principles of distributed circuits

Authors: *S. SRINIVASAN[1], K. POSTON[2], M. BROWN[3], C. F. STEVENS[4]
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Abstract: Distributed circuits are common to olfactory, hippocampal, and cerebellar circuits, and contain sub-circuit components that seem to interconnect randomly, i.e. without any

preference. They present a puzzle as they represent high dimensional information (e.g. faces or odors) with sparse and distributed neuronal ensembles and raise three questions. How is such ensemble activity produced, and how does it encode stimuli? Are circuit design principles conserved across species? and do distributed circuits that handle different functions like olfactory and cerebellar circuits have common organizational principles? To answer these questions, we first examined the olfactory circuit in mice and six mammalian species using stereology techniques and light microscopy. Elegant studies have shown that olfactory bulb input innervates the primary olfactory cortex without any spatial preference and such distributed input and activity is conserved across species. Our explorations yielded two insights. First, with a nearly parameter-free model of the mouse olfactory circuit, we found that the olfactory cortex robustly maintains odor information and discrimination ability present in the olfactory bulb. Second, using anatomical measurements, we show that olfactory circuits across mammalian species share a common organizational principle: the number olfactory neurons n scale with bulb glomeruli g as $n \sim g^{3/2}$. Lastly, to test if this organizational principle might be a common feature of distributed circuits, we examined cerebellar (mammals) and cerebellar-like (teleost fish tectum) circuits, and found that cerebellar granule and Purkinje cells scale similarly.

Disclosures: S. Srinivasan: None. **K. Poston:** None. **M. Brown:** None. **C.F. Stevens:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Program #/Poster #: 305.12/FF11

Topic: D.05. Olfaction and Taste

Support: SFB 1089

Title: Functional characterization of odor-driven modulation of olfactory perception by basal forebrain nuclei

Authors: *M. MÜLLER[1], I. SCHWARZ[2], I. PAVLOVA[2], M. MITTAG[1], M. K. SCHWARZ[2], M. FUHRMANN[1]
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Abstract: The olfactory bulb (OB) acts as a gate for olfactory information entering the mammalian brain and is innervated by centrifugal fibers originating in the horizontal limb of the diagonal band of Broca/magnocellular preoptic nucleus (HDB/MCPO), a basal forebrain area. Afferent projections from the HDB/MCPO connect to the granule cell layer as well as the glomerular layer, where they potentially influence olfactory processing within the olfactory bulb.

However, little is known about the top-down modulation provided by the HDB/MCPO. Therefore, we investigated the HDB/MCPO feedback circuit's modulatory influence on odor processing in the OB and on olfactory-driven behaviors.
Modified rabies virus (mRabV) mediated mono-transsynaptic retrograde-tracing revealed an extensive excitatory and inhibitory monosynaptic input from centrifugal fibers originating within the HDB/MCPO. Tetanus toxin (TnTx) light chain mediated silencing of the HDB/MCPO profoundly affected olfactory driven social/sexual behaviors, leaving intact general cognitive abilities.
We employed two-photon *in vivo* Ca^{2+}-imaging to monitor the activity of GCaMP6 expressing HDB axons in the OB in awake mice during odor stimulation. We identified odor-responding axons in the OB originating in the HDB. Furthermore, we found different classes of odor-tuned axons responding to one, both or none of the presented odors. Interestingly, axons with different response properties were spatially intermingled in the OB. Moreover, silencing the HDB by TnTx injections resulted in reduced glomerular odor-responses compared to sham-treated mice. We conclude that the centrifugal projections from the HDB/MCPO innervating the OB are activated specifically by odors and modulate the activity of targeted cells within the olfactory bulb.

Disclosures: I. Schwarz: None. **I. Pavlova:** None. **M. Mittag:** None. **M.K. Schwarz:** None. **M. Fuhrmann:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

Location: SDCC Halls B-H

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Program #/Poster #: 305.13/FF12

Topic: D.05. Olfaction and Taste

Support: NIH Grant R00 DC014516-05

Title: Distinct cortical amygdala circuits mediate approach and avoidance behaviors

Authors: *C. CHAN[1], J. H. LEE[1], M. H. BASSETT[1], A. J. FAULKS[1], C. M. ROOT[2]
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Abstract: Olfactory information is critical to survival for most animals, driving innate foraging and defensive behaviors. These behaviors are observed in animals without prior experience and are likely driven by neural circuits that are genetically determined and stereotyped. The cortical amygdala is a part of the olfactory neural circuit that mediates innate appetitive and aversive odor-driven behaviors (Root et al., 2014), but it remains unclear how this structure is organized to drive opposing behavioral responses. Here we anatomically and functionally investigate the organization of this structure and it's outputs to downstream structures.

Within the posterorlateral cortical amygdala, we have identified anterior and posterior domains that appear to mediate aversive and appetitive behavior, respectively. Expression of channelrhodopsin in random ensembles of neurons in these regions, and subsequent optical activation, is sufficient to elicit avoidance or approach responses. We are characterizing the projections from these domains to downstream targets. In a preliminary set of experiments, we have observed that neurons responding to aversive versus attractive odor have distinct projections within the limbic circuits. We expressed Cre-dependent channelrhodopsin (ChR2-eYFP) in odor-responsive neurons using the ArcCreER mouse line and found that neurons responding to aversive odor have projections to structures including the BNST, lateral septum and central amygdala, whereas neurons responding to attractive odor have projections to structures in the ventral striatum. Further, when ChR2 was expressed in the posterior region of the cortical amygdala, axonal projections were observed in the lateral region of the nucleus accumbens. These projections were confirmed by Retrobead injection into the lateral nucleus accumbens, which labeled neurons in the posterior cortical amygdala. Behaviorally, we observed that optogenetic stimulation of these projections from the cortical amygdala to the lateral nucleus accumbens elicited approach behavior. Together, these data suggest a functional organization of the cortical amygdala with small domains projecting to different limbic circuits to generate innate odor-driven behaviors.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Topic: D.05. Olfaction and Taste

Support: NST Grant CRC-15-04-KIST
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Title: Characterization of prefrontal local field potential (LFP) in olfaction by using olfactory oddball paradigm with mouse model of olfactory deficit

Authors: *J. KUM[1,2], J. KIM[3], H.-B. HAN[1,4], J.-H. YOON[3], J. CHOI[1,2]
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Abstract: Olfactory disabilities are one of the early symptoms of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. As current medical services depend on self-report to measure olfactory dysfunction, objective assessment of patients' olfactory function will open up opportunities for precise and earlier diagnosis of neurodegenerative disease. Whereas electroencephalogram (EEG) recorded in the primary auditory and visual sensory cortices are used as objective measures of audition and vision, primary olfactory cortices or the olfactory bulb are located deep inside making it difficult to measure perception-related activities non-invasively. Previous EEG studies have shown the possibility of objective measurement of olfactory perception by recording high-order cortices such as frontal cortex, also implied a limitation that it is difficult to understand electrophysiological activity correlates of olfaction without studying cortical activation in relation to activities of the peripheral olfactory system or the olfactory bulb. Here, we measured local field potentials (LFP) of mouse prefrontal cortex (PFC) simultaneously with the main olfactory epithelium (OE), the peripheral area of which contains olfactory sensory neurons and the main olfactory bulb (OB), the direct receiver of signals from olfactory sensory neurons. For this purpose, we characterized LFP responses of healthy control C57BL/6 mice compared to zinc sulfate treated anosmia model mice, which show specific destruction of mature olfactory neurons. We recorded urethane anesthetized mice LFP with olfactory stimulation under oddball paradigm. In control mice, PFC power showed significant increase at all band from delta (1-4 Hz) to gamma2 (70-90 Hz), which were showed coherence with power increases of OE and OB oscillations. Beta (15-30 Hz) and gamma1 (30-50 Hz) oscillations showed persistent response during stimulation in all regions. Power in response to deviant odor was stronger than that of standard odor in the beginning of the stimulation in PFC, which showed coherence with significant power difference of oscillatory response between deviant and standard stimulation in OE and OB. Compared to control mice, the response of all oscillatory band from delta to gamma2 was weaken in zinc sulfate treated anosmia model mice in all regions. Power difference of standard and deviant odor stimulation was also decreased in zinc sulfate mice. Our results shows that PFC oscillatory response have coherence with the OE and OB, which implies possibility for using PFC activations in EEG as a guidance for human olfactory perception in diagnosis of olfactory deficit.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Program #/Poster #: 305.15/FF14

Topic: D.05. Olfaction and Taste

Support: Israeli Science Foundation
Rappaport Foundation

The Adelis Fund for Brain Research

Title: NMDA spikes mediated amplification of odor pathway information in the piriform cortex

Authors: *A. KUMAR[1], O. SCHIFF[1], E. BARKAI[2], B. MEL[3], A. POLEG-POLSKY[4], J. SCHILLER[1]
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Abstract: The piriform cortex (PCx) is the main cortical station for odor recognition and memory. It receives monosynaptic inputs from Olfactory bulb (OB) via Lateral Olfactory tract (LOT). Pyramidal neurons (PN) in PCx are main integration units within which the information from the OB is remapped to form "odor objects". PN in PCx have "discontinuous" receptive fields, i.e., they respond to multiple chemically diverse odorants, while failing to respond to re-combinations of those odorants' component parts. Formation of these "discontinuous" receptive fields from OB inputs is unexplained. A previous study had analyzed dendritic responses of olfactory PNs and reported that pyramidal neurons in the PCx lack sufficient NMDA (or other) regenerative currents that could provide either the combination selectivity or amplification of LOT inputs. They also reported that PN in PCx, unlike their counterparts in other cortical areas, act as intrinsically linear summing units. Counter to this view that olfactory PNs sum their inputs passively, using glutamate uncaging, focal stimulation and compartmental models, we show for the first time that robust NMDA spikes within individual dendrites can be evoked and can both amplify OB inputs and impose combination selectivity upon them. Using a model, we show that these local spikes may serve to effectively amplify clustered versus distributed LOT input, forming basis for a discontinuous field. Their ability to compartmentalize voltage signals allows different dendrites to represent different glomerular combinations, fulfilling the basic requirements for a discontinuous receptive field. We also show that the LOT and Intra-cortical inputs interact nonlinearly, a finding crucial for understanding the recurrent pattern completion functions of PCx.

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Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Topic: D.05. Olfaction and Taste

Support: NIH Grant F32 DC015938
NIH Grant R01 DC016289

NIH Grant R01 DC014453

Title: Coding of odor mixtures in cortical feedback projections to the olfactory bulb

Authors: *J. D. ZAK, V. N. MURTHY
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Abstract: The olfactory bulb not only integrates bottom-up information from the sensory periphery, but also receives dense top-down modulation from other areas of the brain, including the piriform cortex. The piriform cortex is thought to be involved in computations related to odor identity, quality, and predictive coding; however, it is unknown to what degree, if at all, the cognitive aspects of odor processing are transmitted back to the olfactory bulb. Recent studies have demonstrated that projections from the piriform cortex play a critical role in decorrelating the output from olfactory bulb projection neurons for monomolecular odors. We have begun to investigate how cortical feedback projections respond to odor mixtures, especially when individual components have distinct behavioral context. We used multiphoton microscopy to visualize odor responses from cortical axon terminals expressing the calcium indicator GCaMP6f. Individual boutons had diverse responses to monomolecular odorants as well as to complex odor mixtures. For individual odors, across >700 boutons and >11000 bouton-odor pairs, we observed both enhanced and suppressed responses to odor stimulation, as well as diverse temporal structure. The mean lifetime sparseness (a measure of stimulus selectivity) for all boutons was 0.39 ± 0.27, with ~20% of all boutons showing no response to any of the 16 odors in our panel. We next considered how these same feedback projections would respond to odor mixtures. First, we generated binary mixtures over a wide range of dilutions. We observed a strong concentration dependence to the responses, with the highest odor concentration (10%) eliciting the largest positive as well as negative signals. Individual boutons that responded to a particular concentration with a positive response, also exhibited positive responses to all other concentrations (if responses were detected). We also occasionally observed responses that were present for only a subset of the dilutions. Lastly, we delivered odor mixtures containing up to 12 components, and our initial analysis indicate highly non-linear mixture interactions. In summary, complex information about odor composition is broadcast to the olfactory bulb, and ongoing experiments are aimed at dissecting the nature of this information.

Disclosures: J.D. Zak: None. **V.N. Murthy:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 305.17/FF16

Topic: D.05. Olfaction and Taste

Support: DC016782

Title: Odor processing by distinct classes of principal neurons in piriform cortex

Authors: *S. NAGAPPAN, B.-X. HAN, F. WANG, K. M. FRANKS
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Abstract: Odor information is encoded by the activity of dispersed populations of principal neurons in piriform cortex (PCx). PCx is a trilaminar structure with principal neurons largely concentrated within Layer II (LII). LII further subdivides into a superficial layer containing a class of excitatory neurons known as semilunar cells (SLs), and a deep layer containing a morphologically and electrically distinct class of excitatory neurons, superficial pyramidal cells (SPs). SLs have extensive apical dendrites but no basal dendrites and receive afferent inputs predominantly from olfactory bulb (OB). In contrast, SPs have extensive apical as well as basal dendrites and receive both OB and intracortical inputs. These differences in morphology and connectivity between SLs and SPs determined in mouse brain slices suggest a two-stage model for odor processing in PCx, where SLs pre-process afferent, OB inputs, and then transmit this information to SPs. But, does this model hold in awake animals?

To compare how SLs and SPs process odor information *in vivo*, we generated a Netrin-G1-cre knock-in mouse line that selectively expresses Cre recombinase in a subset of PCx neurons. The morphology and laminar properties of these neurons indicate broad and selective labeling of SLs, but not SPs. We then used cre-dependent AAVs to express archaeorhodopsin (Arch) in Netrin-G1-expressing SLs and recorded both light- and odor-evoked spiking in large populations of LII neurons in awake, head-fixed mice. Cells whose spontaneous spiking was rapidly and robustly suppressed by light were determined to be Arch+ SLs, while Arch- cells were determined to be presumptive SPs.

Spontaneous firing in SLs were significantly higher than SPs and SLs were more broadly tuned than SPs. SLs also exhibit a prominent biphasic response, with brief excitation followed by substantial suppression, that was not observed in SPs. Latencies to response peak were equivalent in SLs and SPs. Additionally, optical suppression of SL cells markedly decreased spontaneous firing in SPs, indicating that SPs are, at least, partially driven by SPs. However, interestingly, SL suppression did not abolish the biphasic odor responses in SPs. In fact, if anything, the signal-to-noise ratio of SPs increased in the absence of SLs. Together, these findings suggest that odor processing by SLs may not unambiguously precede and influence odor processing by SPs as proposed in the model. Rather, the independent differences in response properties between these two main classes of PCx principal neurons imply parallel sensory processing streams, potentially serving distinctive higher order functions.

Disclosures: S. Nagappan: None. **B. Han:** None. **F. Wang:** None. **K.M. Franks:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Topic: D.05. Olfaction and Taste

Support: Swartz Foundation
Computational Neuroscience Initiative

Title: Pattern completion and separation via modulation of synchrony in the interplay between olfactory bulb and cortex

Authors: *G. TAVONI, D. KERSEN, V. BALASUBRAMANIAN
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Abstract: How can contextual information change the perception of sensory stimuli? In the olfactory system, we propose a model for this process where descending feedback from the central brain modulates synchrony in peripheral responses during odor discrimination tasks. Our model consists of pyramidal neurons in the piriform cortex receiving input from overlapping "modules" of mitral cells in the the olfactory bulb (OB). Modules are assumed to have different degrees of intrinsic temporal synchrony, and drive their cortical targets through a sigmoid-like transfer function. We propose that feedback from the central brain about the context of odors acts to manipulate the synchrony of mitral cell responses in the OB. The feedback can affect a random, odor-independent subset of modules, but must act so that alternative contexts have opposite effects on synchrony in the affected modules. We argue that this modulation of synchrony can be achieved by the known descending inputs to granule cells, via their widespread connections with mitral cells. Within this model we demonstrate that association of two odors with the same context leads to *pattern completion* in cortex where responses to the two odors become more similar. Meanwhile association with opposite contexts leads to decorrelation of odor responses in cortex, i.e., *pattern separation*.
The model reproduces two striking experimental effects (Chapuis and Wilson, Nat. Neuro., 2012; Shakhawat et al., J. Neurosci, 2014): (1) Pattern completion induced by similar contexts is greater for already similar odors, (2) Pattern separation induced by opposite contexts is larger for previously similar odors. This increased pattern completion and separation for initially more similar odors is greater when cortical units have steeper response functions and higher thresholds that match measurements. We show that alternative response functions can actually produce the *opposite* effects, suggesting that response properties of cortical neurons are tuned to maximally promote the experimentally measured forms of pattern completion and separation.

Disclosures: G. Tavoni: None. **D. Kersen:** None. **V. Balasubramanian:** None.

Poster

305. Olfaction: Information Processing in Higher Order Circuits

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Program #/Poster #: 305.19/GG1

Topic: D.05. Olfaction and Taste

Support: Grants-in-Aid for Science Research on Innovative Areas "Brain Information Dynamics"(18H05114)

Title: Sharp wave-associated activity pattern of olfactory cortical neurons in the mouse piriform cortex

Authors: *K. KATORI[1], H. MANABE[2], A. NAKASHIMA[1], E. DUNFU[1], T. SASAKI[1], Y. IKEGAYA[1], H. TAKEUCHI[1]
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Abstract: The olfactory piriform cortex is thought to participate in olfactory associative memory. Like the hippocampus, which is essential for episodic memory, it belongs to an evolutionally conserved paleocortex and comprises a three-layered cortical structure. During slow-wave sleep (SWS), the olfactory piriform cortex becomes less responsive to external odor stimuli and instead displays sharp wave (SPW) activity similar to that observed in the hippocampus. Neural activity patterns during hippocampal SPW have been extensively studied in terms of memory consolidation; however, little is known about activity patterns of olfactory cortical neurons during olfactory cortex sharp waves (OC-SPWs). In this study, we simultaneously recorded multiple neuronal activity in the anterior piriform cortex in urethane-anesthetized mice. We found that activity pattern of olfactory cortical neurons during OC-SPWs was non-randomly organized. OC-SPWs recruited the discharges of the subsets of olfactory cortical neurons. Individual olfactory cortical neurons varied in the timings of the peak firing rates during an OC-SPW event, constituting sequential neuronal activation as a whole. Moreover, specific pairs of olfactory cortical neurons were more frequently activated than expected by statistical chance. Based on these observations, we speculate that coordinated and sequential activation of specific subsets of olfactory cortical neurons repeats during OC-SPWs, thereby facilitating synaptic plasticity underlying consolidation of olfactory associative memories.

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Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.01/GG2

Topic: D.07. Vision

Support: Australian Research Council Grants DP160104316 and DP160104368

Title: An integrated model linking structural and dynamical properties of local cortical circuits

Authors: *P. GONG, Y. GU
The Univ. of Sydney, Sydney, Australia

Abstract: Experimental studies have begun revealing essential properties of the structural connectivity and the spatiotemporal activity dynamics of cortical circuits. To integrate these properties from anatomy and physiology, and to elucidate the mechanistic links between them, we develop a local cortical circuit model that captures a range of realistic features of synaptic connectivity. We show that the model accounts for the emergence of higher-order connectivity structures, including overrepresented three-neuron motifs and highly connected hub neurons that form an interconnected rich-club. The circuit model exhibits a rich repertoire of activity states, ranging from asynchronous to localized and global propagating wave states. We find that around the transition between asynchronous and localized propagating wave states, our model quantitatively reproduces a variety of major empirical recordings regarding neural spatiotemporal dynamics, which otherwise remain disjointed in existing studies. These dynamics include diverse coupling (correlation) between spiking activity of individual neurons and the population, propagating wave patterns with variable speeds and precise temporal structures of neural spikes. We further illustrate how these neural dynamics are mechanistically linked to the structural connectivity properties by analyzing the contributions of connectivity to neural spiking dynamics and by showing that the rich-club structure is fundamentally related to the emergence of the diverse population coupling. These findings establish an integrated account of structural connectivity and activity dynamics of local cortical circuits, and provide novel experimentally testable predictions.

Disclosures: P. Gong: None. **Y. Gu:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.02/GG3

Topic: D.07. Vision

Title: Building and simulating a biophysically detailed network model of the mouse primary visual cortex

Authors: *Y. N. BILLEH, S. L. GRATIY, K. DAI, R. IYER, N. W. GOUWENS, S. MIHALAS, C. KOCH, A. ARKHIPOV
Allen Inst., Seattle, WA

Abstract: Rapid advancement in neuroscientific tools is yielding an extraordinary amount of data regarding the structural and dynamical properties of cortical circuits. In parallel, there has been vast progress in parallel computing and software to allow for unprecedented simulation capabilities. Herein we describe our efforts in combing these two exciting advances to develop, in a data-driven manner, a model of the mouse primary visual cortex (area V1) comprising ~230,000 neurons from all cortical layers.
For developing our cortical model, we used the Brain Modeling ToolKit (BMTK), a python API developed by the Allen Institute (github.com/AllenInstitute/bmtk). BMTK allowed us to construct our network and integrate seamlessly with NEURON [Hines and Carnevale, 1997] to enable parallel simulations. Approximately 51,000 neurons in our model are biophysically detailed, pooled from >100 models of individual neurons from the Allen Cell Types database (celltypes.brain-map.org). The network receives spike-train inputs from filter models representing a variety of functional cell types from the Lateral Geniculate Nucleus (LGN). The LGN filter models were based on spatiotemporal fits from experimental recordings *in vivo*. The thalamocortical projection architecture and magnitude of excitatory post-synaptic current that V1 neurons receive was based on experimental literature.
After optimizing the LGN input to the column, the recurrent connectivity between cell-types and layers was introduced. The probability of connections, strength of connections (unitary PSP), functional connectivity rules, and synaptic placement between all cell-types was obtained via a thorough literature search, resulting in a knowledge graph that combines the connectivity information with the records of literature sources; assumptions were used where data was not available. As the next critical step, the synaptic weights were optimized to produce irregular network activity in response to visual stimulation.
We will describe the construction and simulations of the V1 model and discuss how available or hypothesized information about properties of cell types, feedforward connectivity from LGN, and recurrent connectivity has resulted in certain functional properties - such as, for example, orientation and direction selectivity. The model represents a milestone in the development of

data-driven simulations of brain activity and computations and should provide a valuable resource for the computational neuroscience community, in conjunction with the standardized model construction and simulation interfaces of the Brain Modeling ToolKit.

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Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.03/GG4

Topic: D.07. Vision

Support: Allen Institute for Brain Science

Title: Characterization of transgenic mouse lines for Allen Brain Observatory pipeline data collection

Authors: A. WILLIFORD[1], S. CALDEJON[1], L. CASAL[1], T. L. DAIGLE[1], N. DOTSON[1], J. LARKIN[1], R. LARSEN[1], T. NGUYEN[1], R. NICOVICH[1], M. ROBERTSON[1], B. TASIC[2], H. ZENG[3], *C. L. THOMPSON[1], J. LECOQ[4], P. A. GROBLEWSKI[1]
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Abstract: Transgenic mouse technology enables the selective labeling of cell populations and, along with genetically encoded calcium sensors, has provided an immensely powerful tool for probing the function of cells and circuits in the mouse brain. However, Cre transgenes, which often involve modifications or disruptions of endogenous genes, and the genetically encoded calcium sensors (which can potentially alter calcium buffering or interfere with gating and signaling of L-type calcium channels), can each result in undesirable abnormal phenotypes in mice. The Allen Brain Observatory is the online portal for a two-photon calcium imaging pipeline that generates functional physiology data in a variety of transgenic mice (www.brain-map.org/visualcoding). Cre-defined cell populations in mouse visual cortex were labeled with GCaMP6 calcium sensor by crosses between 13 Cre lines driven by various promoters(Cux2, Dlx5, Emx1, Fezf2, Ntsr1, Pvalb, Rbp4, Rorb, Scnn1a, Slc17a7, Sst, Tlx3, Vip) and various GCaMP6 reporters (Ai93, Ai94, Ai148, Ai162). Prior to inclusion in our experiments, these transgenic crosses were thoroughly characterized to identify the lines best suited for functional physiology. Animals were assessed for observable phenotypes in appearance, weight, in-cage behavior and locomotor activity. Additionally, the GCaMP6 reporter expression was evaluated in each line; for some Cre driver lines, Ai148 was preferred over Ai93 to achieve greater selectivity of expression. Intrinsic signal imaging was used to assess basic visual function and targetability

of higher visual areas; in one case, abnormal retinotopic maps specific to a particular cross contraindicated that line for use in vision-dependent experiments. Finally, calcium imaging of lines was evaluated for response properties in response to visual stimuli, as well as to assess the frequency of interictal events that might indicate epileptic-like abnormal brain activity. Overall this data set provides a useful reference for experimentalists seeking to identify appropriate lines for functional imaging experiments.

Disclosures: A. Williford: None. **S. Caldejon:** None. **L. Casal:** None. **T.L. Daigle:** None. **N. Dotson:** None. **J. Larkin:** None. **R. Larsen:** None. **T. Nguyen:** None. **R. Nicovich:** None. **M. Robertson:** None. **B. Tasic:** None. **H. Zeng:** None. **C.L. Thompson:** None. **J. Lecoq:** None. **P.A. Groblewski:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.04/GG5

Topic: D.07. Vision

Support: Paul Allen

Title: Nonlinear models of mouse visual cortex

Authors: *M. D. OLIVER[1,2], M. A. BUICE[2], P. LEDOCHOWITSCH[2], N. H. CAIN[2], G. K. OCKER[2], S. E. DEVRIES[2], D. MILLMAN[3]
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Abstract: Building predictive models of neural activity is a central aim of computational neuroscience. To better understand the various representations in mouse visual cortex, we aim to build stimulus-response models for neurons in cortical areas VISp, VISl, VISal, VISrl, VISpm, and VISam. Data from these brain areas was collected as part of the Allen Brain Observatory at the Allen Institute for Brain Science. The Allen Brain Observatory dataset includes data from hundreds of animals exposed to a standardized set of visual stimuli while calcium fluorescence was recorded from a cortical visual area. However, despite this large dataset, learning the stimulus-response mapping function for individual neurons is a challenging problem. The chief difficulty is that stimulus-response mapping functions are inherently high-dimensional and nonlinear while response data for a single neuron is limited by experimental demands and intrinsically noisy. One of the most successful approaches for tackling this problem is to linearize the stimulus-response mapping by preprocessing the stimulus with a carefully chosen nonlinear transform. For our model, we constructed linear and non-linear transforms using a pyramid of spatio-temporal Gabor filters to create a set of linear and quadratic filters that densely

tile the stimulus (Nishimoto & Gallant, 2011). We then use regularized regression to find a linear mapping between the transformed stimuli and the estimated responses of each recorded neuron. This regression can be thought of as a regularized version of Spike Triggered Average / Spike Triggered Covariance analysis. Neural responses were estimated from the fluorescence traces using an L0 regularized deconvolution algorithm (Jewell and Witten, 2017). Before fitting the models, we separated the stimuli used in the Allen Brain Observatory into 'natural' and 'artificial' classes. 'Natural' stimuli included natural movies and images. 'Artificial' stimuli included static gratings, drifting gratings and locally sparse noise. We fit models in these two stimulus regimes separately in order to determine which type of stimulus best allows for the construction of predictive stimulus-response models. We find that models fit using natural stimuli both generalize better and are more interpretable. We also find that across all cortical visual areas the fit models tended to utilize far more quadratic regressors than linear regressors. This suggests that neural representations in mouse cortex, even in the first cortical visual area VISp, contain few if any true “simple cells” and may exhibit higher-order tuning earlier in their visual hierarchy than other species, such as cats and primates.

Disclosures: M.D. Oliver: None. **M.A. Buice:** None. **P. Ledochowitsch:** None. **N.H. Cain:** None. **G.K. Ocker:** None. **S.E. DeVries:** None. **D. Millman:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.05/GG6

Topic: D.07. Vision

Title: Matching cells across two photon images of multiple optical physiology experiments

Authors: *F. LONG, M. GARRETT, S. DE VRIES, J. LECOQ, L. KUAN, C. THOMPSON, D. FENG, W. WAKEMAN, J. GALBRAITH, L. NG
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Abstract: To better understand neural activities in different retinotopically mapped areas of visual cortex, cortical layers, and Cre lines during visual stimulation in behaving mice, we collected two photon (2P) time-series of neuron responses as part of the Allen Brain Observatory. The same location within a cortical visual area of each brain was imaged over multiple sessions, between which the animal was removed from the apparatus and then returned to approximately the same position for the next session. Images acquired from each session vary depending on different visual stimuli and inaccuracy in configuring the exact same depth and field of view. Analyzing these experiments invariably requires identifying which regions of interest (ROIs) from multiple imaging sessions correspond to the same physical cell. We therefore developed an automated matching approach that allows us to find ROI correspondence

across any number of optical physiological experimental sessions. The approach involves multiple steps. First, it estimates the affine transformation required to bring each image in the multiple sessions into a common coordinate space based on intensity correlation. This compensates for the translation and rotation errors that occurred when the apparatus is reassembled for each session. Second, it matches ROIs between any two experiments by considering all the possible combinations of pairwise sessions using bipartite graph matching. ROIs in any two sessions are represented by two sets of nodes in the graph, and matches are represented by edges between the two sets. The overall best match is obtained by maximizing the sum of the edge weights defined as a cost function combining overlap and closeness features between ROIs. Third, pairwise matching results are combined to generate the final matching list of ROIs across all sessions. This involves cascading correspondence from pairwise matching results and resolving their conflicts based on the edge weights of each bipartite graph computed in the second step. Our experiments on a pilot dataset show that the approach generates reasonable cell matching results across multiple optical physiology experimental sessions. Our approach and code will be made publicly available for the global brain research community.

Disclosures: F. Long: None. **M. Garrett:** None. **S. De Vries:** None. **J. Lecoq:** None. **L. Kuan:** None. **C. Thompson:** None. **D. Feng:** None. **W. Wakeman:** None. **J. Galbraith:** None. **L. Ng:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.06/GG7

Topic: D.07. Vision

Title: Testing the astronomical observatory model in systems neuroscience: The allen brain observatory - openscope

Authors: *J. LECOQ[1], C. L. THOMPSON[3], G. K. OCKER[3], M. VALLEY[3], Y. N. BILLEH[2], J. PERKINS[3], S. NAYLOR[3], P. A. GROBLEWSKI[4], S. R. OLSEN[4], C. KOCH[3]
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Abstract: In 2016, the Allen Institute for Brain Science launched the Allen Brain Observatory: the first tool of its kind to create highly standardized surveys of cellular-level activity in the mouse cortex. The creation of this high throughput data collection pipeline presented a new and unique opportunity: building a true astronomical observatory in systems neuroscience whereby both experimental and theoretical scientists around the world could propose experiments to run on the Allen Brain Observatory. Our hope with this model is to streamline hypothesis testing of cortical function by selecting the most impactful experimental proposals.

Here we present results from our first-year pilot. We evaluated the interest and feasibility of the astronomical observatory model in System Neuroscience. (1) A Request For Proposal (RFP) document was communicated to a selected panel of scientists (Summer Workshop on the Dynamic Brain attendees and Allen Institute scientists). (2) Experimental proposals were selected based on feasibility and scientific impacts. (3) Experiments were piloted and conducted on the Allen Brain Observatory optical physiology pipeline. (4) Data is analyzed by the application teams. We report a high interest in the model (10% RFP response rate), discuss the model incentives and associated operational (scientific review, selection criteria and bias) and technical challenges. We conclude with potential future development of the model.

Disclosures: C.L. Thompson: None. **G.K. Ocker:** None. **M. Valley:** None. **Y.N. Billeh:** None. **J. Perkins:** None. **S. Naylor:** None. **P.A. Groblewski:** None. **S.R. Olsen:** None. **C. Koch:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.07/GG8

Topic: D.07. Vision

Support: Tiny Blue Dot Foundation

Title: Functional interrogation of claustrum involvement in a visual change detection task

Authors: *D. R. OLLERENSHAW[1], A. M. SHELTON[1], J. DAVIS[1], Y. WANG[3], H. ZENG[2], S. R. OLSEN[1], C. KOCH[1]
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Abstract: The extensive, reciprocal connectivity between the claustrum and the cortex points to possible roles for the claustrum in coordinating activity across cortical regions during perceptually demanding behaviors. Backing this view, recent studies in this structure have pointed to specific roles for the claustrum in signaling salience of sensory events, or coordinating top-down control of attention during sensory-guided tasks. To further probe the function of the claustrum during behavior, the Allen Institute has developed a mouse line with Cre expression under control of the Gnb4 gene, which expresses preferentially in the claustrum. Whole brain, axonal tracing of Gnb4+ claustral neurons demonstrates widespread, bilateral projection patterns, with axons terminating predominantly in midline cortex. To probe the function of these cells, we have performed single-photon fluorescence imaging of the claustrum using implantable gradient index (GRIN) lenses in Gnb4-Cre mice crossed with GCaMP6 reporter mice to measure claustrum function during a psychophysically demanding change detection task, as well as widefield imaging of the cortical surface to measure activity in cortical projections of Gnb4+

cells. Cells in the claustrum appear to signal both stimulus changes and behavioral choice, with the strongest responses occurring when both conditions are coincident. In addition, chemogenetic perturbation of claustrum cells during the same task interferes with task performance, indicating possible causal involvement of the claustrum in the task. Together, these results further indicate the role of the claustrum in coordinating cortical areas during decision making.

Disclosures: D.R. Ollerenshaw: None. **A.M. Shelton:** None. **J. Davis:** None. **Y. Wang:** None. **H. Zeng:** None. **S.R. Olsen:** None. **C. Koch:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.08/GG9

Topic: D.07. Vision

Title: Large-scale calcium imaging reveals cell class specific roles in a visual change detection task

Authors: *M. GARRETT[1], P. A. GROBLEWSKI[3], J. KIGGINS[2], D. R. OLLERENSHAW[3], L. CASAL[1], A. CHO[1], A. LEON[1], K. MACE[1], S. MANAVI[1], K. ROLL[1], C. THOMPSON[1], A. WILLIFORD[1], S. R. OLSEN[3]
[2]Neural Coding, [1]Allen Inst. for Brain Sci., Seattle, WA; [3]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Detection of moment-to-moment changes in the visual scene is fundamental to an animal's ability to navigate the world. We have developed a go/no-go change detection task in which images are presented serially and mice must respond to changes in the visual stimulus to earn rewards. We show that head-fixed mice can be trained on this task within a few weeks using an automated training regimen, enabling comparison of behavioral performance across dozens of mice from multiple transgenic lines. Mice can detect changes in a diverse set of visual stimuli (e.g. oriented gratings and natural scenes), permitting a range of experimental questions. Despite variability in training times and engagement patterns, the tendency to detect changes between individual natural scene images is highly consistent between mice, indicating that animals rely on similar perceptual cues to detect changes between natural images. Optogenetic perturbation experiments demonstrate that the visual cortex is necessary for task performance.
To understand how behavioral state influences the representation of natural images, we have begun systematically measuring activity in the visual cortex during performance of this task using a standardized 2-photon imaging pipeline (Allen Brain Observatory: http://observatory.brain-map.org/visualcoding/). Using this approach, we find that excitatory and inhibitory populations differ in their selectivity and in the relationship of population activity with behavioral detectability of specific images. Modulation by task engagement is observed in layer 2/3 excitatory and VIP+ inhibitory populations.

By imaging the activity of populations of single neurons across multiple visual cortical regions, cell classes, and cortical depths, this study will provide a comprehensive survey of information processing in visual cortical circuits during visual behavior in mice. As part of the Allen Institute's commitment to open science, the data generated through this project will be made publicly available for download and use by the neuroscience community to drive progress in understanding the neural basis of perception and behavior.

Disclosures: M. Garrett: None. **P.A. Groblewski:** None. **J. Kiggins:** None. **D.R. Ollerenshaw:** None. **L. Casal:** None. **A. Cho:** None. **A. Leon:** None. **K. Mace:** None. **S. Manavi:** None. **K. Roll:** None. **C. Thompson:** None. **A. Williford:** None. **S.R. Olsen:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.09/GG10

Topic: D.07. Vision

Title: Ca^{2+} imaging favors bursty neurons

Authors: *P. LEDOCHOWITSCH[1], N. CAIN[1], J. H. SIEGLE[1], X. JIA[2], G. K. OCKER[1], M. D. OLIVER[3], S. R. OLSEN[1], S. E. DEVRIES[1], M. A. BUICE[1]
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Abstract: To build a bridge between electrophysiology and optical physiology, this work investigated the degree to which spatial receptive fields computed directly from spiking activity could be inferred via models of Ca^{2+}-dependent fluorescence.
(I) We have collected 'ground truth' calibration data by simultaneous juxtacellular patching and 2P imaging *in vivo*. After semi-automated quality control, we identified 15 simultaneous recordings from layer 2/3 pyramidal cells, which expressed GCaMP6f under the pan-excitatory Emx1 promotor, and matched the noise and response profile of the Allen Brain Observatory (BOb). We then calibrated 'MLSpike' [1], a biophysically inspired non-linear model on these data which yielded 15 model parametrizations capturing a spread of relationships between spikes and resulting fluorescence, and allowed simulating fluorescence data for arbitrary spike trains.
(II) We recorded spiking activity in awake, head-fixed mouse, free to run on a wheel 165 mm in diameter. Visual stimuli (locally sparse noise, gratings, natural scenes, and natural movies) were presented on a 24.1" monitor placed 150 mm from the right eye. Six Neuropixels probes [2] were aligned to the center of each of six visual areas: VISam, VISp, VISal, VISl, VISlm, and VISrl. Area maps were obtained via intrinsic signal imaging (ISI) ~2 weeks prior to the experiment. Each probe was inserted approximately 1300 µm into the brain, penetrating through all 6 layers of cortex and down into hippocampus.

(III) Using the results of (I), we modeled 15 “calcium” signals, one for each cortically localized spike train from a regular-spiking cell obtained in (II), and computed putative receptive fields via the Allen Brain Observatory data processing pipeline. We found that these receptive fields, when statistically significant, bear a strong resemblance to those computed directly from the electrophysiology using comparable statistical techniques.
The quality of the correspondence was dependent not only on the calcium model parametrization but also on the degree of stimulus-evoked bursting in the observed areas and layers, respectively. Our results from (III) suggest overall that the BOb receptive field fitting provided an accurate characterization of receptive field parameters whenever the presented stimulus effectively drove bursting activity in the chosen combination of area, layer, and cell type.

References:

[1] Deneux, T., et al. (**2016**). *Nature Communications*, 7, 12190 EP.
[2] Jun, J. J., et al. (**2017**). Nature, 551, 232.

Disclosures: P. Ledochowitsch: None. **N. Cain:** None. **J.H. Siegle:** None. **X. Jia:** None. **G.K. Ocker:** None. **M.D. Oliver:** None. **S.R. Olsen:** None. **S.E. DeVries:** None. **M.A. Buice:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.10/GG11

Topic: D.07. Vision

Support: Paul G. Allen

Title: Stimulus and state-dependence of interactions between vip and sst cells in mouse primary visual cortex

Authors: *D. MILLMAN[1], G. K. OCKER[2], N. H. CAIN[2], P. LEDOCHOWITSCH[2], R. S. LARSEN[3], M. D. OLIVER[4], R. REID[3], M. A. BUICE[2], S. E. DEVRIES[2]
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Abstract: In cortex, vasoactive intestinal peptide-expressing (Vip) interneurons make strong inhibitory synapses onto somatostatin-expressing (Sst) interneurons and, reciprocally, Sst cells make inhibitory synapses onto Vip cells. This reciprocal connectivity establishes a circuit motif of competitive inhibition with poorly understood effects on cortical processing. Using data from the Allen Brain Observatory, supplemented with follow-up experiments, we investigated the visual stimulus tuning and state-dependent modulation of these two major classes of cortical interneurons in mouse primary visual cortex. On long time scales, behavioral state can have a net correlating effect on these cell types as the activity of both cell classes positively correlates with

the running speed of the mouse. The cells have diverse relationships in their responses to visual stimuli. Full-field gratings drive strong and reliable orientation-tuned responses in Sst cells and reliably suppress activity of Vip cells, consistent with direct inhibition from Sst onto Vip cells. Although previous reports on the relative size tuning of these cells suggest that Sst cells should have much larger receptive fields than Vip cells, we find that Sst and Vip cells both have large receptive fields. Despite this similarity in receptive field size, Sst and Vip cells have distinct spatial frequency tuning. Unexpectedly, Vip and Sst cells are both among the most responsive cell types to natural movie stimuli out of all Cre-lines sampled in the Allen Brain Observatory. We compare the correlation of these cells with natural movies to better understand their functional interactions. These results suggest that the net interaction between these cell types is both stimulus and state-dependent.

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Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.11/GG12

Topic: D.07. Vision

Support: Helen Lyng White Fellowship
NIH R01EY024294
Simons Foundation SCGB-325407

Title: Cellular resolution mesoscale study on correlation structure during visual encoding

Authors: *Y. YU, S. L. SMITH
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Abstract: In mammalian neocortex, visual information is processed by primary visual cortex (V1) and multiple higher visual areas (HVAs). Neural circuitry can lead to shared variability in spiking responses between neurons. These are called “noise correlations” (NCs), and can be due to shared input and/or direct or indirect connectivity. Thus, NCs provide insight into the functional connectivity of neuronal circuits. In this study, we used subcellular resolution mesoscale field-of-view two-photon calcium imaging to systematically characterize the NCs of layer 2/3 neurons across V1 and four HVAs (LM, LI, AL and PM) of mice. First, we found that the average NCs for pairs of neurons within a cortical area (intra-areal) and pairs of neurons where each neuron is in different cortical area (inter-areal) are orders of magnitude larger than control (e.g., intra-V1: 0.015, shuffled trials: 0.0004; inter-V1-PM: 0.014, shuffled trials:

0.0006). Overall, NCs were higher for neuron pairs with high tuning similarity. Firing rates and receptive field overlap were also positively correlated with NCs in most cases. Second, we found intra-areal NCs declined with distance between neurons, but for inter-areal NCs the distance-dependence was mixed (e.g., V1-LM and V1-LI NCs increased with neuron distance; and LM-LI NCs declined with neuron distance). These trends in NCs provide clues into HVA-specific transformations of visual stimulus representations. Third, to explore tuning-specific NCs in finer detail, we used an unbiased clustering approach to classify neurons based on their responses to orientated grating (8 directions, 3 spatial frequencies, 3 temporal frequencies). This analysis revealed biases in the coverage of spatiotemporal frequency space across HVAs, and relationships between orientation tuning biases and spatiotemporal frequency preferences. Using the resulting functional groupings, we found group-specific intra- and inter-areal patterns of NCs. Thus, there are functionally-specific subnetworks within and among visual cortical areas. Fourth, we analyzed the full covariance matrix to infer network structures that could underlie the measured NCs. We factored the covariance matrix into a low-rank component and a sparse component. The functional networks differed from random networks in the prevalence of well-connected units, whose spatial distribution varied by cortical area. Overall, these results have revealed a comprehensive picture of correlation structure with individual neurons across mesoscale distances and multiple cortical visual areas, which can inform and constrain computational theories of cortical network structure and function.

Disclosures: Y. Yu: None. **S.L. Smith:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.12/GG13

Topic: D.07. Vision

Support: Simons Foundation Grant #543029
Swiss National Foundation Grant #31003A_165831

Title: Detecting information-limiting correlations experimentally

Authors: J. S. MONTIJN[1], R. G. LIU[1], *A. POUGET[1], P. E. LATHAM[2]
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Abstract: How does information scale in neural circuits? For most patterns of correlations, information should be proportional to the number of neurons. In contrast, it should saturate to a finite value in the presence of what is known as information-limiting, or differential, correlations. Detecting such differential correlations is important since their presence is required for efficient

computation in neural circuits whenever a large number of neurons are coding for a scalar variable. However, current methods for detecting differential correlations require recording thousands of neurons simultaneously in a small cortical volume, which is not yet feasible. We report here a new method, which requires on the order of hundreds, rather than thousands, of neurons. This method relies on testing whether the 'information' and 'communication' subspaces overlap more than predicted by chance. For a scalar stimulus, the information subspace—where information refers to Fisher information—is a one-dimensional subspace colinear with the **f'** direction, where **f'** is the vector of derivatives of the tuning curves. The communication subspace, on the other hand, is based on the linear predictability of the activity of one neural population given another neural population: the D-dimensional communication subspace is obtained by recording, simultaneously, the responses of two neural populations to multiple presentations of the same stimulus; then using reduced rank regression to find the rank D weight matrix that best predicts the activity of one population based on the other. To test whether the information and communication subspaces overlap, the fraction of information transmitted in the communication channel is compared to the information transmitted in a random subspace of equal dimension. If the former is much higher than the latter, the information and communication spaces overlap. We have found analytically that when the information and communication subspaces overlap with D small (e.g. less than about 10), the neural code is likely to contain differential correlations. Using simulations with a leaky-integrate-and-fire (LIF) neuron model of the LGN-V1-V2 circuits, we confirmed that the method can indeed determine, with 100 neurons or fewer, whether differential correlations are present. This method can be easily applied to existing recordings in primates and rodents.

Disclosures: J.S. Montijn: None. **R.G. Liu:** None. **A. Pouget:** None. **P.E. Latham:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.13/GG14

Topic: D.07. Vision

Support: Fondecyt 1170027

Title: Unraveling the hidden lamination of the avian visual DVR

Authors: S. FERNANDEZ, C. WEISS, M. D. FERNÁNDEZ, *J. MPODOZIS
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Abstract: In birds the most prominent sensory pallial territory is the dorsal ventricular ridge (DVR), which consists of two dorso-ventrally apposed cellular masses: the mesopallium (M) and the nidopallium (N). The internal most aspect of the N contains discrete nuclei receiving

ascending afferents from different sensory modalities. Interestingly, these sensorecipient nuclei are reciprocally connected with dorsally adjacent sublayers of N and M by columnarly organized axonal processes. Recent gene expression studies have shown that these DVR layers differentially express mammalian layer-specific molecular markers. Thus, the neural organization of the DVR has been reinterpreted as following a laminar/columnar arrangement resembling that of mammals and layer-specific equivalences have been proposed. The sensorecipient area of the visual DVR is the Entopallium (E). Based on its connectivity and its molecular profile, E has been considered as the layer 4-like component of the visual DVR, but the existence of a robust projection from E to the underlying subpallium (the lateral striatum, LSt), a feature more consistent with that of neocortical layers 5-6, conflicts this proposal. Here we complemented immunohistochemistry, in situ hybridization essays and neuronal tracing to further characterize the laminar organization of the DVR, focusing on the palliostriatal population "hidden" within E. Tracer injections, both in vivo (pigeon) and in vitro (chicken), confirm that the E's intrapallial efferents mostly originate from its external region (Eex), whereas cells projecting to the LSt define in it a conspicuous internal domain (Ein). This division strikingly coincides with that defined by parvalbumin immunoreactivity, in which Ein exhibits an abundance of densely packed PV+ cells and fibers. ISH assays for the layer 4 specific marker RORß showed that cells of Ein exhibit a lower level of RORß expression than that of Eex. Lastly, anterograde tracer injections revealed that Ein is afferented almost exclusively by the central subdivision of the thalamic nucleus Rotundus (Rt), whereas Eex received fibers from dorsal anterior and posterior Rt. Our results indicate that E contains two superposed sublayers: an external, "layer 4-like" and an internal, "layer 5-like". The former exhibits a higher expression of RORß and exclusively originates intrapallial projections, while the latter lacks RORß expression and originates, mainly but not exclusively, projections to subpallial targets. The results point to the existence of a close relation between the visual flow and subpallial structures, which is more robust and direct than previously illustrated.

Disclosures: S. Fernandez: None. **C. Weiss:** None. **M.D. Fernández:** None. **J. Mpodozis:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.14/GG15

Topic: D.07. Vision

Support: National Eye Institute Grant EY02874
Simons Collaboration on the Global Brain

Title: Beyond gratings: Flow stimuli reveal ecologically-appropriate responses in mouse visual cortex

Authors: *M. HOSEINI[1], L. DYBALLA[2], M. C. DADARLAT[1], S. ZUCKER[2,3], M. P. STRYKER[1]
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Abstract: The mouse is a widely used model for studying vision because of the molecular, imaging, and genetic tools that are available. Assessments based on spatial frequency analysis imply that the visual capacity of the mouse is of low quality, with few neurons responding to spatial frequencies greater than 0.5 cycles/deg. Visually-mediated behaviors, such as prey capture, suggest that the mouse visual system is more precise. We have used 128-site silicon microelectrodes to measure the simultaneous responses of single neurons in the primary visual cortex (V1) of alert mice with a new stimulus class—visual flow patterns—that is more like what the mouse would encounter in the natural world than are sine-wave gratings but are more tractable for analysis than natural images (Dyballa et al, this meeting). Flows formally approximate natural visual scenes like those that would be seen by a mouse running through grass. Specifically, we have explored a class of drifting patterns of black or white dots that have energy only at higher spatial frequencies than those that produce responses to gratings while holding temporal-frequency content fixed. Flow patterns were displayed to the contralateral eye on a screen subtending 76 deg in azimuth and 58 deg elevation centered in the monocular segment of the visual field. These flow stimuli evoke strong visually-mediated responses well beyond those predicted by spatial frequency analysis. Flow responses predominate in higher spatial-frequency ranges (0.15 - 1.6 cycles/degree); many are orientation- or direction-selective; and flow responses of many neurons depend strongly on sign of contrast. Together these results challenge conventional linear approaches to visual processing and extend the mouse's visual capacity to behaviorally-relevant ranges.
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Disclosures: L. Dyballa: None. **M.C. Dadarlat:** None. **S. Zucker:** None. **M.P. Stryker:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.15/GG16

Topic: D.07. Vision

Support: Simons Collaboration on the Global Brain
National Eye Institute grant EY02874

Title: Flow stimuli reveal hidden dimensions in mouse visual cortex

Authors: *L. DYBALLA[1], M. HOSEINI[3], M. P. STRYKER[3], S. W. ZUCKER[1,2]
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Abstract: We have analyzed responses of single neurons in primary visual cortex of alert mice to conventional and novel visual stimuli (Hoseini et al., this meeting). Repeated presentations of a given stimulus, or of stimuli drawn from related families, evoke an ensemble of spike trains. We work with gratings and flow patterns, a class of naturalistic visual stimuli that span spatial frequency, contrast, orientation and directionality, and ask: What are the significant commonalities and differences among responses to them? Conventional receptive-field or spatial-frequency analyses yield little insight into flow-stimuli responses. Instead, we have performed a purely data-driven analysis applied to spike-train data from the full stimulus ensemble. Our unsupervised approach organizes cells' responses—at individual and population levels—into meaningful classes, while making no assumption about spike encoding strategies or stimulus classes. Novel dimensionality reduction techniques reveal that (i) diffusion map embeddings of neural data can be clustered to infer the stimulus; (ii) diffusion map embeddings can remain invariant across brain state. (iii) Although raw PSTHs are high-dimensional, they contain only about 8 significant dimensions; (iv) when projected into these dimensions, PSTHs organize into about 12 clusters. (v) Each of these clusters indicates a different type of processing, from the expected simple-type cells to more complex and transient responses. (vi) Some clusters contain mostly flow responses, many of which are delayed. Such delays seem likely to result from feedback originating in other visual areas. The majority of clusters challenge the widely-deployed 'receptive field' model of visual cortex suggesting, instead, much richer networking models.

Disclosures: L. Dyballa: None. **M. Hoseini:** None. **M.P. Stryker:** None. **S.W. Zucker:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.16/GG17

Topic: D.07. Vision

Support: NIH Grant 2T32HD007348-26A1
NIH Grant EY023337
NIH Grant EY027696

Title: A hallucinogenic serotonin-2A receptor agonist reduces visual response gain and alters temporal dynamics in awake mouse V1 neurons

Authors: *A. MICHAIEL, P. R. L. PARKER, C. M. NIELL
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Abstract: Sensory perception arises from the integration of externally and internally driven representations of the world. Disrupted balance of these representations leads to perceptual deficits and hallucinations. The serotonin-2A receptor (5-HT2A) is known to create conditions under which such perceptual alterations occur, as in schizophrenia and after psychedelic drug administration. Despite its drastic influence on perception, almost nothing is known about how activation of 5-HT2A influences sensory processing in the neocortex. Using widefield/two-photon calcium imaging and single unit electrophysiology in awake mice, we found that administration of the selective 5-HT2A agonist DOI (2,5-Dimethoxy-4-iodoamphetamine) drastically altered temporal and spatial processing of visual stimuli in primary visual cortex while leaving basic retinotopic maps, tuning properties, and receptive field structure intact. The net result of DOI-induced changes was a signficant decrease in sensory drive and reduced contextual modulation in visual cortex. Our results are consistent with models of hallucination in which reduced bottom-up sensory drive is a key factor leading to altered perception.

Disclosures: A. Michaiel: None. **P.R.L. Parker:** None. **C.M. Niell:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.17/HH1

Topic: D.07. Vision

Title: Impact of behavioral sources of noise correlation on population coding across the mouse visual system

Authors: *G. K. OCKER[1], N. H. CAIN[1], P. LEDOCHOWITSCH[1], D. MILLMAN[2], M. D. OLIVER[3], S. E. DEVRIES[1], M. A. BUICE[1]
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Abstract: The visual system encodes during different behavioral states which modulate neurons and neural circuits and impact the structure of visual stimuli. Diverse neuronal populations, of different cell types and in different brain areas and cortical layers, encode and transform visual stimuli with state-specific modulations or computations that have only begun to be revealed. The Allen Brain Observatory contains 2P calcium imaging from simultaneously recorded populations of hundreds of neurons in awake, passively viewing mice on a running wheel. Its recordings together span layers 2-5 in areas V1 and the secondary areas LM, AL RL, AM and PM and are in response to both synthetic and naturalistic stimuli. Locomotion and arousal provide low-

dimensional sources of variability to networks in murine primary visual cortex, but the impact of these low-dimensional fluctuations and other intrinsic sources of joint variability on information coding in higher cortices and across different genetic neural populations remains to be understood. We classify the mouse's behavior during image presentations by a Gaussian mixture model of the running speed. We observe low-dimensional trial-by-trial noise correlations across all examined locations in the mouse brain. This low dimensionality remains when restricting the responses to non-locomotion trials. To measure information coding, we decode the visual stimulus from the single-trial population responses. We see that locomotion improves decoding performance in a location-specific fashion, with differential impacts due to its modulation of single-neuron response properties and joint variability in different visual areas, layers and cre lines. Shuffling trials to destroy noise correlations generally improves stimulus decoding, suggesting that noise correlations negatively impact population coding. However, restricting to non-running trials reveals that, in certain locations, this impact is due to the behavioral modulation of noise correlations - and that noise correlations actually improve decoding performance during a single behavioral state. Together, our results show the differential impact of different sources of joint variability on population coding, highlighting the importance of behavioral context for a population stimulus code.

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Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.18/HH2

Topic: D.07. Vision

Support: DARPA
HHMI

Title: Time-dependence of sensory cortical neural fluctuations in awake mice performing a visual discrimination task

Authors: *M. EBRAHIMI[1,2,3], J. A. LECOQ[4,2], O. I. RUMYANTSEV[5,2], C. IRIMIA[4,2], M. J. SCHNITZER[6,2,4,7]
[1]Electrical Engin., [2]James H. Clark Ctr. for Biomed. Engin. & Sci., [3]CNC Program, [4]Biol., [5]Applied Physics, [6]Applied physics, [7]Howard Hughes Med. Inst., Stanford Univ., Stanford, CA

Abstract: Sensory perception is fundamentally limited by the coding accuracy of sensory neural ensembles. A substantial body of theoretical and experimental research suggests that populations of sensory cortical neurons exhibit positively correlated noise fluctuations that may bound the

precision of cortical neural coding and sensory discrimination. However, due to the limited size of past datasets, it has generally not been possible to examine how noise correlations vary across sensory cortical areas and over time during sensory decision-making. Here we analyzed the signaling and noise correlation properties of neural ensemble dynamics monitored by large-scale neural calcium imaging in the neocortex of behaving mice performing a GO/NO-GO visual decision-making task. Multiple neocortical areas accurately encoded the visual stimulus, as well as the animal's discriminative response. Our analysis also revealed positively correlated noise fluctuations across neural populations in multiple neocortical areas. The mean strength of these noise correlations varied as a function of time across the visual stimulus presentation, delay period and response period of our decision-making assay. Notably, sensory cortical neurons generally exhibited noise fluctuations that were more positively correlated at the start of visual stimulation, but then less so as a decision-making trial proceeded. Neural populations lying within the same visual cortical area and those spanning distinct cortical areas both exhibited this time-dependent modulation in noise correlation strength. These results show the widespread presence of positively correlated neural noise across the cortex and suggest that sensory cortical noise patterns may reflect a time-dependent gating of signal flow between cortical areas.

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Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.19/HH3

Topic: D.07. Vision

Title: Registration of multiple cortical layers across individuals improves the relative positioning of neurons

Authors: *C. LEE[1], R. DALLEY[2], A. MUKORA[2], D. SANDMAN[2], G. WILLIAMS[2], S. KEBEDE[2], S. SORENSEN[2], U. SÜMBÜL[1]
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Abstract: Laminar organization is a hallmark of cortical tissue. Cell classes are typically defined with respect to their laminar position, which plays an important role in the study of canonical cortical circuits. However, neuronal arbors typically occupy large fractions of the laminar axis, potentially obscuring finer laminar organization. Here, we reconstruct the arbors of cortical neurons from the mouse visual cortex (adult P45-P70 mice), and annotate the corresponding laminar borders together with the pial surface and the white matter boundary using the DAPI and brightfield 20x images. We propose a nonlinear registration algorithm to represent all the neurons in a common laminar axis to account for the variability in laminar thickness across

individuals. We generate cortical depth profiles of individual neurons and compare these profiles with the ones obtained from classical pia/white matter based scaling. Our approach produces narrower depth profiles for individual neurons in the common axis, as measured by the Crest factor, the ratio of the peak value to the root-mean-squared value (Figure 1). These results emphasize the potential role of laminar positioning in the definition of cell types and their organization into canonical circuits.

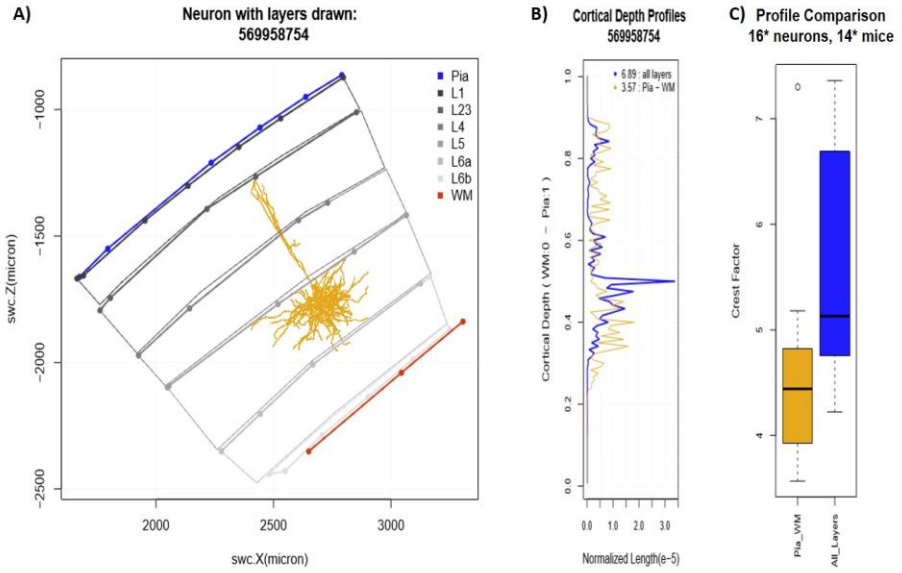

Figure 1. A) A representative neuron with the arbor trace and the cortical layers identified, B) The classical cortical depth profile for the neuron in A is calculated based pia and white matter boundaries (yellow). The depth profile obtained by a nonlinear registration using all the cortical layers (blue) occupies a smaller fraction of the common cortical depth axis. C) Summary of the Crest factors of the cortical depth profiles of a population of neurons obtained by the two methods. The Crest factor indicates how extreme the peak is in a given profile (the higher the better for identifiability). *Many more neurons are to be added.

Disclosures: C. Lee: None. **R. Dalley:** None. **A. Mukora:** None. **D. Sandman:** None. **G. Williams:** None. **S. Kebede:** None. **S. Sorensen:** None. **U. Sümbül:** None.

Poster

306. Visual Cortex: Circuits and Populations I

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Topic: D.07. Vision

Support: Jane Coffin Childs Memorial Fund
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Title: Eye movement information in V1 is carried through feedback projections

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Abstract: Saccades have a profound impact on vision, both perceptually and physiologically. Using mouse primary visual cortex (V1) as a model system, we have begun to dissect the circuit that carries saccade information to cortex. Similar to previous reports in cats and monkeys, we find that saccades modulate activity in mouse V1. This activity is caused by input of extra-retinal origin that persists even under suppression of all neuronal activity in the eyes. Who provides this saccade information to V1? To address this question, we took a candidate approach in which we silenced different brain regions while recording saccade-related activity in V1. First, we considered the possibility that this activity is inherited from the dorsal lateral geniculate nucleus (dLGN) in thalamus, as this is the major driver of V1 activity. Indeed, recording in the dLGN showed that its activity is also modulated by saccades. However, silencing the dLGN did not eliminate the modulation in V1. In contrast, silencing V1 eliminated saccade-related activity in the dLGN, suggesting that V1 is the source of saccade-information input in the dLGN and not vice-versa. Upon further exploration, we identified the latero-posterior (LP) nucleus in the thalamus as the source of saccade information in V1. LP is a higher order thalamic nucleus that receives inputs not only from visual cortical areas but also from other brain regions including the superior colliculus, a midbrain structure responsible for generating saccades. In turn, V1 receives projections from LP. Consistent with previous studies in monkeys, neurons in mouse LP are also modulated by saccades. When LP was silenced pharmacologically, V1 was no longer modulated in response to saccades. From our analyses, we suggest that saccade information flows from LP through V1 to the dLGN through the feedback pathway. The identification of the source of saccade information in V1 now enables us to explore the precise circuit mechanisms by which the saccade-related activity impacts different cell types within V1. This will allow us to understand the interaction of saccade information with visual information, and how this affects perception of the animals.

Disclosures: S. Miura: None. **M. Scanziani:** None.

Poster

306. Visual Cortex: Circuits and Populations I

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Program #/Poster #: 306.21/HH5

Topic: D.07. Vision

Support: 5 T32 NS 62443-9

Title: Parvalbumin-positive interneuron ensemble dynamics in the primary visual cortex during mouse visual detection

Authors: *A. I. MORE[1,2], C. A. DEISTER[1,2], C. I. MOORE[1,2]
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Abstract: Neocortical computations emerge from the functioning of, and interactions between, neural circuit motifs. While the key components of such motifs are still being determined, there is consensus that tightly regulated interactions between excitatory and inhibitory neurons are key to normal circuit function, and that neocortical activity can be dynamically regulated to enhance information processing. Parvalbumin-expressing fast-spiking interneurons (PV/FS) are hypothesized to be a key mediator of this dynamic balance.
We recently showed that trial-to-trial variation in PV/FS activity in primary somatosensory neocortex (SI) predicts task success during tactile detection of threshold-level stimuli. Specifically, subgroups of PV/FS fire either more or less on a 'hit' than a 'miss' trial (Deister et al., under review). Computational modeling indicates that these subgroups may be key to dynamic implementation of a basic motif, including an ensemble of pyramidal neurons that predict detection with rate increases and decorrelation in the broader population that does not show rate modulation. To test the generality of these task-predictive PV/FS dynamics and related pyramidal behavior, we have begun to image PV/FS in visual cortex during simple visual detection and discrimination. After using wide-field imaging to localize specific sub-domains responsive to discrete retinotopic positions, we have conducted 2-photon microscopy in head-posted mice during behavior. We have to date obtained sigmoidal contrast detection psychometric curves in multiple animals, and mapped PV/FS orientation, contrast, and direction tuning curves (N = 3 mice). We are now obtaining task dependent-activity in PV/FS and surrounding pyramidal networks to test whether parallel dynamics are observed to those found in SI.

Disclosures: A.I. More: None. **C.A. Deister:** None. **C.I. Moore:** None.

Poster

306. Visual Cortex: Circuits and Populations I

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Program #/Poster #: 306.22/HH6

Topic: D.07. Vision

Support: NIH Grant EB02291
NIH Grant EY018322

Title: Representation of concurrent stimuli by population activity in mouse primary visual cortex

Authors: *D. L. RINGACH
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Abstract: It has previously been shown that, in cat primary visual cortex, the responses to two superimposed gratings are the weighted sums of the individual grating responses (Busse et al, *Neuron*, 2009). The relative weights of the responses are explained very well by a contrast normalization model. We studied the same phenomenon in mouse primary visual cortex. We presented two individual visual stimuli *A* and *B*, and their superposition, *A+B*. We measured the corresponding mean population vector responses *r(A)*, *r(B)* and *r(A+B)*. Finally, we measured the angle between *r(A+B)* and the plane spanned by the individual responses *r(A)* and *r(B)*. If *r(A+B)* can be represented as a linear combination of *r(A)* and *r(B)*, as previously reported, the angular deviation is expected to be near zero. Surprisingly, we found this is not the case in mouse primary visual cortex. The population responses to plaid stimuli are far from ***any*** linear combination of the individual granting components. This result is due, in part, to the fact that some cells in mouse V1 respond to *A+B*, but not to *A* or *B*. Thus, in mouse primary visual cortex, the population response to the superposition of two visual stimuli cannot be predicted by a linear combination of the individual population responses.

Disclosures: D.L. Ringach: None.

Poster

306. Visual Cortex: Circuits and Populations I

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Topic: D.07. Vision

Support: MRC
Wellcome Trust
BBSRC
ERC

Title: All-optical interrogation of functional connectivity in mouse visual cortex during behaviour

Authors: *L. E. RUSSELL[1], A. M. PACKER[2], M. HAUSSER[3]
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Abstract: Understanding how the structure of connectivity underlies the processing carried out by cortical circuits is a fundamental problem in neuroscience. Layer 2/3 of mouse visual cortex consists of functionally distinct subnetworks of recurrently connected neurons. Neurons sharing similar stimulus response properties (i.e. cotuned to the same stimuli) preferentially share monosynaptic connections. This specific synaptic connectivity rule may facilitate and maintain robust representations of visual stimuli even under situations when those stimuli are weak or

degraded. Here we have trained mice on a visual detection task and used simultaneous two-photon calcium imaging and two-photon optogenetics to ask: 1. How does this pattern of paired connectivity extend to, and influence, activity at the population level in vivo? and 2. How does the functional signature of subnetworks impact upon the neural representation, and ultimately the behavioural salience, of weak or ambiguous stimuli? To address these questions, we performed targeted photostimulation of ensembles of either cotuned, non-cotuned or non-stimulus responsive L2/3 visual cortex neurons and observed the response of the local network as well as the animal's performance in reporting the current visual stimulus. Our preliminary results show that when a sufficient number of cells are photostimulated during reduced contrast visual stimulus presentation, the behavioural response rate to that stimulus is enhanced. We are currently dissecting how enhancing the behavioural response to a sensory stimulus depends on the functional identity of the photostimulated ensembles and their engagement of the local network. These results provide a bridge between connectomics, sensory stimulus coding and behaviour.

Disclosures: L.E. Russell: None. **A.M. Packer:** None. **M. Hausser:** None.

Poster

306. Visual Cortex: Circuits and Populations I

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Program #/Poster #: 306.24/HH8

Topic: D.07. Vision

Support: NIH Grant NS091335-04

Title: Somatostatin interneurons exhibit divisive inhibitory influence on nonlinear synaptic integration in layer 2/3 pyramidal neurons of the visual cortex

Authors: *C. DORSETT[1], I. T. SMITH[2], S. L. SMITH[2]
[1]Univ. of North Carolina - Chapel Hill, Chapel Hill, NC; [2]UNC Sch. of Med., Chapel Hill, NC

Abstract: Active mechanisms (voltage-gated Ca^{2+} and Na^{+} channels, and NMDA receptors) on the dendrites of cortical pyramidal neurons support dendritic spike generation. Dendritic spikes are a key component of synaptic integration that can enhance stimulus selectivity in visual cortex. Thus, modulation of dendritic spiking would have a powerful influence on cortical circuitry. Somatostatin (SOM) interneurons send a portion of their projections to distal dendritic compartments, and could exert a specialized influence on dendritic spiking. We investigated the role of SOM interneuron-mediated inhibition on dendritic excitability in layer 2/3 pyramidal cells from slices of mouse visual cortex using patch clamp electrophysiology and optogenetics. SOM cells expressing channelrhodopsin-2 (ChR2), responded to trains of light pulses with reliable depolarizations (mean ± SEM: 8.73 ± 0.27 mV, n = 16) to each pulse, but typically only

fired action potentials in response to the first pulse. Application of a GABA antagonist resulted in SOM cells reliably firing action potentials in response to every pulse of light up to 20Hz (n = 4). Thus, ChR2 stimulation likely causes direct release of GABA from SOM cell axons, and SOM cells mutually inhibit each other. We next recorded electrically-evoked synaptic potentials from pyramidal cells. Synaptic potentials increased in a supra-linear fashion above a cell-dependent stimulus intensity, indicating the recruitment of voltage-gated mechanisms on the dendrites. The frequency of non-linear increases was reduced in the presence of an NMDA receptor antagonist, although not abolished in every cell, thus both NMDA receptors and other voltage-gated channels can contribute to nonlinear synaptic integration. Optogenetic stimulation of SOM cells resulted in a mild hyperpolarization of pyramidal neurons (-2.31 ± 0.31 mV, from a baseline of -78.81 ± 1.46 mV, n = 23). Optogenetic SOM cell activation resulted in a reduction in the magnitude of electrically evoked synaptic potentials, especially at higher stimulus intensities, consistent with divisive inhibition (~75% of cells). Of cells with non-linear responses (n = 17), nonlinearities persisted during SOM cell activation (14 of 17), although the magnitude of the non-linearity was reduced or shifted by SOM cell activation. These results argue against a simple model in which SOM cells powerfully inhibit dendritic excitability. Instead, the effects of SOM cell activity appear to be more subtle. SOM cells can often affect the gain of pyramidal neurons, and in some cases modulate nonlinear dendritic integration, and either modulation affects the processing of synaptic input in visual cortex.

Disclosures: C. Dorsett: None. **I.T. Smith:** None. **S.L. Smith:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.25/HH9

Topic: D.07. Vision

Support: Gatsby Charitable trust GAT3138/GAT3213

Title: A sparse unreliable distributed code underlies the limits of behavioral discrimination

Authors: *B. SRIRAM[1], L. LI[2], A. CRUZ-MARTIN[3], A. GHOSH[1]
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Abstract: The nature of cortical code must enable subjects to perceive the world at the timescale most relevant for behavior. In rodents, we verify that visually directed orientation discrimination behavior is dependent on activity in the primary visual cortex (V1). Yet, the nature of the activity in V1 has only been characterized on timescales that last many hundreds to many thousands of milliseconds. To test if this is the relevant timescale, we measured the timescale of visual

integration in rodents performing an orientation discrimination task. We find that mice can integrate visual stimuli very quickly (<100 ms) to reach plateau performance. We recorded the activity of neurons across all layers of cortex to such short stimuli in both naïve mice as well as mice that have been trained in the orientation discrimination task. While significant differences exist across layers, such stimuli drive extremely sparse and unreliable responses in V1 such that the activity of no individual neuron is sufficient to decode the stimulus. Integrating information across neurons, however, quickly improved performance. Using a linear decoding model, we estimate that the animal integrates over ~100 neurons to perform the orientation discrimination task. We further find that for such short stimuli, prior training in an orientation discrimination task did not change the population requirements. Thus, visually guided behavior at the limits of perception relies on effective integration of information across units with sparse and unreliable responses to stimuli.

Disclosures: **B. Sriram:** A. Employment/Salary (full or part-time):; Biogen. **L. Li:** None. **A. Cruz-Martin:** None. **A. Ghosh:** A. Employment/Salary (full or part-time):; Biogen.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

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Program #/Poster #: 306.26/HH10

Topic: D.07. Vision

Support: European Research Council
DFG SFB 870

Title: Synaptic mechanism of orientation selectivity in layer 4 of mouse visual cortex

Authors: *Y. CHEN, T. SATO, B. SONG, A. KONNERTH
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Abstract: Classical work by Hubel and Wiesel has established that in several mammalian species, including cats and non-human primates, orientation selectivity of the primary visual cortex (V1) is determined by the specific arrangement of non-tuned thalamic lateral geniculate nucleus (LGN) inputs at the cortical entry stage in layer 4 (L4). Such inputs would produce non-tuned synaptic potentials at individual spines at dendrites of L4 neurons and contribute through various mechanisms to the eventually orientation selective output response. While evidence from different laboratories supports a similar model also for mouse V1, several studies revealed an orientation-tuned thalamo-cortical pathway, with axons projecting to multiple layers of V1, including L1 to L4. Thus, the synaptic and circuit mechanisms contributing to orientation selectivity in mouse V1 may be more complex than initially assumed. In the present study, we established methods for single spine imaging in L4 of mouse V1 involving the use of

genetically-encoded calcium indicators. We performed a two-step experiment to achieve sparse labeling of functionally defined V1 neurons. We first performed population imaging with a red-shifted synthetic indicator (Cal-590) and then delivered plasmids of GCaMP6s, GCaMP7b or GCaMP7s to selected individual neurons via targeted single-cell electroporation. This protocol allowed us to chronically monitor calcium signaling in spiny dendrites of such L4 neurons over several days. We found that GCaMP7b was best suited for imaging spines in deep cortical layers. By combining *in vivo* spine calcium imaging and electrophysiology, we determined the specific properties of visual stimulation-evoked synaptic signals as opposed to calcium signals evoked by back-propagating action potentials. Our results demonstrate that in orientation-tuned L4 neurons the vast majority (about 70 - 80%) of responsive single spine inputs were tuned to the same orientation as that of the neuron's output response. Only a small fraction of L4 spines (< 5%) showed non-tuned calcium transients, a property that is expected for a Hubel-Wiesel type synaptic mechanism. Thus, our results demonstrate that the by far dominating factor underlying orientation-selective action potential firing in mouse L4 neurons is the synaptic drive provided by tuned axonal inputs, which are likely to be arising from LGN. In conclusion, we elucidated the synaptic mechanism of orientation selectivity of L4 neurons in mouse V1. The results are not consistent with the Hubel and Wiesel model and suggest an additional, distinctly different mechanism of cortical orientation selectivity in the mammalian visual system.

Disclosures: Y. Chen: None. **T. Sato:** None. **B. Song:** None. **A. Konnerth:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

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Program #/Poster #: 306.27/HH11

Topic: D.07. Vision

Support: Wellcome Trust 205093
ERC 694401
Simons Foundation 325512

Title: Predicting excitatory-inhibitory dynamics in the corticothalamic network

Authors: *I.-C. LIN[1], M. OKUN[2], M. CARANDINI[1], K. D. HARRIS[1]
[1]Univ. Col. London, London, United Kingdom; [2]Dept. of Neuroscience, Psychology & Behaviour, Univ. of Leicester, Leicester, United Kingdom

Abstract: Although cortical circuits are highly complex, their global dynamics are often approximated by simple mean-field models involving interactions between the average activity of excitatory (E) and inhibitory (I) populations. How accurately can such models predict cortical dynamics? More generally, can such models treat a cortical region as an isolated system, or must

they include interactions with other brain regions such as the thalamus?
To address these questions, we used dichromatic optogenetics to independently stimulate pyramidal and parvalbumin-inhibitory neurons in the primary visual cortex (V1) of quietly awake mice, while using multisite silicon probes to record the dynamics of E and I populations in V1, and of neurons in the lateral geniculate nucleus (LGN).
Stimulating E neurons strongly but transiently activated first E then I neurons. This activation was followed by a prolonged suppression of both neural populations, and a recovery above baseline (rebound) >100 ms later. Similar events were observed when presenting brief visual flashes to awake mice. These events could not be explained by I activity alone: stimulating I neurons caused a shorter, less visible suppression of both populations without incurring a rebound.
These observations could be well captured by a mean-field model, but not a model of cortex alone. The classical Wilson-Cowan (1972) model was insufficient, as it failed to predict prolonged suppression. Adding a term for cortical slow GABAergic inhibition captured the effects of I but not E stimulation. We were able to account for the latter with a corticothalamic network model including both reticular inhibition and rebound bursting.
To investigate the role of thalamus in responses to optical stimulation on V1, we paired stimulation of cortical E and I neurons with LGN recordings. Stimulating cortical E neurons affected LGN neurons similarly to V1 neurons: initial activation, prolonged suppression, and a rebound. By contrast, stimulating cortical I neurons had only minimal effects. These findings are consistent with the behavior of the corticothalamic mean-field model.
To further validate the model, we tested its ability to predict responses to pairs of optical stimuli. We found that the corticothalamic mean-field model was able to account for responses to pairs of E and I stimuli, in either order, using a single set of parameters fit for each recording.
We conclude that cortical dynamics can be well approximated by mean-field models, but not by mean-field models of cortex alone.

Disclosures: I. Lin: None. **M. Okun:** None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.28/HH12

Topic: D.07. Vision

Support: Neuroscience Research Center, Shahid Beheshti University, M.C., Tehran, Iran.

Title: The effect of basal forebrain activation on the trial to trial variability of neuron’s subthreshold response in mice primary visual cortex (v1)

Authors: *P. GHADERI, S. ROSTAMI, M.-S. SAFARI
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Abstract: Literature and Purpose: Acetylcholine is released from neurons projecting to a broad range of cortical and subcortical sites. These projections can be split into two groups: the basal forebrain (BF) cholinergic system and the brainstem cholinergic systems. In this study, we have investigated the effect of BF stimulation on the subthreshold response variability of a single neuron in v1 area of the mice visual cortex. **Material and Method:** Whole-cell patch clamp recordings in the current clamp mode were obtained from neurons from the V1 of the mice visual cortex. Whole-cell current-clamp recordings were performed using the bridge mode (Manually Tuning series resistance and compensate capacitor) of an Axoclamp 200B amplifier. Electrical stimulation was delivered to the Nucleus Basalis of Meynert(NBM) in Basal Forebrain. A custom-made Matlab code was used to display drifting sine wave grating for 7 level of stimulus contrast at preferred orientation. Recording for each group war repeated 3 times. We investigated both the effect of sensory input and BF stimulation on Trial to Trial variability of subthreshold activity of neurons. **Result:** the experiment and our analysis were performed on 29 neurons. The overall average of trial to trial variability (n=29) is declined during visually evoked activity compared to spontaneous activity (Pvalue<0.05, paired t-test). And also it has been shown that this effect is not significant on different layers. We investigated the effect of visual input on trial to trial variability for a different level of contrast. There is a decrease in trial to trial variability in evoked activity in comparison to spontaneous activity for all level of contrast (Low, Medium and High Contrast).in addition, we investigated the effect of BF stimulation on trial to trial variability. It has been shown that BF stimulation decreases the Trial to Trial variability (pvalue<0.05, paired t-test). Ach effect on trial to trial variability was observed significant on the layer 2/3 but not significant for layer1. BF stimulation decrease trial to trial variability for all level of contrast but the effect was observed statistically significant in medium level of contrast (pvalue <0.05). **Conclusion:** in this study, we investigated the BF stimulation effect on the variability of subthreshold activity of neurons in mice V1. It has been shown that BF stimulation decreases the variability of neurons response, in other words, it made neurons response more reliable. Also, the visual input from LGN to V1 decreases the trial to trial variability of neurons response.

Disclosures: P. Ghaderi: None. **S. Rostami:** None. **M. Safari:** None.

Poster

306. Visual Cortex: Circuits and Populations I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 306.29/HH13

Topic: D.07. Vision

Support: Allen Institute Founders Paul G Allen and Jody Allen
NIH Grant R01NS092474
NIH Grant R01MH104227

Title: Cell-class-specific census of synapses in mouse visual cortex

Authors: *F. C. COLLMAN[1], M. M. NAUGLE[2], S. SESHAMANI[2], R. SERAFIN[2], O. GLIKO[2], J. SCHARDT[2], S. DAVIS[2], L. ELABBADY[2], H. ZENG[3], S. J. SMITH[2]
[2]Synapse Biol., [3]Structured Sci., [1]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Modern molecular neuroscience has described an increasing number of distinct neuron types, particularly in the visual cortex (Tasic B, et al., bioRxiv. doi.org/10.1101/229542), but a description of how these types interconnect is incomplete. Inventories of neuron-class-specific synaptic connections in transgenic mice offer the prospect of improved models of cortical synaptic network connectivity. Toward this end, we have developed methods for quantitatively characterizing the laminar distribution of synapses to and from Cre-driver-defined neuron classes using conjugate fluorescence/electron array tomography. Using manual annotation of 1023 EM identified synapses from Layer 4 and layer 2/3, we have trained a convolutional neural network (CNN) to identify synapses with at least 85% precision and 85% recall, using 803 EM identified synapses in layer 5 as a validation set. This CNN was then deployed to detect 1,192,731 synapses across all cortical layers of VISp cortex of a mouse derived from crossing a Rorb-Cre driver line into a TdTomato reporter line. Furthermore, synapses can be classified into 4 types based upon the transgenic TdTomato labelling of their pre and post-synaptic compartments. This allows us to systematically measure the density of synapses to, from and between transgenically defined neuronal subtypes. In addition, we can further subdivide synapses based upon analysis of their molecular composition using the multiplexed immunofluorescence labelling, including GABA, synapsin1, GAD2, VGluT1, PSD95, GluN1 and gephyrin. Repetition of these measurements will enable a census of synaptic types as a function of neocortical depth.

Disclosures: F.C. Collman: None. **M.M. Naugle:** None. **S. Seshamani:** None. **R. Serafin:** None. **O. Gliko:** None. **J. Schardt:** None. **S. Davis:** None. **L. Elabbady:** None. **H. Zeng:** None. **S.J. Smith:** None.

Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 307.01/HH14

Topic: D.07. Vision

Support: New Energy and Industrial Technology Development Organization(NEDO), Japan

Title: Does CNN explain the properties of the middle face patch area of primate?

Authors: *R. RAMAN, H. HOSOYA
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Abstract: In recent computational studies, convolutional neural networks (CNN) optimized for image classification have been found to be highly predictive of neural responses in the primate inferotemporal (IT) cortex. However, these predictions have been made in terms of linear regression of the responses of model units onto those of IT neurons, which leaves a potential computational gap between CNN and IT. One approach that can directly investigate similarity between these two in a unit-to-unit manner would be to compare their tuning properties. Since currently known tuning properties in IT are mostly concentrated on the face processing system, we study here the tuning properties of CNN's related to face stimuli in comparison to those of face-selective neurons.
Specifically, we took two state-of-the-art deep CNN's: VGG-face, trained on face images and Alexnet, trained on Imagenet. We chose two experimental protocols used in past physiological studies on the face-processing middle lateral (ML) area, namely, Freiwald et al. (2009) using cartoon faces stimuli with controllable facial feature parameters and Freiwald and Tsao (2010) using natural faces at various positions and sizes. While simulating these experiments on each CNN, we recorded the responses of the face-selective units in different layers and compared their tuning properties with the experimental data. As a result, we made the following observations consistently for both CNN's. First, across all the layers, the tunings were mostly ramp-shaped and their amplitude depended on the presence of a whole upright face, similar to physiological results. Second, though higher (fully connected) layers captured the position and size invariance properties similar to ML neurons, the units in these layers were typically tuned to higher feature dimensions, quantitively dissimilar to the reported lower feature dimensions (on average three). Third, contrary to the experimental results, which showed that the ML population mainly focused on a small number of features related to eye and facial geometry, these higher layers put nearly equal focus to almost all the features. Fourth, lower-middle layers had smaller tuning dimensions (similar to physiological results), but these layers failed to capture the invariance properties. Thus, we could find no layer which captured all the investigated response properties simultaneously. Taken together, these results indicate that the CNN's capture only partial properties of the ML and require a more comprehensive model to fully explain it.

Disclosures: R. Raman: None. **H. Hosoya:** None.

Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 307.02/HH15

Topic: D.07. Vision

Title: Perceptual and mnemonic mechanisms underlying the other-race effect

Authors: *J. YAROS, ESQ[1,2], D. A. SALAMA[2], B. A. MIRADA[2], M. S. LARSON[2], M. A. YASSA[2]
[1]UC Irvine, Irvine, CA; [2]Dept. of Neurobio. and Behavior, Univ. of California Irvine, Ctr. for the Neurobio. of Learning and Memory, Irvine, CA

Abstract: The Other-Race Effect (ORE) is a social phenomenon in which people are better at recognizing individuals within their own race, relative to other races. While behavioral research suggests the ORE is due to extensive experience with one's own race group, the neural mechanisms underlying the effect remain unclear. The locus of the ORE is subject to ongoing debate; Some believe the ORE is entirely dependent upon differential visual processing mechanisms for same and other-race faces. We show data consistent with the alternative view that both visual and memory processing mechanisms give rise to the effect. More specifically, in addition to visual representational differences, same-race (SR) and other-race (OR) recognition disparities may be dependent on differential mnemonic discrimination (MD) profiles. MD is the ability to discriminate among similar experiences to encode new events as distinct from familiar events. This process requires pattern separation - a neurocomputational process by which overlapping experiences are stored using distinct neural codes.
We therefore investigated the ORE using an MD task with computer-morphed faces, which afforded us a more nuanced picture of the phenomenon than standard recognition tasks have previously provided. MD tasks are similar to standard old/new face recognition paradigms, with the exception of the use of lure stimuli varying in similarity to previously presented stimuli. This gave us the opportunity to characterize recognition accuracy in terms of the ability to resolve interference between prior experiences and new experiences of faces.
Specifically, we found that face recognition performance is modulated by race and similarity (or interference) among stimuli. Subjects demonstrate enhanced recognition accuracy for SR over OR stimuli even when distractor faces were highly similar to the originals. In fact, SR recognition was significantly better than OR recognition at all but the lowest similarity level. Subjects only performed equally on SR and OR faces when morphed pairs were maximally distinct (50% morph). In contrast, no ORE was found in a match-to-sample (MTS) task using the same stimuli and parameters but without a mnemonic load. Taken together, our data identifies a critical component of the ORE that is mnemonic and not perceptual in nature.

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Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 307.03/HH16

Topic: D.07. Vision

Support: NIH Grant R01-EY014681

Title: Effect of familiarity on neural dynamics of face selective cells in monkey inferior temporal cortex during a demanding face discrimination task

Authors: *W. DANG, D. L. SHEINBERG
Brown Univ., Providence, RI

Abstract: It is well known that visual familiarity can profoundly impact human visual perceptual experience. Monkey studies similarly shown that neural responses can be systematically altered as a function of stimulus familiarity at multiple visual processing stages in neocortex, including the inferior temporal cortex (ITC). However, most previous non-human primate studies have used a passive viewing paradigm to probe these effects, so it remains unclear how neural signatures of familiarity affect behavior. Furthermore, most previous studies of long term familiarity have used visual stimuli taken from different categories, which are highly variable in terms of underlying image statistics. Little is known about how individual neurons respond to familiar exemplars vs. unfamiliar exemplars within a highly familiar, visually homogeneous, category. In the current study, we used computer generated realistic human face images as test stimuli. We trained a macaque monkey to discriminate familiar and novel faces from highly similar perturbations using a successive same-different task. During the task, we recorded single-unit responses from face selective cells in ITC. We found that 1) There is an asymmetry in animal performance: the discrimination accuracy is highest when the original familiar faces was shown as the sample, but lowest when a perturbed familiar faces was the sample. This suggests a possible attractor dynamic, wherein ITC cells may respond to stimuli close to familiar ones as they would to well-known exemplars; 2) Neural responses during the sample period, as well as behavioral performance, changed over several hundreds of trials, but the changes in neural response occur in different temporal epochs for familiar and novel stimuli sets; and 3) In contrast to previous reports of an overall suppression across all time epochs of neural response in the test period of a delayed match to sample test, we found small suppression in early epochs, and strong facilitation in late epochs of test period response. Together, these data deepen our understanding of how long- and short-term experience can affect high order visual processing in the brain and how these changes may affect behavior.

Disclosures: W. Dang: None. **D.L. Sheinberg:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Topic: D.07. Vision

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BIAL Grant 207/2016

Title: Human MT+ is sensitive to the dynamics of motion of a single dot representing or violating the biological motion of real human walkers

Authors: *J. V. DUARTE[1], B. ARAGÃO[2], J. A. SANTOS[2], M. CASTELO-BRANCO[1]
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Abstract: Perception of biological motion is important for daily life activities, such as non-verbal communication. Understanding how the visual system perceives biological motion, even from point-light displays depicting human activity, remains a neuroscientific challenge. The mechanisms that allow us to interpret biological motion from the local motion of individual dots, which is characteristic for the local motion of parts of living beings and can be defined as *life motion*, are largely unknown. The functional separation into distinct neural stages of the correlates of the perception of *life motion* from perception of global motion of a coherent body bearing multiple articulated joints remains to be achieved. We hypothesized that *life motion* processing can be separated, by using a single dot motion paradigm featuring the biomechanical details of local realistic motion of a single joint. Equipped with such a paradigm, we studied the neural correlates of *life motion* perception. Low level visual areas, such as the human hMT+ complex, are known to respond to simple and variable motion patterns. To investigate if this region also responds to biological motion paths that a given center of gravity undergoes through space, we manipulated the constraints imposed by gravity and inertial forces on acceleration/deceleration patterns of foot motion, by mapping realistic foot movement on a single dot motion stimulus. We therefore developed an event-related fMRI experiment to study the neural basis of *life motion* perception from a single moving dot embedding the kinematic properties of local feet motion that only contained local properties. We could isolate more low-level (*life motion*) aspects of biological motion processing from aspects related to social perception of animated shapes. We hypothesized that such local biological motion computation is achieved in hMT+ by assessing, using BOLD fMRI, the neural correlates underlying the decision the decision whether local instantaneous acceleration patterns were truly biological or

not. We found that hMT+ is sensitive to signals that encode *life motion* (local biological motion), which places this region in the initial biological motion processing network.

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Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 307.05/II1

Topic: D.07. Vision

Support: Intramural Research Program of the NIH (National Eye Institute/National Institute of Mental Health)

Title: Color responses of face cells in alert macaque monkey

Authors: I. ROSENTHAL[1], J. FULLER-DEETS[1], T. HAILE[1], S. C. EASTMAN[1], T. GRUEN[1], L. TELLO[1], *B. R. CONWAY[1,2]
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Abstract: Consistent with a role in face perception, face-selective cells in the temporal lobe are sensitive to luminance contrast in a face and are thought to be insensitive to color. But although color is not needed for face recognition, it is an important social signal, prompting us to ask: are face cells color tuned? We measured the responses to hue, saturation, and lightness of neurons in the middle face patch of three male macaque monkeys using fMRI-guided microelectrode recording. Responses were recorded to a set of monochromatic photographs of faces (38 images, monkey and human), body parts (17 images), and fruits (16 images). Stimuli were flashed in pseudorandom order on a computer monitor while animals maintained fixation for a juice reward. Each photograph was rendered in 16 hues evenly sampling the maximum gamut of DKL cone-opponent color space, in versions depicting normal luminance contrast and no luminance contrast (pure color). Responses were also measured to normal-contrast images rendered in 8 hues at 3 lightness levels, at intermediate saturation. Here we present results on the population of clearly isolated single units. Consistent with prior work, we found that most neurons were strongly face selective [$(R_{face}-R_{body})/(R_{face+}R_{body})$, = 0.36, STD = 0.13, R_{face}= mean face response, R_{body}= mean body response], and sensitive to lightness ($p<0.05$). But surprisingly, many face-selective neurons also showed broad color tuning [$(R_{best}-R_{worst})/ (R_{best}+R_{worst})$ = 0.34, STD= 0.22; R_{best} = mean response to best color; FWHM = 150°, STD = 108°). Moreover, when using face stimuli, the population showed a consistent color bias (1-way ANOVA, p= 0.02), towards the intermediate L+S color direction (47°; 95% CIs [13°, 90°]), appearing pink. Responses to non-

face stimuli were significant (>2.5*STD baseline) in most cells (86%) but showed no obvious color bias (mean=127°; CIs [21°, 321°]). The average response to faces using stimuli with luminance contrast (4.2*baseline spikes/s, SEM=1.2) was much stronger than the average response to faces defined by pure color (1.54*baseline spikes/s; SEM=.6; t-test, p=0.0001); and only a quarter of face cells showed color tuning that was tolerant (< 60°) to changes in saturation and lightness. These results show that color responses are substantially weaker for face cells than for cells in fMRI-identified color-biased regions of nearby cortex (Bohon et al, eNeuro, 2016), supporting the parallel-processing model of face and color (Lafer-Sousa and Conway, Nat. Neurosci., 2013). The subtle color bias of face cells suggests these cells encode a prior about the likely color of faces, which may hint at a role in color-dependent social signaling.

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Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 307.06/II2

Topic: D.07. Vision

Support: Intramural Research Program, NIMH

Title: Neural responses to internal versus contextual face information in two anterior face patches

Authors: *E. WAIDMANN[1], K. W. KOYANO[1], J. J. HONG[1], B. E. RUSS[2,1], D. A. LEOPOLD[1]
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Abstract: The fMRI-defined face patches of the macaque inferotemporal cortex contain neurons that respond preferentially to faces. Previous studies have investigated the tuning of neurons in several face patches to a range of internal facial features. Here we investigate the relative contribution to single-unit responses of internal and contextual aspects of face images in the anterior medial (AM) and anterior fundus (AF) face patches. We used a stimulus paradigm in which we swapped image parts to investigate the relative influence of internal facial features, the surrounding head and hair, the attached bodies, and realistic background scenes. Each test stimulus was a photorealistic composite image containing a combination of face and body parts excised from ten original full body images of individual macaques. The two subject monkeys viewed the briefly presented images during a passive task requiring strict fixation. We recorded local neural populations in areas AM and AF longitudinally across sessions using chronically-

implanted microwire bundles, whose electrode tips typically span < 1mm^3. Stimulus images were in four combinatorial categories: (1) inner faces, with upper and lower portions of the face exchanged, (2) heads, with internal and external facial features exchanged, (3) whole monkeys, with heads and bodies exchanged, and (4) scenes, with whole monkeys and backgrounds exchanged. All component image parts (e.g. upper face or uncombined external head alone) were also shown. We found that most neurons in the AM face patch were strongly modulated by either internal or external facial features, but not both. Nearly all AM neurons sensitive to internal features responded selectively to variations of the upper, but not the lower, face. By contrast, many AF neurons were sensitive to details of the outer head and hair, but not to inner facial features. A small subset of AF neurons were strongly modulated by variation in bodies. None of the neurons in either area were strongly modulated by background scene. In sum, while neurons in both AM and AF are face selective, our parts-swapping paradigm demonstrates separate neural populations specialized for internal and external facial features within AM, and a comparatively higher sensitivity for external facial features and body context in AF.

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Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

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Program #/Poster #: 307.07/II3

Topic: D.07. Vision

Support: Leverhulme Trust research grant (RPG-2014-392)

Title: Examining the content of neural representations of faces and voices: Which brain regions represent perceptual and social information?

Authors: *M. S. TSANTANI[1], N. KRIEGESKORTE[2], A. WILLIAMS[1], C. MCGETTIGAN[3], L. GARRIDO[1]
[1]Brunel Univ. London, Uxbridge, United Kingdom; [2]Zuckerman Mind Brain Behavior Institute, Columbia Univ., New York, NY; [3]Royal Holloway, Univ. of London, Egham, United Kingdom

Abstract: We perceive a wealth of information from faces and voices, such as whether we recognise, trust, and like them. Previous studies have shown a number of brain regions that respond more to faces (such as the FFA and OFA) or to voices (such as regions in STS/STG) compared to control visual or auditory stimuli. There are also a number of multimodal brain regions that respond to both faces and voices (such as the pSTS). However, there is limited information on the type of face and voice information that is represented in these different face-responsive, voice-responsive, and multimodal brain regions. Here, we aimed to shed light on

what is the *content* of the representations of faces and voices in these regions by (1) comparing neural representations with perceptual and social judgments of the same stimuli, and (2) comparing the similarity of neural representations across different brain regions. In an event-related fMRI study with 30 participants, we measured brain activity patterns while participants viewed the faces and listened to the voices of 12 famous people. We defined multimodal, face-, and voice-responsive brain regions with independent localisers. In a separate behavioural session, participants rated the same faces and voices on pairwise visual (for faces) and auditory (for voices) similarity, and on perceived trustworthiness, dominance, attractiveness, and positive-negative valence. We used representational similarity analysis (RSA) and computed neural representational distance matrices (RDMs) for each brain region and modality. These RDMs showed the pairwise neural discriminabilty between the faces or the voices of all 12 people. Our first analysis compared the neural RDMs for faces and voices with RDMs based on the behavioural judgments, separately for each participant and modality. Our results showed that the perceived visual similarity of faces was correlated with the neural discriminability of faces in the OFA, and the perceived auditory similarity of voices was correlated with the neural discriminability of voices in several regions along the STS/STG. No significant correlations were found between neural RDMs and behavioural RDMs for trustworthiness, dominance, attractiveness, and positive-negative valence. These findings suggest that the OFA represents perceptual characteristics of faces, and regions of the STS/STG represent perceptual characteristics of voices. We will also present results of the analysis correlating neural RDMs across different brain regions to assess the similarity of neural representations across difference face-responsive, voice-responsive, and multimodal regions.

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Poster

307. Vision: Representation of Faces and Bodies

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the New Energy and Industrial Technology Development Organization (NEDO)

Title: Receptive-field characteristics of neurons which temporally code global/fine information of faces in area TE

Authors: *K. HAYASHI, N. MATSUMOTO, K. MATSUDA, K. KAWANO, Y. SUGASE-MIYAMOTO
AIST, Tsukuba, Japan

Abstract: Face recognition ability is important for social interaction. In our previous studies, we have shown that face-responsive neurons in the temporal cortex of macaque monkeys represented information about a global category of stimuli, namely, human vs. monkey vs. shapes earlier than information about more detailed categories associated with facial expression and identity (Sugase et al., 1999; Sugase-Miyamoto et al., 2014). In this study, we further investigated the correlation between receptive-field characteristics of face-responsive neurons and the temporal processing stages. Neuronal activities were recorded in area TE of one rhesus monkey (*Macaca mulatta*) performing a fixation task. Test stimuli were colored pictures of monkey faces, human faces (three models with three expressions, respectively) and geometric shapes. The size of the stimuli was within 6° x 6°. To identify the receptive field of each neuron, a stimulus that evoked the strongest response was presented at one of 15 positions (in a 5 x 3 grid located in the center of the monitor, the size of each cell was 6° x 6°), while the monkey fixated a central fixation point. To determine the dependence of each neuron on the stimulus position, the responses to the stimulus at each position were averaged in a window 50-450 ms after the stimulus onset, and the baseline activity (the average response during 400 ms before the stimulus onset) was subtracted, and the responses were normalized. To visualize the dependence on the stimulus position across 25 face-responsive neurons, principal component analysis was applied on the normalized responses across 25 face-responsive neurons. It revealed that the receptive fields can be classified into three groups according to the scores for the first principal component: central visual field type (n = 12), wide field type (n = 7) and others (n = 6). Mutual information was calculated for the neuronal responses of each type when the test stimulus was presented at the center of the screen. The neurons of the central visual field type represented information about both the global category of the stimuli (monkey faces, human faces or shapes) and the more detailed facial category items (individuals and expressions). The neurons of the wide field type represented information about the global category. Together with our previous findings, these results suggest that the global information is rapidly processed by both the central and wide visual field types of face-responsive neurons, while the information about the facial identity and expression is relatively slowly processed by the central visual field type.

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Poster

307. Vision: Representation of Faces and Bodies

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Program #/Poster #: 307.09/II5

Topic: D.07. Vision

Support: NSF CAREER Award (BCS-1752921) awarded to B.A.K.

Title: Evaluating approaches for reconstructing face images from distributed patterns of fMRI activity

Authors: *M. L. DRASCHER[1], H. LEE[2], B. A. KUHL[1]
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Abstract: Reconstruction of visual stimuli from neural data has been a valuable tool for understanding how stimuli are represented in the brain, and further, how these representations both vary across cortical regions and change in response to task demands. Previous efforts to reconstruct stimuli from neural data have run the gamut from simple line gratings (e.g. Serences et al., 2009; Kamitani & Tong, 2005) to complex, dynamic stimuli such as movies (e.g. Nishimoto et al., 2011). Here, we consider reconstruction of face images—a stimulus class of particular interest because (a) faces can be readily dimensionalized and (b) humans are highly skilled at perceiving and remembering faces.

We have recently demonstrated that face images can be successfully reconstructed from human fMRI data utilizing an unsupervised approach in which face images are first dimensionalized using the Eigenface model and face dimensions are then mapped to fMRI activity patterns (Cowen, Chun, & Kuhl, 2014; Lee & Kuhl, 2016). More recently, Chang & Tsao (2017) achieved high-fidelity reconstructions of faces from electrophysiological recordings of macaque monkeys. They found that an alternative model for dimensionalizing face stimuli—the Active Appearance Model (AAM)—yielded significantly more accurate reconstructions than an Eigenface model. The AAM also has the added benefit of dissociating shape and non-shape dimensions of face stimuli, which allows for potential dissociation of face processing regions that code for shape vs. non-shape face features.

Here, we replicate and extend the findings of Chang & Tsao (2017) by applying a similar AAM-based reconstruction approach to human fMRI data. In the scanner, participants completed a continuous recognition memory task with 432 unique face images. Consistent with the findings by Chang and Tsao, we found reliable face reconstructions using the AAM approach and that this model performed better than the Eigenface model. Above-chance reconstructions were obtained from voxels widely distributed across visual cortical areas as well as from regions outside of visual cortex. Additionally, successful reconstructions were obtained both for the shape and non-shape dimensions of faces with partially distinct populations of voxels representing shape vs. non-shape dimensions.

Finally, we consider potential applications of AAM-based face reconstructions for measuring and characterizing the representations of stimuli in visual perception and memory.

Disclosures: M.L. Drascher: None. **H. Lee:** None. **B.A. Kuhl:** None.

Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 307.10/II6

Topic: D.07. Vision

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NIH Grant DP1HD091947 to N.K.
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Title: MEG decoding reveals early representations of face identity, age and gender that are enhanced by familiarity

Authors: *K. DOBS, L. ISIK, D. PANTAZIS, N. KANWISHER
MIT, Cambridge, MA

Abstract: From a brief glimpse of a face, we extract not just the presence of a person, but many different kinds of information about that person, such as their gender, age, familiarity and specific identity. Here we ask two questions. First, how quickly are these specific dimensions of face information extracted, and do some arise before others? Second, given the considerable evidence that familiar faces are processed differently than unfamiliar faces, which of these dimensions are affected by familiarity, and how early in processing do these effects occur?
To answer these questions, we used Magnetoencephalography (MEG) and representational similarity analysis (RSA) to measure the time course of extraction of each of these dimensions of face information and their modulation by familiarity. Subjects (n = 16) viewed 80 different face images (five images of each of 16 different celebrities), while monitoring for consecutive repetitions of identical images (one-back task). Each of the 80 images was presented 28 times upright and 28 times inverted in separate sessions (in counterbalanced order). Half the celebrities were familiar (US actors) versus unfamiliar (German actors), young (< 36 years) versus old (> 59 years), and female versus male.
RSA analyses showed that we could decode identity, gender and age of face images within 130 ms after stimulus onset, significantly later than image decoding (i.e. discriminating any pair of stimulus images; $p < 0.05$, peak analysis), which occurred ~100 ms after stimulus onset. To further exclude the contribution of low-level stimulus features, we computed correlations between representational dissimilarity matrices derived from candidate models (identity, gender and age) and MEG neural data, while partialing out the correlation between similarity patterns based on physical stimulus features (e.g. image pixels or early layers of a face deep neural network). All model correlations remained significant ($p < 0.05$, sign permutation test) suggesting that this decoding is unlikely to be accounted for by low-level image properties, a

conclusion further supported by the fact that decoding accuracy was significantly reduced by face inversion ($p < 0.05$, peak analysis). Importantly, familiarity significantly enhanced the decoding accuracy of all three face dimensions (age, gender, and identity), and did so at similar latencies for each dimension (~120 ms after stimulus onset).
Overall, our results indicate that different kinds of face information become available extremely rapidly, within 130 ms of stimulus onset, and that familiarity enhances representations of face dimensions already at this early stage.

Disclosures: K. Dobs: None. **L. Isik:** None. **D. Pantazis:** None. **N. Kanwisher:** None.

Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

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Program #/Poster #: 307.11/II7

Topic: D.07. Vision

Support: NIH T32 EB008389-07
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NIH P41 EB015894

Title: Selectivity for individual body parts within body selective visual cortex

Authors: *A. BRATCH[1], L. VIZIOLI[2], E. YACOUB[2], S. A. ENGEL[1], P. C. BURTON[3], D. J. KERSTEN[1]
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Abstract: Spatially localized patches of cortex containing neurons selective for specific features are a major characteristic of sensory cortices. Such organization has been well demonstrated for simple visual features in primary visual cortex (e.g., orientation, ocular dominance, etc.) using electrophysiology in primates. In recent years, ultra-high field (7T) fMRI has afforded the ability to investigate these organizational principles non-invasively in humans. While these methods have revealed the same organization in primary visual cortex, it remains unclear the extent to which similar organization is present for higher level visual features represented in later visual areas. Here, we tested for the spatial organization of responses to images of individual body parts in the extrastriate body area (EBA), a cortical region that responds selectively to images containing the human body (Downing et al., 2001). Using 7 Tesla fMRI with a gradient echo pulse sequence (0.8 mm isotropic resolution, TR = 2.2 s, TE = 26.4 ms, 84 slices, iPat = 3, multiband = 2), we measured neural activity in 3 human subjects. Subjects viewed images of 5 different body parts (hands, arms, feet, legs, and torsos) in a blocked design. Functional localizers for object, motion, and body selective cortex were run in separate scans. We found that

the right EBA is actually comprised of three areas surrounding motion selective area MT, replicating the results of Weiner and Grill-Spector (2011). We then implemented a winner-take-all procedure, based on the response amplitude to each body part on a voxel-by-voxel basis, to create voxel preference maps. Cross validation on an independent portion of the data was used to assess the consistency of these maps and to establish tuning curves for each subject. Statistical significance was inferred using 95% bootstrap CIs. In all 3 subjects, this analysis revealed patches of voxels in the left and right EBA showing reliable tuning for all 5 individual body parts, with the strongest tuning found in patches selective for hands and torsos. These data not only reveal a distinct organization of body selective visual cortex but demonstrate spatial organization of high level visual features in human visual cortex. Furthermore, this work provides the foundation for assessing whether these patches are arranged topographically and whether they extend uniformly through cortex.

Disclosures: A. Bratch: None. **L. Vizioli:** None. **E. Yacoub:** None. **S.A. Engel:** None. **P.C. Burton:** None. **D.J. Kersten:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Program #/Poster #: 307.12/II8

Topic: D.07. Vision

Support: Simons foundation
NIH
HHMI

Title: Face coding in the macaque perirhinal face patch

Authors: *L. SHE, D. Y. TSAO
Caltech, Pasadena, CA

Abstract: Face-selective regions in inferior temporal cortex encode the identity of visually perceived faces, but how this code interfaces with memory remains unclear: how is a new face remembered, and how is this memory re-activated during perception? To address this, we recorded in a face patch located in perirhinal cortex, a region that has been strongly implicated in processes related to visual memory. We used fMRI to locate the perirhinal face patch (PR). Single-unit recordings targeted to this region revealed a high concentration of face-selective cells. Measurement of responses to human faces, monkey faces, and objects, at different views and levels of familiarity (personally familiar, pictorially familiar, and unfamiliar), revealed that most cells were view tolerant and modulated by both identity and familiarity. Measurement of responses of each cell to thousands of human and monkey faces revealed that many cells inherit

the previously described “axis code” of IT face patches (Chang and Tsao, Cell 2017). A subset of these were also modulated by familiarity, and some cells were even ‘grandmother cell’-like, responding only to a few faces, often personally familiar. In addition, we found that PR cells are strongly modulated by scene context, often showing a nonlinear interaction between face and context. Together these results suggest that PR cells implement a critical stage in the process of face memory storage and retrieval.

Disclosures: L. She: None. **D.Y. Tsao:** None.

Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: D.07. Vision

Support: German Research Foundation (DFG TH425/12-2)

Title: Reflexive gaze following in common marmoset monkeys

Authors: *S. SPADACENTA, P. DICKE, P. THIER
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Abstract: The ability to follow the gaze of a conspecific to an object of interest to the other allows human observers to shift the attention to the same object, i.e. to establish joint attention. The observer may develop a concept of the other's desires, beliefs and intentions, in short a theory of mind (ToM), by attributing his own assessment of the object significance to the other. Although old world monkeys such as macaques may lack a full-fledged ToM, they are able to deploy gaze following and joint attention, essential social skills, orchestrated by a generic gaze following network with a central node in the superior temporal sulcus, likely shared with humans. The common marmoset is a highly social species of new world monkey which separated from the old world line about 30 million years ago. Casual observations indicate that marmosets are interested in the other´s face and that they may follow the gaze. Yet, it has been unclear if they establish joint attention, which features of the other one may be relevant for gaze following and joint attention and if the underlying brain circuitry is similar and eventually homologous to those of old world primates. As a first step to address these and related questions we embarked on quantitative behavioral experiments deployed in a well controlled experimental environment. We trained 3 marmosets to voluntarily enter a monkey chair and accept immobilizing their heads by permanently implanted head holders to measure eye movements using video eye tracking. Our animals were then studied in a free choice task. This started with the presentation of a central dot which had to be fixated for 500 msec. If fixation was acquired, at the end of the 500 msec a portrait of a marmoset face looking either to the left or the right

appeared in the center of the screen. After a viewing time of 100 to 600 ms, varied at random from trial to trial, during which the animal was allowed to freely explore the portrait, the face disappeared while at the same time two peripheral targets popped up. The monkey was rewarded with a small amount of marshmallow or fruit juice if it executed a saccade to either one of the two targets within 500 ms. Both choices were equally rewarded, independently of facial orientation. We found that when the face viewing time was 200, 300, 400 or 500 ms the animal's choice was significantly biased towards the target congruent with the face´s orientation, while staying at chance level for the shortest and the longest times. Our results clearly show that marmosets follow the gaze of conspecifics in a reflex-like manner, very similar to old world primates, supporting the hypothesis of a phylogenetically old faculty shared by both old and new world primates.

Disclosures: S. Spadacenta: None. **P. Dicke:** None. **P. Thier:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Topic: D.07. Vision

Support: CAS Pioneer Hundred Talents Program
CAS grant (XDB02050001)
NSFC grant (No. 31322025)
NSFC grant (No. 31540078)

Title: Investigating fine-scale functional diversity in face-processing network with 7T MRI and correlation-based clustering analysis

Authors: *J. ZHANG[1], Y. WANG[1], S. HE[1,2]
[1]Inst. of Biophysics, Chinese Acad. of Sci., Beijing, China; [2]Univ. of Minnesota, Minneapolis, MN

Abstract: Many functional magnetic resonance imaging (fMRI) studies revealed the existence of face-processing areas with strong selective responses to faces. However, it is difficult to address the functional diversity within these areas by only investigating their sensitivity to different visual features. Here we used dynamic visual stimuli and data driven analysis to explore this issue. In particular, movies depicting various natural and social activities were presented to human participants while they were scanned in 7T and 3T MRI scanner to obtain the time courses of neural activity in face-processing areas (7T) and through the whole brain (3T). Correlation maps between voxels in face areas and in other brain regions were calculated based on the neural activities driven by the same movies. Then principal components analysis and

clustering algorithm was applied to such maps for separating face-selective voxels into different clusters. Results showed multiple clusters in the right fusiform face area and occipital face area and each cluster demonstrated different strength of correlation to the brain regions outside the face-selective regions. Our data indicate the feasibility of using dynamic visual stimuli to examine the fine-scale functional diversity across voxels in a visual processing network. The multiple clusters of voxel within face selective region suggest that they have different visual feature sensitivities and warrant further investigation in future studies.

Disclosures: J. Zhang: None. **Y. Wang:** None. **S. He:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Program #/Poster #: 307.15/II11

Topic: D.07. Vision

Support: CAS grant (XDB02050001)
NSFC grant (No. 31322025)
NSFC grant (No. 31540078)

Title: The top-down processing of faces in occipital-temporal cortex

Authors: *X. FAN[1], H. SHAO[1], F. WANG[1], S. HE[1,2]
[1]Inst. of Biophysics, Chinese Acad. of Sci., Beijing City, China; [2]Departments of Psychology, Univ. of Minnesota, Minneapolis, MN

Abstract: The processing of face information involves a distributed network of face-sensitive areas in the occipitotemporal cortex and beyond. Both hierarchical and non-hierarchical models have been proposed to understand the neural mechanisms of face perception. To explore the temporal dynamics of bottom-up processing and top-down modulation of face processing, we analyzed the activation timing of the face-selective areas in "core face processing system" using fMRI and Magnetoencephalograpy (MEG).Subjects were presented with various pictures including normal faces and two-tone Mooney faces (containing little facial features) while MEG signals were recorded. From the MEG sensor data, we reconstructed the cortical responses to faces using the beamforming approach; and in conjunction with information from fMRI localizer, we extracted the time courses of face-selective areas in each individual subjects. First, the feedforward processing sequence along ventral occipitotemporal cortex was revealed in their responses to normal face pictures. The top-down operation in face processing was highlighted in their responses to the two-tone Mooney faces. Our results showed that when processing Mooney faces for which top-down modulation is critical, the right Occipital Face Area (rOFA) was activated later than both hemispheres' posterior Fusiform Face Area (pFFA) and the direction of

information flow is from pFFA to rOFA. Together, these findings indicate that both bottom-up and top-down processing are involved in the occipital-temporal face network and the processing sequence in the rOFA and r/lpFFA depends on the stimuli and task demand.

Disclosures: X. Fan: None. **H. Shao:** None. **F. Wang:** None. **S. He:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Program #/Poster #: 307.16/II12

Topic: D.07. Vision

Support: NIH R01 EY25670
NIH R01 EY16187

Title: Effects of experience on face and body selective neurons in macaque IT

Authors: *P. F. SCHADE, M. J. ARCARO, M. S. LIVINGSTONE
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Abstract: The primate visual system is a hierarchically structured network of increasingly abstract feature detectors. It culminates with cells in inferotemporal cortex (IT) that are selective for particular image categories, such as faces, bodies, text, and places. Recent work in our lab has shown that the domain organization of IT is malleable by early experience. Here, we report that face and body-selective neurons in lab-raised non-human primates are often selective for human faces or bodies wearing personal protective equipment (PPE; e.g. face masks, lab coats). We targeted face and body domains and recorded single unit and multiunit activity in posterior and central IT while macaques passively viewed thousands of different images. We found clusters of cells and sites that were selective for human faces and/or bodies wearing PPE. These clusters were intermixed with cells that were selective for monkey faces and bodies. Our results emphasize the importance of experience in molding the selectivity of IT neurons.

Disclosures: P.F. Schade: None. **M.J. Arcaro:** None. **M.S. Livingstone:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Topic: D.07. Vision

Support: FWO Vlaanderen

Title: Effect of electrical microstimulation of the anterior Superior Temporal Sulcus body patch on visual categorization tasks

Authors: *S. KUMAR, E. MERGAN, R. VOGELS
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Abstract: fMRI studies in primates show patches in the temporal cortex that are more strongly activated by images of bodies compared to other visual categories (objects and faces). Single unit studies in macaques have shown that in at least two of these fMRI defined body patches neurons respond on average stronger to bodies, including bodies of humans, monkeys, and other four-legged mammals, compared to images of objects and faces (Popivanov et al., J.Neurosci., 2014; Kumar et al., Cerebral Cortex, 2017). The body patch spiking activity contains sufficient information to categorize bodies vs. objects (including faces). Here we examine the contribution to categorization behavior of the anterior Superior Temporal Sulcus body patch, ASB, which is located rostrally in the lower bank of the Superior Temporal Sulcus (Kumar et al., Cerebral Cortex, 2017). In a first experiment, we trained two monkeys to categorize a broad set of images of four-legged mammals versus images of objects (excluding houses), with each category being associated with a saccadic choice target and using saccades as operants. Images were shown centrally (maximum image extent 4 deg) and were partially occluded by white noise at various signal to noise ratios. In both animals, unilateral electrical microstimulation (EM; 150 uA) of ASB increased the overall proportion of mammal target responses without affecting the slope of the psychometric function. In one monkey, EM did not affect body categorization at another location (1mm further but still inside ASB), which may suggest a heterogeneity of ASB in its contribution to body categorization behavior. Both monkeys were tested on faces vs. objects categorization where faces were paired with the same choice target as for the mammals. EM of ASB increased also the overall proportion of face choices. To dissociate face from mammal targets and evaluate the stimulus selectivity of EM, we associated each of 4 categories, i.e., mammals, human faces, objects, and houses, with each of 4 saccadic choice targets. EM (50 uA) during the performance of this 4-alternative categorization task affected mammal and house category choices but not faces and objects. In one monkey, EM increased mammal choices, while in the second animal, the opposite effect was present. In each animal, this effect of EM was absent in a site of the STS that was not body category selective (3-5 mm away from ASB stimulation site). Subsequent pairwise testing of the mammal category with objects also showed increased or decreased mammal target choices, depending on the monkey, with EM of ASB. These data suggest that low current EM of a body patch affects choice biases during categorization of complex visual images.

Disclosures: S. Kumar: None. **E. Mergan:** None. **R. Vogels:** None.

Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

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Program #/Poster #: 307.18/II14

Topic: D.07. Vision

Support: HHMI

Title: Binocular rivalry in macaque without active report

Authors: *J. K. HESSE, D. Y. TSAO
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Abstract: When two incongruent stimuli are presented to the two eyes, the conscious percept alternates between the two stimuli, even though the physical input stays constant. This paradigm, also known as binocular rivalry, offers an entry point to study how switches between conscious interpretations of ambiguous stimuli are represented and broadcasted across the brain. Logothetis et al. (e.g. 1989) measured for different brain regions how much neural activity was modulated by reported switching. However, Fraessle et al. (2014) found that during active report, modulation by conscious percept is confounded with the act of reporting and introspection itself, and that when active report is stopped, modulation vanishes in most parts of the human brain. We thus set out to identify a brain region with broad connectivity whose activity reflects perceptual switching that could be used to "trigger" analysis of neural activity across the brain during binocular rivalry without any active report. We performed multi-channel population recordings from a number of areas including the amygdala, claustrum, and face and body patches in inferotemporal and prefrontal cortex, while monkeys fixated: (1) a perceptually switching binocular rivalry stimulus, (2) an unambiguous non-switching monocular stimulus, or (3) a physically switching stimulus. We analyzed time courses and correlations of simultaneously recorded neurons across these areas as well as pupil data to determine how activity is coordinated in these regions, in an effort to understand the extent to which population dynamics during the rivalry condition resembles that during the physically switching condition.

Disclosures: J.K. Hesse: None. **D.Y. Tsao:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Topic: D.07. Vision

Support: NIH R01DC014701

Title: A framework of robust sensory processing

Authors: *R. RAJ, D. DAHLEN, K. DUYCK, C. YU
Yu Lab., Stowers Inst. for Med. Res., Kansas City, MO

Abstract: Brain is remarkably effective in creating consistent internal representations of perceptual objects present around us. These representations allow for recognition and discrimination of stimuli and are formed even in situations when input is corrupted or incomplete. It has been theorized that, to construct such consistent representations, brain should be able to extract statistical dependencies present in the stimulus space. However, the elemental rules that may guide brain to extract these dependencies remain unclear and how consistent perceptual experiences arise from incomplete input is unknown.We reason that individual objects are independent sources of perceptual experience whereas individual features that define an object are mutually dependent. Following this rationale, we developed a computational framework that captures the structural dependence among the stimuli features, which allows individual objects to be encoded as sparse, statistically independent representations. The framework, which relies on sparse, non-negative matrix blind source separation, is effective in extracting various linear and non-linear dependencies present in the stimulus space. Moreover, we introduce a novel decoding process that is similar to sparse recovery. When the two elements of the framework are used together, the coding scheme allows for robust sparse representations of stimuli that are resistant to corruption due to noise and occlusion. We show that in the mouse olfactory system, it is possible to recover odor identity accurately and robustly from the responses of small numbers of randomly selected olfactory glomeruli, and in the presence of high levels of noise. We also show that when used in facial recognition, faces that are learned in a single shot can be precisely identified even when corrupted or occluded. We suggest that framework can be used to understand how the nervous system may employ a robust neural code.

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Poster

307. Vision: Representation of Faces and Bodies

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Program #/Poster #: 307.20/II16

Topic: D.07. Vision

Support: NIH Grant MH107797

Title: The representation of orientation and identity in human ventral face processing areas as measured by intracranial electroencephalography

Authors: *A. ALREJA[1], M. J. WARD[2], M. RICHARDSON[2], A. S. GHUMAN[2]
[1]Ctr. for Neural Cognition, Carnegie Mellon Univ., Pittsburgh, PA; [2]Neurolog. Surgery, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Faces can be recognized across a remarkable degree of transformations, including viewpoint, which greatly shifts the position and orientation of facial features. Primate electrophysiology studies provide evidence that identity and facial orientation representations evolve along a three level hierarchy across the monkey face patch system. These levels proceed from viewpoint dependence at the lowest level, mirror-symmetry at the mid-level, and viewpoint invariance at the highest levels. In the human brain, face identity processing is thought to involve a distributed network of several brain areas including the occipital face area (OFA) and fusiform face area (FFA). FMRI studies in humans have begun to shed light as to how the levels of face viewpoint coding are reflected in the human face processing system, however many questions still remain.

To help resolve these questions, we recorded intracranial electroencephalography (iEEG) data from 13 patients with a combined total of 43 electrodes in the OFA andor FFA. The stimulus set is composed of 40 unique identities (20 male + 20 female), each with 5 different emotional expressions, presented either straight, facing away (left or right) 90 degrees, or facing tilted (right or left) 45 degrees. Using nearest centroid classifiers, we can reliably predict face orientation in 11 out of the 13 patients. Evidence for mirror symmetric coding (confusion between left and right facing away faces and significant classification between straight, away, and tilted in a 3-way classifier) was seen in 6 out of 13 patients. Significant identity classification was seen when all orientations are present in trainingtest data in all 13 subjects. However, when a viewpoint was left out of the training sample for the classifier identity classification fell to chance for that viewpoint, suggesting the identity code was viewpoint dependent.

These results suggest that the OFA and FFA code for both viewpoint and identity, however the identity representation was viewpoint dependent despite some broad mirror generalization for faces. Further analyses will examine how these effects spatially distribute across these face processing areas and how they evolve over time.

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Poster

307. Vision: Representation of Faces and Bodies

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Program #/Poster #: 307.21/II17

Topic: D.07. Vision

Support: NIMH IRP

Title: Whole-brain fMRI analysis of face-selective neurons in cortex and thalamus

Authors: *S. PARK[1], K. W. KOYANO[1], B. E. RUSS[1,2], A. P. MURPHY[1], R. A. BERMAN[1], D. A. LEOPOLD[1,3]
[1]SCNI, Lab. of Neuropsychology, NIMH, NIH, Bethesda, MD; [2]Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY; [3]Neurophysiol. Imaging Facility, NIMH / NINDS / NEI, NIH, Bethesda, MD

Abstract: Face-selective neurons are found clustered in the macaque temporal cortex, forming multiple isolated "patches." Recently we compared spiking responses within the anterior fundus (AF) patch to fMRI signals throughout the brain in monkeys viewing natural video stimuli. We found diverse correlation maps from neurons occupying a few hundred microns, indicating that neighboring neurons bear markedly different relationships to activity throughout the whole brain (Park et al., 2017). Here, we extended this whole-brain mapping method to the middle lateral (ML) and anterior medial (AM) face patches, as well as the thalamic pulvinar, to gain new insights into the functional differences among face-selective neurons in the different regions. Whole-brain fMRI responses were measured separately in two rhesus macaque monkeys, and electrophysiological recording of single neurons in the ML, AF, and AM face patches and the pulvinar were conducted in seven other monkeys viewing the same video. For all isolated neurons, we created single-unit fMRI maps by computing the Spearman's rank correlation coefficients between the spiking time course, convolved with the hemodynamic response function, and the fMRI time course of each voxel throughout the brain. Among the three face patches, we found partially overlapping populations of neurons, as characterized and categorized by their fMRI correlation maps. One common motif in all three areas was a selective and positive correlation restricted to the face patches, with the proportion of such neurons varying across recordings in ML, AF, and AM. Other categories of whole-brain maps were observed in only a subset of face patches. For example, positive correlation with caudal STS motion areas was prominent in AF but entirely absent in ML and AM. On the other hand, neurons in ML and AM, but not AF, exhibited positive correlation with foveal region of V1 and V2. Initial analysis of pulvinar neurons indicate significantly less consistency across trials during video watching and less robust whole-brain correlations. In summary, we found a dense, local mixture of

complex neural responses to the video, as well as a sharing of similar responses across distant regions in the face network. Together, these results present a new perspective on cortical pathways carrying visual information in the face patch system, posing challenges for theories of brain organization that hinge on strict spatial segregation.

Disclosures: S. Park: None. **K.W. Koyano:** None. **B.E. Russ:** None. **A.P. Murphy:** None. **R.A. Berman:** None. **D.A. Leopold:** None.

Poster

307. Vision: Representation of Faces and Bodies

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Program #/Poster #: 307.22/II18

Topic: D.07. Vision

Support: NSERC Discovery Grant RGPIN-2017-04088

Title: What is the contribution of faces to the representations of animate and inanimate objects in the ventral temporal cortex?

Authors: *D. PROKLOVA[1], M. A. GOODALE[2]
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Abstract: Animate and inanimate objects elicit distinct response patterns in the human ventral temporal cortex (VTC), but the exact features driving this distinction are still being investigated. In a recent fMRI study, we showed that the animate/inanimate distinction in VTC was still present even after controlling for visual (shape) similarity of the stimuli. Another prominent feature that distinguishes most familiar animals from inanimate objects and that could potentially explain the animate-inanimate distinction in the VTC is the presence of a face. In the current fMRI study we investigated the role of faces in the animate/inanimate distinction of VTC representations. To address this question, we created a stimulus set that consisted of eighteen unique stimuli, divided into six subsets of three stimuli. Within each subset, all three objects shared a similar shape, with one inanimate and two animate objects per set (e.g, rope-snake-worm). Critically, the two animals within each shape subset were selected so that one of them had a distinct face and the other did not. This stimulus selection was confirmed in a separate behavioral experiment, in which participants rated the degree to which a given animal is perceived as having a face (e.g., a snake received significantly higher “faceness” ratings than a worm). To test whether the presence of a face can explain the animate-inanimate distinction in the VTC, we estimated the response patterns to all stimuli within this region and computed pairwise pattern correlations between them. We found that within-category pattern similarity was significantly higher than between-category similarity, consistent with the animate-inanimate

distinction. Interestingly, this was true even after all the animals with faces were removed from the analysis, showing that even the animals without a distinct face are represented differently than inanimate objects in the VTC. Furthermore, the results stayed the same even when the analysis was restricted only to stimuli from the same shape cluster, suggesting that animate/inanimate distinction is still present in VTC even for stimuli that are closely matched for shape, both for animals with or without a distinct face. These results suggest that the presence of a face is not a defining feature driving the distinction between representations of animate and inanimate objects in the ventral temporal cortex.

Disclosures: D. Proklova: None. **M.A. Goodale:** None.

Poster

307. Vision: Representation of Faces and Bodies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 307.23/JJ1

Topic: D.07. Vision

Support: NSF CAREER BCS 1151805
UC San Diego Academic Senate Award

Title: Predictive coding account of action perception: Evidence from effective connectivity

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Abstract: Visual perception of actions is supported by a network of regions in the occipito-temporal, parietal, and premotor cortex in the primate brain, known as the Action Observation Network (AON). Although significant progress has been made in understanding the neural correlates of action perception, one open question is how the nodes of this network communicate. According to the predictive coding account of action perception (Kilner et al. 2007), this network is not a purely feedforward system but rather has feedback connections through which prediction error signals are communicated between the regions of the AON. In the present study, we investigated the effective connectivity of the AON in an experimental setting where the human subjects' predictions about the observed agent were violated (via a mismatch between appearance and motion), using fMRI and Dynamical Causal Modeling (DCM). We specifically examined the influence of the lowest and highest nodes in the AON hierarchy (pSTS and ventral premotor cortex, respectively), over the middle node (inferior parietal lobe) during prediction violation. To this end, we constructed three specific models that differ in the connection that is modulated by the mismatch condition: 1) connection from pSTS to parietal cortex, 2) connection from the premotor cortex to the parietal cortex, and 3) both connections. In

all models, parietal node has reciprocal intrinsic connections with pSTS and premotor cortex, and action information modulates all intrinsic connections. Our results show that the most likely model that explains data is one in which the connection from premotor cortex to parietal cortex was modulated by mismatch, which indicates a top-down influence. Examination of the parameter estimates of the optimal model shows that all of the intrinsic connections were significant, confirming the well-known anatomy between these regions. In addition, all of the intrinsic connections were modulated significantly by the observation of actions suggesting that action-related information is processed via both feedforward and feedback connections in the AON. In sum, our DCM results provide empirical support for the predictive coding account of action perception.

Disclosures: A.P. Saygin: None. **B.A. Urgen:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.01/JJ2

Topic: E.04. Voluntary Movements

Support: JSPS Postdoctoral Research Fellow 29.2601
JSPS Research Grant 80815358

Title: Not movement duration but movement velocity is altered by implicit adaptation to movement-amplitude perturbation in self-paced reaching task

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Abstract: When reaching for a cup of coffee, the motor system must determine a movement time and trajectory from an infinite number of repertoires. For instance, you can make a reaching movement towards an explicit target (e.g., a cup) with low velocity and long duration or with high velocity and short duration. This indicates that movement velocity (MV) and movement duration (MD) are redundant parameters, which would be determined by optimizing several cost functions (Haith et al., J Neurosci, 2012; Shadmehr et al., Curr Biol, 2016). Similarly, when a movement amplitude is altered by implicit motor adaptation, the motor system needs to solve the redundancy. Previous studies have just focused on how movement amplitude is altered to minimize a sensory prediction error (Krakauer et al., J Neurosci, 2000; Pearson et al., J Neurophysiol, 2010), while It is still unknown whether the motor system operates the same optimization during identical movements generated by implicit motor adaptation and directed towards an explicit target. To clarify it, in this explement, we investigated how the redundant parameters, namely MV and MD, are altered during implicit motor adaptation as those aiming an

explicit target. Eight participants made self-paced reaching movements while holding a manipulandum to land a cursor on a target on the screen. The cursor was not visible during a movement, but only the final position was fed back. Consistent with the previous studies (Gordon et al., Exp Brain Res, 1994a, b), both of the MV and MD were systematically altered when the explicit target extents were varied from 6 to 14 cm. Then, while reaching towards the target located at 10 cm, the participants adapted to cursor shifting perturbations in which the cursor was gradually shifted up or down to 3 cm. Statistical analyses revealed that the participants implicitly but successfully altered their movement amplitude to approximately 7 or 13 cm. Surprisingly, although the MV was correspondingly altered with changes in the movement amplitude, the MD remained unchanged. The result illustrated that the resultant of MV and MD altered by implicit motor adaptation were clearly different from those directed towards explicit target extent, suggesting that the motor system may solve the redundancy for MV and MD differently between implicit motor adaptation and explicit movement control.

Disclosures: T. Hayashi: None. **K. Takiyama:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.02/JJ3

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI JP16H06566

Title: Different eye-hand coordination forms distinct motor memories in visuomotor adaptation

Authors: *N. ABEKAWA, H. GOMI
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Abstract: Recent theories of motor control emphasize the role of behavioral context in learning multiple motor skills that could interfere with each other. Human can simultaneously adapt two opposing novel environments (e.g. CW or CCW force-filed) when each environment is associated with distinct reaching movements. More recent study (Sheahan et al. Neuron, 2016) further suggested that motor planning rather than execution is crucial for such context-dependent learning. Meanwhile, it is still unclear whether the hand-eye coordination can be used as a context for distinct motor learning while gaze direction relative to the reaching target is crucial information in reaching planning. Here, we examine whether distinct motor memories can be formed and retrieved depending on different coordination between gaze and hand movement. Participants (n=6) moved hand on a digitizing tablet, and the hand position was presented by a cursor on a monitor. They moved the cursor toward a reaching target while looking at a fixation point. For each trial, locations of the target and the fixation point were independently selected

from three possible locations. Nine possible combinations of the reaching targets and the fixation points were categorized into two types of reaching: foveal-reaching and peripheral-reaching. Visuomotor rotation was applied to the hand cursor, and its rotation angle gradually increased from 0 to 30 deg throughout the training session (40 blocks of 12 trials). Importantly, the direction of rotation (CW or CCW) was randomly selected trial by trial, but uniquely specified by foveal or peripheral reaching. The result showed clear decrease in the initial direction error of reaching in each rotation. When the rotation was removed after the training, we observed strong aftereffect in the direction opposite of each rotation corresponding to the foveal and peripheral-reaching. Error-decrease and aftereffects did not differ between both rotations, indicating that two opposing rotations can be simultaneously adapted with less interference. In control experiments, the direction of rotation was associated with blue or red background color (n=6), or with visual cue presented in the foveal or peripheral field (n=6), instead of with gaze-reach coordination. In both groups, clear direction error decrease was not observed. These results suggest that, unlike weak association with external visual information such as color or spatial cue, distinct motor memory would be clearly formed and retrieved associated with the state of eye-hand coordination.

Disclosures: N. Abekawa: None. **H. Gomi:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.03/JJ4

Topic: E.04. Voluntary Movements

Support: Grant-in-Aid for Young Scientists(B)(16K16429)
Tateisi Science and Technology Foundation

Title: Effect of offline transcranial alternating current stimulation at alpha and beta frequencies on visuomotor learning task

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Abstract: The number of studies on transcranial alternating current stimulation (tACS) has been growing exponentially. The behavioral effects of tACS have been related to the entrainment of ongoing oscillatory neural activity by stimulation frequency, and such interaction between an externally applied stimulation and brain oscillations has been shown to manipulate brain functions by promoting neural activity to resonate at the stimulation frequency. In particular, online tACS has been reported to be associated with the modulation of motor learning and

memory. However, there have been few reports on the effect of offline tACS on the modulation of motor learning. The aim of the present study was thus to investigate the effect of offline tACS targeted at motor-cortical alpha (10 Hz) and beta (20 Hz) frequencies on the acquisition of motor learning. Twenty-seven right-handed healthy participants were randomly assigned to 10-Hz tACS (n = 10), 20-Hz tACS (n = 9), and sham (n = 8) groups. The participants underwent a visuomotor learning task before (baseline task,BT) and after (training task,TT) tACS. Each visuomotor learning task consisted of 40 blocks. In each block, five targets were randomly presented and the subjects controlled a lever-type controller to reach the target with the cursor (center-out reaching task). In the TT, 30° clockwise or counterclockwise transformation was applied to evaluate the effect of tACS on the modulation of motor learning. The angular transformation was counterbalanced in each group. tACS was delivered by a DC stimulator plus (NeuroConn) via a sponge electrode (5 × 7 cm). tACS at 10 and 20 Hz containing sham stimulation was performed between the BT and the TT over the left primary motor cortex for 10 min at 1 mA. The average angular error in each block of 10 in the TT was defined as the learning index. The average angular errors were compared between the groups using ANOVA. The results showed a significant difference in angular error in the initial average block (block 1-10) ($F = 5.20$, $p < 0.05$). Post hoc analysis showed that the average angular error in the 10-Hz tACS group was significantly smaller than that in the sham and 20-Hz tACS groups (sham vs. 10 Hz, $p < 0.05$; 10 Hz vs. 20 Hz, $p < 0.05$). The present study demonstrates the effect of offline 10-Hz tACS over M1 on the acquisition of motor learning. Previous studies have shown that motor learning was improved by applying 10-Hz offline tACS. Additionally, the aftereffect of 10-Hz tACS has been shown to persist for at least 30 min in the alpha band. Thus, our results support these previous studies. Therefore, offline tACS can be a useful conditioning tool for the brain before rehabilitation for various diseases.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.04/JJ5

Topic: E.04. Voluntary Movements

Title: The effects of subjective value for meta-learning in visuomotor transformation

Authors: *T. SUGIYAMA[1], N. SCHWEIGHOFER[3], J. IZAWA[2]
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Abstract: The rate of motor learning is often altered by various types of information such as statistics of the environment (Herzfeld, 2014) and motivational feedback (Galea, 2015). In theory, an ultimate goal of motor learning is to maximize future performance by updating motor memory after observing sensory prediction error. Thus, modulation of memory update, which is manifestied as an altered learning rate, may follow reinforcement learning because its goal is indeed maximizing performance. If memory update at a certain step is expected to improve performance (e.g., amount of reward) at the next step, the brain should upregulate sensitivity to prediction error (i.e., learning rate) to facilitate future learning. In contrast, if memory update degrades performance, the brain should suppress the learning rate. Thus, it is beneficial to optimize the rate of learning proactively by forming a subjective value of the rate of memory update and evaluating it. Here, we hypothesize that there is a meta-learning architecture in human motor learning that optimizes the learning rate for different reward structures. To test this hypothesis, we have devised a novel visuomotor meta-learning task that involves a gain/loss of numerical score (i.e., reward/punishment). In the task, people have to adjust their adaptation rate to maximize performance because a better performance is achieved with more adaptation in one condition and less in another condition. The results confirm our hypothesis, showing that the participants successfully adjust learning rate in such a way that increases the performance (repeated measure-ANOVA, the effect of group, $p = .01$). This suggests that neither the statistics of the environment or the motivational feedback but the trial-to-trial structure of reward is the fundamental cause of the learning rate modulation. In addition, a post hoc analysis on the later phase of learning reveals a marginally significant effect of the valence (type of numerical score feedback) that sensitivity is higher when training is accompanied by loss of score than gain (two-way ANOVA, $p = .07$). Interestingly, this trend is opposite to the one found in motivational decision-making task (e.g., Go/Nogo task), where taking action is easier to learn with gain than loss (Dolan, 2012). We speculate that the decision-making task involves the cortico-basal circuit that is sensitive to rewarding information, whereas motor adaptation involves the cerebellar circuit that is sensitive to aversive information.

Disclosures: T. Sugiyama: None. **N. Schweighofer:** None. **J. Izawa:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.05/JJ6

Topic: E.04. Voluntary Movements

Support: NSERC RGPIN 238338 Discovery Grant

Title: Select changes in the fast and slow adaptive processes based on learning context

Authors: *S. K. COLTMAN[1], J. G. CASHABACK[2], P. L. GRIBBLE[3]
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Abstract: By analysing properties of movement errors, we aim to uncover underlying mechanisms of motor adaptation such as learning and retention. Short-term motor adaptation is believed to be supported by two separate processes, each with distinct timescales that operate simultaneously. Characteristically, the fast process learns quickly, but has poor retention; while the slow process has better retention but learns more slowly. We tested the hypothesis that repetition of the same motor task influences properties of the fast and slow processes (fast & slow learning rates and retention rates) differently than when switching to a novel motor learning task. Healthy adult participants grasped the handle of a robotic manipulandum and performed reaches to virtual visual targets while the hand/arm were occluded. Participants completed one of two experiments, each of which was divided into two sessions, separated by a 5 minute break. In the first session participants adapted their reaches to a viscous (velocity-dependent) force field (FF). In the second session participants reached in the same FF as the first session (Experiment 1, n=54) or in the opposite FF (Experiment 2, n=46). The experimental sequence was null field (no force) trials, FF adaptation, FF reversal, and finally a series of channel trials. During FF adaptation we probed learning using randomly interspersed channel trials in which the path of the robot handle was constrained to a straight line. In Experiment 1, in which participants experienced repetition of the same perturbation, we found an increase in learning rate both in the fast and slow processes that resulted in savings. In Experiment 2, in which participants experienced a novel perturbation in the second session, we observed a statistically reliable difference in the fast process retention parameter. Given that the sequence of trials within a session included a brief FF reversal, the FF in session 2 was not completely novel and this difference could reflect spontaneous recovery. Our work suggests that the well-known phenomena of savings and spontaneous recovery can be linked to select changes in the two-state model. Further demonstrating that the underlying mechanisms of short-term motor adaptation are not fixed, but malleable based on learning context.

Disclosures: S.K. Coltman: None. **J.G. Cashaback:** None. **P.L. Gribble:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.06/JJ7

Topic: E.04. Voluntary Movements

Title: Adaptation and de novo learning can be distinguished by the presence of aftereffects: A system identification approach

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Abstract: It has been proposed that new motor tasks can be learned through two different mechanisms (Telgen et al., 2014): 1) Adaptation: parametric adjustment of an existing controller, or 2) De novo learning: building a new controller from scratch. Although the difference between these two types of learning is conceptually clear, it can be difficult to determine which learning mechanism is engaged to counter an imposed perturbation. We propose that the existence of aftereffects provides a means of dissociating the two learning mechanisms. De novo learning results in the formation of a new controller, and when the perturbation is removed, one may expect quick reinstatement of the baseline controller (i.e., zero or transient aftereffect). On the other hand, adaptation to a perturbation results in modifying one's baseline controller, thus removing a perturbation results in the slow restoration of this controller to its baseline state (i.e., persistent aftereffect). Here, we tested whether different perturbations might be solved through different learning mechanisms and thus might exhibit different patterns of aftereffects. Human participants made point-to-point movements under one of two perturbations: 1) 90 degree visuomotor rotation (presumably learned through adaptation) 2) mirror reversal about an oblique 45 degree axis (presumably learned through de novo learning). In order to precisely examine participants' ability to counter the perturbation at different points during learning, including possible aftereffects, we employed a system identification approach: Periodically during learning, participants were asked to track a target moving along a sum-of-sinusoids trajectory. Assaying the strength, direction, and timing of the tracking responses at different frequencies allowed us to comprehensively characterize each participants' controller. We found that compensation was more successful at low frequencies of target motion than high frequencies, likely due to greater influence of feedback control. Across all frequencies, however, participants in the rotation group exhibited strong aftereffects while mirror-reversal subjects did not, consistent with our hypothesis that these two perturbations are learned through distinct mechanisms.

Disclosures: N.J. Cowan: None. **A. Haith:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.07/JJ8

Topic: E.04. Voluntary Movements

Title: The influences of a switching cue on aftereffects in visuomotor adaptation

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Abstract: The present study investigated the influences of a switching cue on aftereffects in visuomotor rotation task by multiple measurements. Previous studies have used aftereffects as a measure reflecting the degree of acquisition of a new internal model; if aftereffects are observed in a catch trial, one is regarded to successfully adapt a new visuomotor environment. Considering our daily activities where we retain multiple internal models at the same time and voluntarily switch them for an upcoming situation, aftereffects may reflect not only the achievement of acquisition but also switching efficiency. To address this question, we measured aftereffects multiple times in the time course of visuomotor adaptation with or without a switching cue. In the experiment, participants carried out a visuomotor rotation task, in which they continuously followed a randomly moving dot with a mouse cursor as accurately as possible. In adaptation trials, visual feedback of the mouse cursor was rotated by 150 degrees. We manipulated the measurement times as an independent variable; in the time course of the adaptation task, catch trials were introduced four times with or without a switching cue. A two-way ANOVA found main effects of group and phase in the tracking error and the initial directional error. The aftereffects in the group without a switching cue were consistently larger than those in the group with the cue. Aftereffects in the group with a switching cue turned to decrease from the 3rd evaluation. These results suggest that aftereffects with a switching cue would be a good indicator for an explicit strategy for visuomotor rotation tasks.

Disclosures: Y. Itaguchi: None. **C. Yamada:** None. **K. Fukuzawa:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.08/KK1

Topic: E.04. Voluntary Movements

Support: NINDS R01NS084948

Title: Distinct effects of motor adaptation and proprioceptive recalibration in visual error clamp tasks

Authors: *E. POH, J. A. TAYLOR
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Abstract: The idea that we predict the consequences of our motor commands has emerged as an important theoretical concept for accurate motor control. When an initial motor command is

generated but the observed sensory feedback does not match the predicted sensory consequences, the next movement will be updated to reduce the occurrence of similar errors. This prediction error is thought to be the dominant signal driving learning during visuomotor adaptation tasks and is responsible for the presence of aftereffects. However, some studies have shown that aftereffects can also arise when the hand is passively moved and there is a mismatch between the visual feedback and hand location. Because passive movements should not produce prediction errors and, thus, not updated a forward model, these results have been attributed to proprioceptive recalibration. Indeed, separate tests of perceived hand location have shown a systematic shift in the direction of the mismatched visual feedback. This presents a complication for the prediction error account since aftereffects may be largely attributed to a shift in state estimation rather than an updated forward model. A potential counterargument could be that passive movements still generate prediction errors reflexively and, perhaps, both processes are occurring. Here, we set out to test if aftereffects are primarily driven by sensory prediction errors or proprioceptive recalibration. In three experiments, subjects performed either active or passive movements toward a training target, while visual feedback was fixed in a direction angled 15° away. In this visual error clamp task, significant aftereffects emerge through passive movements. The size of aftereffects was similar irrespective of whether the target was present or absent, suggesting that the aftereffects could not have emerge from prediction errors due to latent motor commands that are reflexively generated when a target is presented. In a second study, we showed that linking conflicting visual error clamps to active and passive movements allows concurrent adaptation in opposing directions. This suggests different mechanisms for aftereffects that emerge from active and passive training. In the third study, we quantify the degree of proprioceptive recalibration in both passive and active error clamps task. Preliminary results show significant proprioceptive recalibration for active movements in the error clamp task, suggesting that a portion of the aftereffects might be derive from the change in localization of the hand. Taken together these results underscore the multiplicity of processes that contribute to learning and aftereffects in visuomotor adaptation tasks.

Disclosures: E. Poh: None. **J.A. Taylor:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

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Program #/Poster #: 308.09/KK2

Topic: E.04. Voluntary Movements

Support: Hong Kong Research Grants Council, GRF 17407914

Title: Transfer of implicit and explicit learning components of sensorimotor adaptation

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Abstract: Sensorimotor adaptation can involve two types of learning: implicit learning driven by sensory prediction error that accumulates slowly, and explicit learning driven by target error that can occur quickly. In this study, we tested how implicit and explicit components of learning transfer across tasks, and the specificity of transfer. Experiment 1 tested adaptation and transfer between pointing and stepping toward a target, using virtual reality to perturb visual feedback. Experiments 2 and 3 tested transfer between these tasks and a novel hand locomotion task, in which subjects used pointing movement to simulate self-motion. The hand locomotion task used the same physical movement as pointing, but performed the same function as stepping. During an experimental block, subjects performed adaptation trials with perturbed feedback and interspersing test trials with no feedback. The test trials were either the same task to measure adaptation, or a different task to measure transfer. Perturbations on adaptation trials varied over time as a sum of sinusoids with different frequencies. Fast explicit learning would be expected to produce equal responses to these components, while slower implicit learning would dampen the higher frequency component. Subjects were not aware of the smoothly varying perturbations, but showed detectable adaptation for all three tasks. Only pointing produced significantly different responses to high and low frequency components, consistent with slow implicit learning. Pointing adaptation produced more transfer to hand locomotion, which shared the same effector and physical movement, than to stepping. The other tasks showed little or no implicit learning, and equal transfer to tasks with different effector or function. Our results suggest that the slower implicit components of sensorimotor adaptation are more movement specific, while explicit learning is more generalizable.

Disclosures: X. Xing: None. **J. Saunders:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

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Program #/Poster #: 308.10/KK3

Topic: E.04. Voluntary Movements

Support: NSF Grant 1553895

Title: Handedness influences how limb motion is used to compensate for arbitrary dynamical perturbations

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Abstract: Previous work (Sing et al. 2013) has shown that adaptive responses to non-motion dependent perturbations during reaching movements are based on limb motion state (e.g., position, velocity, and acceleration of the limb). Additionally, prior work suggests handedness reflects a differentiation of control processes focused on either limb dynamics or position (Sainburg 2005). Here, based on these previous studies, we examined single-trial adaptive responses to non-motion dependent dynamics (force-pulse perturbations, FP). We trained two groups of subjects (right-handed and left-handed individuals, N=14 in both groups) to perform 10 cm point-to-point reaching arm movements using a robotic manipulandum. All subjects performed two experimental sessions (counterbalanced across subjects), one limb on the first day, and the other on day two. Following an initial baseline block, subjects completed 15 experimental blocks with the FP perturbation (18N in magnitude). We randomized (1) the movement direction the FP was applied (towards or away from the body), (2) the FP direction (right or left), and (3) when the FP was applied (either 2, 5 or 8 cm into the movement). We used an error clamp triplet (EC-FP-EC) to determine the single trial response and 5 null-field trials to washout the learning. The single-trial adaptation was well-characterized by a linear combination of the velocity, position, and acceleration profiles associated with movement (R^2>0.9). For the 2 cm perturbation, for both subject groups, the adaptive responses were more velocity dependent and there was no significant difference between the dominant and nondominant limb (P>0.64). However, when the FP was applied later in the movement (8 cm), the adaptive responses were more position dependent (greater position gain) with no significant difference between the two limbs (P>0.6). When the perturbation was applied in the center of the movement (5 cm) the motion state dependence was significantly different based on handedness (P<0.013); left-handed subjects applied greater position gain in the adaptive response, while right-handed subjects applied a greater velocity gain. These results suggest that subjects adjust the motion state the FP perturbations are associated with based on when the manipulation occurs (early versus late). However, when the perturbation is arbitrary, handedness significantly influences the motion state emphasized in the adaptive response.

Disclosures: W. Zhou: None. **M. Dickerson:** None. **C. Dennis:** None. **S. Kelly:** None. **W.M. Joiner:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.11/KK4

Topic: E.04. Voluntary Movements

Title: M1 beta oscillation control over learning rates in sensorimotor adaptation

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Abstract: When there is a divergence between expected and actual sensory outcomes of a movement, people readily adapt their subsequent movements to these prediction errors. Predominant computational models have presumed adaptation rates are error-size invariant. This has led studies of neural mechanisms underlying sensorimotor learning to focus mainly on encoding of prediction errors. However, recent evidence from human and animal models suggests that adaptation rates are flexible and depend both on the error size and history. This raises the question of whether there are distinguishable neural markers for prediction errors versus adaptation rates. Our previous work has demonstrated EEG oscillatory frequencies occurring in the motor (M1), somatosensory, and medial prefrontal cortex may encode prediction-error signals and learning rates at different task stages (Fine et al., 2017). Motor cortex beta (15-30 Hz) rebounds occurring post-movement (PMBR) could potentially be a neural marker of prediction error as they tend to increase as motor error decreases. However, extant results are mixed, suggesting PMBR may respond to errors independent of learning rate, or may index inhibition of an action. To address this gap, we ran two experiments on 27 subjects to examine whether M1 PMBR is solely related to error size independent of learning, or whether its relation to error size is also modulated by the history of errors. Both studies required subjects to produce fast planar reaching movements to a target 10 cm ahead. Adaptation was examined by perturbing reaches with a force field on random trials. In Experiment 1, we examined the relation of PMBR to error history by clamping the error to zero on 50% of trials before a perturbation trial. This manipulation revealed that (1) error sizes were the same for a given force-field size across trial sets with or without preceding clamps, and (2) that adaptation rates were lower when preceded by a clamp trial compared to trials without a clamp. EEG source analysis revealed that M1 PMBR magnitude was sensitive to this manipulation, with PMBR being lowest for large errors without a leading clamp trial. This result suggests that the M1 PMBR indexed changes in adaptation rate. We further tested the relation of PMBR to adaptation rate in Experiment 2 by using the same behavioral paradigm while applying 5 pulses of 20 Hz (beta) rhythmic transcranial magnetic stimulation (rhTMS) over M1 after movement cessation. During rhTMS trials, we found ~12% decrease in learning rate. These findings offer the first causal evidence that M1 PMBR is directly involved in scaling learning rates in short-term sensorimotor adaptation.

Disclosures: J.M. Fine: None. **K. Uehara:** None. **M. Santello:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.12/KK5

Topic: E.04. Voluntary Movements

Support: UT Health San Antonio 2017 School of Health Professions Seed Grant

Title: Task practice intensity estimation in individuals with traumatic brain injury

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Abstract: Traumatic Brain Injury (TBI) is one the leading causes of mortality and morbidity in the United States. Individuals sustaining a TBI often have motor impairments involving the lower (LL) and upper limbs (UL), with lower levels of improvement seen in the UL compared to the LL. These factors may continue to limit UL involvement in performance of functional activities of daily living, well after cessation of rehabilitation. UL motor improvement after a TBI is attributable in part to adaptive neuroplasticity and motor learning, with the intensity of task-practice representing a key influence. Intensity of task-practice has many definitions, including the time spent in therapy and the number of repetitions employed in a single session. There is a growing consensus that the numbers of repetitions used in a session may be the better choice. The minimum number of repetitions per session of therapy for optimal levels of UL motor improvement in people with TBI is currently unknown. One potential solution, used previously in individuals who sustained a stroke, is to estimate the number of repetitions necessary to achieve a plateau in the performance of a motor task (pointing to a target) using kinematic analysis. Our study objective was to estimate the minimal number of repetitions to achieve an asymptote in a UL pointing task in individuals with TBI. We recruited TBI patients with UL hemiparesis along with age-matched controls. The TBI group was further sub-divided into participants having mild and moderate severity of injuries (based upon 12-hour post-injury Glasgow Coma Scale scores). Both groups of participants were seated. They pointed repeatedly to a target placed in front of them at a distance equal to their UL length. We aligned the target to their sternal notch and placed it at a height of 90° of shoulder flexion. The trial duration was 3-5 seconds and recording frequency was 100 Hz. The primary outcome was the number of trials necessary to achieve an asymptote in the endpoint error during pointing movements. The root mean squared error between the endpoint position and the center of the target at the end of the movement quantified the endpoint error. Secondary outcomes included movement speed and ranges of motion of UL joints (elbow, shoulder) and trunk. Preliminary results indicate that compared to controls, individuals with TBI needed more trials to reach an asymptote in the performance of the pointing movement. In addition, the TBI group had slower movements and used less shoulder horizontal adduction range of motion. Results of this study will help in providing information on the minimal number of repetitions necessary to achieve optimal UL motor improvement in individuals with TBI.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.13/KK6

Topic: E.04. Voluntary Movements

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Title: Short-term structural change in fractional anisotropy correlates rapid performance improvement

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Abstract: Researches on human brain imaging during skill acquisition have revealed structural changes in task-relevant areas. A recent study demonstrated that short-term changes were detected after only 2 h of training, pointing to a rapid timescale of structural plasticity (Sagi et al., 2012). Another study (Wenger et al., 2017) proposed expansion-renormalization model that explains the process of human brain plasticity detected by MRI. According to the expansion-renormalization model, learning-related neural processes often follow a sequence of expansion, selection, and renormalization of neurobiological candidates (e.g., neurons, synapses, astrocytes, and glia cells). However, how such process drives the subsequent behavioral improvement remains unknown. In the current study, we shed light on the short-term (i.e., hour-to-day) plasticity that would reflect the expansion processes and investigated the relationships between short-term plasticity and subsequent motor learning with a longitudinal study.
Fifteen healthy, right-handed participants performed an upper-arm reaching task under left-right mirror-reversal for 5 consecutive days, using KINARM Exoskeleton lab (BKIN Technologies, Canada). To investigate the process of motor learning (i.e., learning speed and final error level), endpoint errors of the participants during the training period (i.e., 1-5 days) were fitted with a

simple exponential function. Participants were scanned with diffusion tensor imaging, an MRI framework which is sensitive to tissue microstructure, before, after the first and fifth days, and 1 week and 1 month after training. Track-based spatial statistics was used to conduct a voxel-wise analysis of fractional anisotropy (FA). In left primary sensorimotor area (SM1), we set region of interest where gray matter increase occurred in the first day of training detected by voxel-based morphometry, which had previously been reported. The ratio of FA decrease after the first day of training in the region of interest was correlated with learning speed of endpoint error ($r = 0.604$, $p < 0.05$ (FDR)), and learning rate from day 1 to day 2 ($r = 0.657$, $p < 0.05$ (FDR)). Considering that FA quantifies the directional dependence of water diffusion and depends on features such as axonal integrity, myelination, axon diameter and density, it is reasonable to assume that FA decreases occurred due to expansion process of Wenger's model (e.g., dendritic branching and axon sprouting). These results suggest that the experience-dependent short-term plasticity drives the subsequent motor learning rapidly.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.14/KK7

Topic: E.04. Voluntary Movements

Support: Viterbi Graduate School Fellowship

Title: Gradual and abrupt virtual surgeries elicit two different muscle activation adaptation strategies

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Abstract: Individuals post-stroke often exhibit "abnormal synergies", pathological patterns of upper limb muscle co-activation that lead to a compromised ability to perform daily life activities. Reducing abnormal muscle co-activation via a myoelectric computer interface has been shown to be feasible for a small set of muscles using arbitrary muscle-to-cursor mappings (Wright et al. 2013). Our long-term goal is to investigate whether abnormal synergies can be reduced by gradually normalizing the activity of multiple muscles via "virtual surgeries". A virtual surgery is a type of unintuitive myocontrol task in which participants control the position of a cursor on a screen using EMG signals collected from multiple upper limb muscles while isometrically producing forces at the wrist (Berger et al. 2013). Here, we investigated how non-

disabled participants learn a virtual surgery task that mimics the abnormal synergies observed post-stroke. Because such surgeries generate low controllability for some directions, and are consequently hard to learn (Berger et al. 2013), we compared learning virtual surgeries abruptly to gradually. In addition, we investigated whether learning such a task exhibits savings following a washed-out task. During the baseline phase of the myocontrol task, the mapping from EMG signals to cursor position corresponds to the direction and magnitude of the forces generated at the wrist on the horizontal plane. Afterwards the virtual surgery is introduced: the mapping is modified, and participants must learn to complete the task under the new mapping. We quantified task performance as the error in cursor initial direction. Preliminary results show that subjects learned how to decrease initial angular error to baseline levels, and exhibited similar levels of washout in the two conditions. We analyzed EMG patterns during the learning, washout, and re-learning phases using methods developed by Golub et al. (2018) and found that while abrupt surgery leads to rescaling of baseline EMG activity, gradual surgeries lead to re-association. Our results suggest that gradual virtual surgery training could be effectively applied in a post-stroke rehabilitation protocol comprised of multiple short bouts of training.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.15/KK8

Topic: E.04. Voluntary Movements

Support: Ramanujan Fellowship

Title: Interlimb transfer of newly learned motor skills

Authors: *G. YADAV, P. MUTHA
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Abstract: Motor learning is beneficial when it transfers to unpracticed conditions. Transfer of learning within and across limbs has been widely investigated in motor adaptation, where people learn to modify motor output while moving under novel conditions. However, whether and how learning of new motor skills, in which subjects overcome performance-limiting relationships, and which is presumably mediated by distinct neural mechanisms, transfers across limbs has not been well studied. We investigated interlimb transfer of newly acquired motor skills in order to understand whether such transfer has features similar to motor adaptation. 58 healthy right-handed individuals learned a new motor task in which they were required to accurately move their hand to one of 8 randomly presented targets within 550 msec. Subjects were divided into

two groups: 1) RL, who practiced with the right arm first followed by the left arm, and 2) LR, who practiced in the reverse order. We assessed transfer by comparing naïve performance of an arm with its performance after the other arm had undergone learning (e.g., the right arm of the RL and LR groups was compared). Based on these findings, we recruited two more groups who practiced the same task, except that they moved only to 1 target instead of 8. We found significant interlimb transfer in both the 8-target and the 1-target cases. Further, unlike adaptation, this transfer was symmetric, i.e. occurred from the left to the right arm and vice-versa. Additionally, we found that in the 8-target condition, subjects learned the new skill consistently faster with their left arm compared to the right. We hypothesized that this might be due to a previously suggested left arm-right hemisphere advantage for control of actions under variable task environment. We confirmed this using the 1-target condition; when task variability was removed by using single target, subjects learned at the same rate with the two arms. In line with prior suggestions, the current study demonstrates a left arm-right hemisphere advantage for motor control under variable task conditions which enables the left arm to learn faster than the right arm. Our study also reveals, perhaps for the first time, that learning a new motor skill in different task conditions can transfer to the untrained arm; and this can have implications for rehabilitation. Such transfer could occur because learning leads to neuroplastic changes in both the hemispheres; or because the untrained arm/hemisphere system has access to neuroplastic changes that occur only in the trained hemisphere. Future studies could help disambiguate these possibilities.

Disclosures: G. Yadav: None. **P. Mutha:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

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Program #/Poster #: 308.16/KK9

Topic: E.04. Voluntary Movements

Title: Functional coupling between the basal ganglia and cerebellum during visuomotor adaptation learning

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Abstract: Converging evidence suggests that sensorimotor learning can be decomposed into multiple distinct mechanisms; an implicit process, driven by sensory prediction errors, and an explicit process, driven by a deliberate, strategic process. Work in cerebellar ataxic patients and neurophysiological recording studies heavily implicate the cerebellum in implicit, error-based adaptation, with recent evidence of direct functional connections between the cerebellum and

basal ganglia providing a possible source for the error signals used by the cerebellum during such adaptation. Here, using functional MRI, we examined functional connectivity between the cerebellum (CB), basal ganglia (BG), and cortical motor structures in 34 subjects during the learning and subsequent re-learning of a visuomotor rotation task on two separate days. We found increased coupling between the CB and BG coinciding with the onset of visuomotor rotation learning, which was gradually reduced throughout learning in subjects who exhibited rapid adaptation to the rotation (rapid learners), but which was relatively sustained in subjects who only managed to reduce their errors gradually (slow learners). Further, a subset of slow learners, who displayed rapid learning during the second session, exhibited network profiles remarkably similar to the fast learning subjects during the first session. This suggests that the initial recruitment and timecourse dissolution of a CB-BG subnetwork is linked to individual differences in rates of learning and relearning, and that such subnetwork integration reflects reliance on implicit learning processes.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

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Program #/Poster #: 308.17/KK10

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI 16J04573

Title: Muscle-based perturbation using electrical stimulation revealed sensorimotor coordination in multiple muscles during motor adaptation

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Abstract: Human sensorimotor system can flexibly modify motor commands to relevant muscles in order to adapt movements to a novel condition resulting from usage of new tool, fatigue, or injury. A lot of researchers have tried to investigate the characteristics of the sensorimotor adaptation using experiments in which the interaction between internal and external states in the motor system was modified with novel force fields or visuomotor rotation during reaching movements (Shadmehr et al., 1994; Krakauer et al. 2000). However, the sensorimotor coordination in multiple muscles during the adaptation has not been fully elucidated. To approach to this problem, in the present study, we proposed the adaptation paradigm to the alteration of the mechanical output in a single muscle; we built the system for inducing fatigue to

a target muscle using high-frequency electrical muscle stimulation (EMS). Participants sat in a chair and held a handle attached to six-axis force transducer by their right hand. A cursor was displayed in a screen located in front of their body, the xy-coordinates of which represented the vectors of horizontal isometric force, F_x and F_y, produced against the handle. The experimental session consisted of baseline and EMS blocks. In the baseline block, the subjects were instructed to move the cursor from a start position to one of the 8 equally placed targets by 45° as straight as possible and maintain the cursor position at the target for 1.5 seconds. The magnitude of force was determined based on the force during maximal voluntary isometric contraction (MVC). In the EMS blocks, a triceps brachii muscle (TrBrac) was electrically stimulated through surface electrodes. Trains of rectangular, balanced, biphasic and asymmetric pulses were applied at fixed frequency (80 Hz), fixed duration (1 msec), and the amplitude was adjusted to produce approximately 20 % level of MVC at the beginning of the EMS trial. The continuous high-frequency EMS rapidly reduced the force induced by the EMS up to 2 minutes (Bigland-Ritchie et al. 1979). To measure the learning response, we randomly interleaved the cursor-clamp trials, with which the trajectory of the cursor was constrained to a straight path from the start position to the target. After the EMS to TrBrac, the produced force was deviated to the lateral direction from the straight path to the target, which was opposite to the force direction produced by TrBrac stimulation. However, the participants rapidly reduced the errors to adapt to the change of the dynamics in the motor system due to muscle fatigue. The EMS for muscle-based perturbation enabled us to unravel the sensorimotor coordination in multiple muscles during the adaptation.

Disclosures: S. Hagio: None. **D. Nozaki:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

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Title: Age-related decline in motor cortical GABA promotes retention of sensorimotor adaptation

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Abstract: Sensorimotor cortex mediates the early consolidation of motor memories. Using a prism adaptation task, we have shown that individual differences in retention are causally related to the neurochemical balance of excitation/inhibition (GABA/Glutamate) in sensorimotor cortex. In young adults, lower levels of GABA are associated with greater retention. Here we investigated whether this relationship between sensorimotor cortex neurochemistry and retention is preserved with age. We predicted that: 1) individuals with lower GABA would show greater retention; 2) individuals with higher GABA concentration would be more responsive to brain stimulation that lowers GABA—resulting in increased retention. We recruited 32 men (mean age of 67.5 years, SD = 8.1). To test prediction 1, participants underwent magnetic resonance spectroscopy (MRS) and a single session of prism adaptation. Participants adapted to a 10-degree rightward optical shift. Retention of the leftward prism after-effect was assessed after 10 minutes and 24 hours. MRS data quantified the concentration of GABA and Glutamate/Glutamine (Glx) in sensorimotor cortex (2 cm^3 isotropic VOI) and occipital cortex (control). To test prediction 2, participants underwent two further sessions of prism adaptation, combined with real or sham anodal transcranial direct current stimulation (TDCS; 1mA, 20minutes, 7 x 5 cm electrodes) of sensorimotor cortex. Prediction 1 was confirmed. Participants adapted to prisms and showed short (10 minutes) (t = -11.2, p<.001) and long-term retention (24 hours) (t = -2.70, p < .01). We observed three inter-related correlations: 1) older individuals showed greater long-term retention (r = -.50, p <.05); 2) older individuals had lower GABA levels in sensorimotor cortex (r = -.52, p = 0.012); 3) individuals with lower GABA levels in sensorimotor cortex showed greater 24-hour retention (r = .73, p < 0.001). We performed mediation analysis: GABA concentration explained the relationship between age and retention (66% variance). Prediction 2 was confirmed. At the group mean level, there was no significant overall increase in retention with anodal stimulation compared to sham. However, across individuals, higher basal GABA levels correlated with stimulation-increased long-term retention (anodal>sham; r = .52, p < .05). This relationship was temporally, neurochemically and anatomically specific. We observed similar findings in the elderly to our earlier work in young adults. Individual differences in the balance of neurochemical excitation/inhibition in sensorimotor cortex is causally related to individual differences in behavioural retention of sensorimotor adaptation.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

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Program #/Poster #: 308.19/KK12

Topic: E.04. Voluntary Movements

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Title: The effect of task-irrelevant outcome on implicit sensorimotor adaptation

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Abstract: When performing motor tasks, humans adapt to variations in the environment and changes in their body state. This learning process can be driven by both error and reward signals. How these signals interact has been the subject of considerable research. We recently addressed this question, using a visual error clamp in which the spatial trajectory of a feedback cursor is independent of the movement path; this method allows us to measure error-based adaptation when the error signal remains invariant and is not influenced by behavioral changes (Morehead et al. 2017; Kim et al., 2018). By varying the size of the target, the cursor could land consistently inside or outside of the target. The learning rate and aftereffect are smaller in the former compared to the latter case (Kim et al., in prep). Based on a series of control experiments, we concluded that, even though participants are aware that they do not control the path of the cursor, an "intrinsic reward" signal is generated when the cursor lands inside the target, and this signal attenuates the error-based learning process that underlies sensorimotor adaptation.
In the current study, we explored whether an "intrinsic reward" would occur even when the cursor hit a task-irrelevant landmark. On each trial, a ring of grey landmarks was presented, one of which turned blue to indicate the target location. The participant made a rapid reaching movement, attempting to intersect the target. After a baseline session in which the cursor feedback was veridical, the clamp manipulation was described, with the instructions emphasizing that the path of the cursor was independent of their hand movement. The clamped feedback followed a path that deviated from the target by 15^0. For one group of participants, the landmarks were spaced by 15^0; thus, the clamped cursor always terminated inside a landmark adjacent to the target. For the other group, the landmarks were spaced by 22.5^0; here, the clamped cursor always landed between the target and adjacent landmark. In this manner, we sought to test the hypothesis that "reward signals" are generated in an implicit and automatic manner if a feedback cursor lands within an object, even if that object is not part of the task goal. Preliminary results indicate that the size of the aftereffect is attenuated when the cursor lands inside a landmark. However, the learning functions in this condition are highly variable, with some participants showing a marked non-monotonicity and a corresponding increase in reaction time during the clamped feedback session. These results suggest that hitting a task-irrelevant landmark can alter behavior through a change in strategy, rather than modulating adaptation directly.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

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Topic: E.04. Voluntary Movements

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Title: Learning of kinematic and dynamic transformations after spinal cord injury

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Abstract: A critical component of motor learning is the ability to form internal models for sensorimotor transformations, which largely rely on afferent inputs from the periphery. Spinal cord injury (SCI) often disrupts the integrity of afferent axons projecting through the spinal cord dorsal columns to the brain. The aim of our study was to examine adaptations to kinematic (visuomotor rotation) and dynamic (velocity-dependent force) transformations in humans with cervical SCI and uninjured controls. We found that individuals with SCI showed slower adaptation rates to kinematic but not dynamic errors compared with controls participants. Individuals with SCI with greater deficits in limb position sense exhibited slower adaptation rate to kinematic but not dynamic errors. SCI participants showed a weaker kinematic internal model compared with controls, as exhibited by weaker after-effects. These findings suggest that spinal cord integrity is critical for learning kinematic models. We propose that enhancing sensory function can be used for improving learning of kinematic errors after human SCI.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

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Program #/Poster #: 308.21/LL2

Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant 04829-2017

Title: Individual patterns of sensorimotor adaptation to novel mechanical loads and visuomotor rotations

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Abstract: Humans can perform a range of motor actions, from playing piano to throwing a baseball, but vary in how well they learn to perform these skills. It has been challenging to understand individual patterns of motor adaptation because studies have focused on the average behaviour of groups of subjects when adapting their arm movements to counter visual or mechanical disturbances. It is unclear if, and to what extent, individual patterns of motor adaptation are preserved when exposed to diverse visual or mechanical disturbances. Here we examine how individual participants adapt their reaching movements when exposed to novel mechanical environments and visual transformations. Experiments were performed using a planar robotic exoskeleton (BKIN Technologies, Kingston, ON). Subjects completed 15 cm reaching movements within 500 ms of leaving the start position (diameter = 2 cm). The goal target (diameter = 2 cm) turned green if the participant completed their movement on time and blue if they did not. We first exposed subjects (n=20) to novel velocity- and position-dependent force fields. We then examined how a separate group of subjects (n=20) adapted to a visuomotor rotation (30° CCW) and velocity-dependent force field. After a baseline period (50 trials), we introduced a novel visual or mechanical disturbance (200 trials). Adaptation was washed out (50 trials) before subjects performed the second task. We generated adaptation profiles for each subject by measuring peak perpendicular (mechanical loads) or angular (visuomotor rotation) deviations between their hand path and a straight line joining the start and end targets for each movement. We also calculated the amount of adaptation participants attained over the last 25 trials they performed in each condition. We found participants attained similar amounts of adaptation when exposed to position and velocity-dependent forces ($p > 0.1$), but adapted faster to the position-dependent forces. Interestingly, we observed a moderate correlation between the amount of adaptation participants attained when learning to counter position- and velocity-based forces ($r = 0.51$, $p < 0.05$). In the second experiment, participants adapted faster ($p < 0.05$) but to similar amounts ($p > 0.1$) when exposed to velocity-based forces compared to the visuomotor rotation. The amount participants adapted did not correlate across visual rotation and mechanical load tasks. Our results reveal commonalities in the amount individual participants adapt to mechanical disturbances, despite marked differences in the shape of their adaptation profiles. Adaptation patterns were not conserved when exposed to novel visual and mechanical disturbances.

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Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

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Topic: E.04. Voluntary Movements

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Title: Reaching movements in force-fields simulated by a motor control-learning model without desired trajectory

Authors: *H. KAMBARA, H. SHIMIZU, T. KAWASE, A. TAKAGI, N. YOSHIMURA, Y. KOIKE
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Abstract: Arm reaching is one of the motor tasks that has been studied a lot to clarify mechanism underlying neural motor control. Force-fields adaptation task is one of the motor task frequently used to investigate the process of motor learning (or motor adaptation) when normal reaching movement is disturbed by the force imposed to the hand.
Several computational models have been proposed to explain how the brain adapts reaching skill to compensate perturbing force and to became able to generate accurate and smooth reaching motion. Some of them assume the existence of desired trajectory, and claim that the brain is learning set of motor command signal that can move the hand along with the desired trajectory under the force. On the other hand, Izawa et al. (2008) observed that the movement trajectories after adapting to the force became different from the ones in baseline condition. And they suggested that the movements are re-optimized to behave optimally under force perturbation rather than canceling the force to trace same trajectory as baseline movement. Although optimal feedback controlled based models have succeeded in reconstructing kinematic features of force adaptation task, all of them simplified the dynamics of the arm to a point-mass model.
Here we apply our motor control-learning model to force-fields adaptation task in which arm is driven by nonlinear musculoskeletal dynamics. An advantages of our model is that it does not require prior knowledge about the dynamics of controlled object and. As results of simulation, we show that kinematic features during before and after adaptation to velocity-dependent force-field can be reproduced without assuming desired trajectory. In addition, we show that muscle activation pattern found in divergent force-field experiment can also by reproduced by our model.

Disclosures: H. Kambara: None. **H. Shimizu:** None. **T. Kawase:** None. **A. Takagi:** None. **N. Yoshimura:** None. **Y. Koike:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.23/LL4

Topic: E.04. Voluntary Movements

Support: NIH NS092079

Title: Implicit adaptation is sensitive to relevance of multiple cursors

Authors: *D. E. PARVIN[1], J. R. MOREHEAD[2], K. V. DANG[3], A. R. STOVER[3], R. B. IVRY[1]
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Abstract: Implicit sensorimotor adaptation is thought to be driven by discrepancies between 'predicted' and 'actual' feedback, or sensory prediction errors (SPEs). It has been suggested that this process is automatic and obligatory, even when detrimental to task success (Srimal et al., 2008; Mazzoni & Krakauer, 2006). To explore whether implicit adaptation is truly insensitive to the task conditions, we manipulated the relevance of the sensory feedback. Specifically, using a center-out reaching task, multiple feedback cursors with different rotations were presented simultaneously (Kasuga, Hirashima & Nozaki, 2013). By using redundant feedback signals, the movements and feedback could be held constant while instructions were used to manipulate the task relevance of the feedback signals.

In experiment 1, three cursors were simultaneously presented as participants reached towards a target located at one of three locations. In the baseline phase, the cursor rotations were -45º, 0º and 45º with respect to hand position and participants were instructed to hit the target with the middle, 0º cursor. Three conditions in the training phase were compared. For each condition we varied the mean rotation of all three cursors, and the "task-relevant" cursor, defined by the one they were instructed to hit the target with. The other two cursors were irrelevant distractors. If adaptation was insensitive to task relevance, adaptation should be driven by the mean rotation of all three cursors. If on the other hand, adaptation was sensitive to task relevance, adaptation should be driven specifically by the rotation of the task-relevant cursor with respect to the hand. In all groups, participant's performance and aftereffects were consistent with them effectively ignoring the irrelevant cursors.

In experiment 2 we assess the strength of the effect of relevance by contrasting it to another manipulation known to affect the strength of implicit adaptation - delaying feedback. In the training phase, two cursors are presented: The first cursor is rotated by 45º and is presented immediately with online feedback. The second cursor follows the veridical trajectory of the hand, but is presented after a delay of two second after the completion of the reach. Participants are instructed to hit the target with the delayed and non-rotated cursor, and to ignore the

immediate and rotated cursor. If using delayed cursor feedback is sufficient to attenuate adaptation from irrelevant cursors, we would expect no adaptation, whereas if it is not sufficient, we would expect to see adaptation.

Disclosures: D.E. Parvin: None. **J.R. Morehead:** None. **K.V. Dang:** None. **A.R. Stover:** None. **R.B. Ivry:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.24/LL5

Topic: E.04. Voluntary Movements

Support: NSERC Discovery Grant
CIHR PJT-389243 Project Grant

Title: Neural substrates of reward and sensory error based reach adaptation

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Abstract: Adaptation of motor output to changing environments occurs by multiple distinct processes. In sensory error based learning, it is thought that the nervous system predicts the sensory outcomes of motor commands, and that sensory prediction error drives learning when sensory input differs from these predictions. In reinforcement learning, it is thought that the brain predicts the subjective value of actions, and that reward prediction error, signaled by midbrain dopamine neurons, drives learning when outcomes differ in value from these predictions. Actions that produce better than expected outcomes are reinforced, while actions that produce worse than expected outcomes are deterred. We recorded EEG activity to identify and dissociate the neural correlates of reward and sensory prediction error elicited by feedback in two different sensorimotor learning tasks designed to isolate each response. We observed sensory error based learning in a visuomotor rotation task, in which feedback was provided in the form of a cursor that indicated movement endpoint. During randomly selected trials, the cursor was rotated around the starting position of the reach to induce sensory prediction error. Participants adapted their reaches on a trial by trial basis to compensate for these perturbations. In a reward learning task, binary reward feedback indicated whether each reach was successful or unsuccessful without revealing hand position at movement endpoint. Reward was delivered probabilistically according to reach angle, and participants adapted their reaches to produce reach angles that resulted in higher reward probability. We administered levodopa, a dopamine agonist, and placebo in a repeated measures double blind randomized controlled design to test the role of

dopamine signaling in neural and behavioural responses to reward and sensory error processing. We found that a fronto-central event related potential called the feedback related negativity specifically encoded reward prediction error during reward based learning, but did not occur during the sensory error based learning task. These findings suggest that the feedback related negativity is specific to processing reward prediction error, as opposed to general error processing. Furthermore, distinct patterns of event related spectral modulation were evoked by sensory error feedback and reward feedback. We evaluate the effect of dopaminergic manipulation on behavioral learning and neural responses to feedback. Our results reveal a dissociation between EEG signatures of error and reward processing in two distinct motor learning processes.

Disclosures: D. Palidis: None. **P.L. Gribble:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.25/LL6

Topic: E.04. Voluntary Movements

Title: Value of segmental kinematic information for learning external locomotor dynamics

Authors: P. F. JALILI[1], S. E. GOODMAN[2], *C. J. HASSON[2]
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Abstract: In the field of human sensorimotor control, there is significant evidence that proprioception plays a key role in learning novel dynamics. There is also evidence that vision can make meaningful contributions in more complex dynamical situations; however, this is less well-understood. The role of vision in learning dynamics is an important practical question, particularly in rehabilitation. In manual gait training, therapists need to effectively control the complex locomotor dynamics of patients. However, the segmental kinematics of a locomoting patient, which influence the mapping between joint torques and end-point forces, cannot be directly sensed through proprioception. Thus, vision of segmental kinematics should be important when learning external locomotor dynamics. This study tests the hypothesis that seeing the segmental kinematics of a patient's leg improves the ability to manipulate locomotor patterns, and is associated with a stronger internal representation of patient locomotor dynamics. Because this study focuses on the learning of the caregiver (e.g., therapist) instead of the patient, variability on the patient-end was controlled with a newly developed interactive locomotor simulator. This consists of an impedance-based model of stroke patient locomotor dynamics, called a virtual patient (VP), which subjects interact with through a small robotic manipulandum. Subjects were asked to use their dominant hand to practice moving the VP into a healthy gait pattern; the point of interaction was the VP's ankle. To accomplish this, subjects had to

compensate for the resistive force field created by the VP, which attempted to walk in an asymmetrical, non-healthy, locomotor pattern. Random catch trials were used to probe the presence of aftereffects and the degree of generalization was used to assess internal representations. One group of subjects saw a stick-figure representation of the VP's leg during training; a second group only saw a point representing the VP's ankle. Early results support the hypothesis that seeing stick-figure segmental kinematics aids subject manipulation performance by reducing kinematic errors, and this is associated with a stronger internal representation of locomotor dynamics (i.e., larger aftereffects/improved generalization). If supported with further data, this would highlight the importance of visual information when interacting with complex dynamics external to the body. It may also open the door for augmentation of therapist visual feedback to improve care delivery and patient rehabilitation outcomes.

Disclosures: P.F. Jalili: None. **S.E. Goodman:** None. **C.J. Hasson:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.26/LL7

Topic: F.03. Neuroendocrine Processes

Support: NIH Grant DA017637

Title: Quantification of active phase corticosterone during baseline, oral nicotine, and withdrawal conditions

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Abstract: In spite of heightened education and prevention strategies, cigarette smoking remains a major health risk. As nicotine is the major psychoactive component in tobacco, it is of interest to understand the behavioral and physiological effects of nicotine and nicotine withdrawal that could contribute to ongoing tobacco use. One physiological effect of nicotine use and withdrawal from chronic nicotine is a disruption in the hypothalamic-pituitary-adrenal (HPA) axis. This drug-induced disruption in HPA function is thought to be important for drug dependence. The present study aimed to assess disruption of the HPA axis via the observation of corticosterone levels during baseline, oral nicotine, and withdrawal conditions. Adult female C57BL/6J mice were individually housed and maintained on a 12 hr light/12 hr dark cycle with ad libitum access to food and a 0.2% saccharin drinking solution. Pre-nicotine baseline (BL) blood samples were collected at ZT12 one week after placement in individual cages. To establish nicotine dependence, 200µg/ml nicotine was added to the 0.2% saccharin water. After 14 days of nicotine exposure, withdrawal was induced by excluding the nicotine from the water. Animals served as

their own control, and blood samples were collected at ZT12 on nicotine day 8 (N8) and withdrawal day 1 (WD1). Compared to BL, corticosterone levels were significantly decreased for both N8 and WD1 suggesting a blunted HPA axis activity in the animals. No significant difference was observed between N8 and WD1 time points. These data are consistent with human literature, yet it remains unclear whether the WD1 response is a consequence of abstinence or whether it is a symptom of the disruptive effect of exposure on the HPA axis that persists during withdrawal. Samples will be collected for WD5 to see if blunted corticosterone levels persist throughout withdrawal. In addition, samples will be collected at ZT0 to determine if there is diurnal variation and to explore whether this physiological measure is time-of-day dependent. These data could elucidate long-term disruptions in the HPA axis that make smoking cessation increasingly difficult.

Disclosures: A. Alvarado: None. **H. Matthews:** None. **J. Stitzel:** None.

Poster

308. Voluntary Movements: Reaching Control: Motor Learning: Human I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 308.27/LL8

Topic: E.04. Voluntary Movements

Support: NIH Grant

Title: Thalamus modulates cortical gamma oscillations via a chain of phase coupling and phase amplitude coupling

Authors: *S. NIKETEGHAD[1], M. MALEKMOHAMMADI[2], E. TSOLAKI[3], H. SPARKS[2], N. POURATIAN[3]
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Abstract: Objective We have previously shown thalamo-cortical α and low-β oscillations are dampened during voluntary movement. This change in oscillatory power in both thalamus and cortex is accompanied by a suppression in thalamo-cortical phase coupling as well as thalamo-cortical/cortico-cortical Phase Amplitude Coupling (PAC) between phase of α /low-β and amplitude of γ oscillations. Investigating the causal relationship among these measures is a crucial step towards understanding the oscillatory mechanism of the thalamo-cortical network and its role in regulating voluntary movement. **Method** Local Field Potentials (LFPs) from Ventral Intermediate (ViM) nucleus of the thalamus were recorded from Essential Tremor (ET) patients during Deep Brain Stimulation surgeries. Simultaneously, we recorded LFPs from sensory-motor cortex via a subdural ECoG strip. Causality analysis was performed using Directed Transfer Function (DTF) method between Thalamic and cortical signals. Phase

Amplitude Coupling (PAC) among all possible contacts in the thalamo-cortical network was measured using Modulation Index (MI) method. The phase lag likelihood was measured between ViM and cortex and was compared against the difference between preferred phase of the thalamo-cortical and cortico-cortical PAC. **Results** In subjects with significant resting state thalamo-cortical phase coupling and PAC, the phase lag likelihood matched the difference between thalamo-cortical and cortico-cortical PAC in alpha/low-beta band. Moreover, causality analysis showed that ViM leads the thalamo-cortical coupling. **Conclusion** Our findings indicate that γ oscillations which are associated with the execution of voluntary movement may be modulated by ViM via a chain of thalamo-cortical α /low-β phase coupling and cortico-cortical PAC. This provides a basic understanding of subcortico-cortical communications through phase and cross frequency coupling and may be extended to other brain areas during different functions.

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Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.01/LL9

Topic: E.04. Voluntary Movements

Title: The relationship between implicit and explicit visuomotor task learning in hippocampus and parietal cortex

Authors: *R. LIENKÄMPER, M. SAIF-UR-REHMAN, Y. PARPALEY, J. WELLMER, C. KLAES
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Abstract: It has been shown that different brain structures are active while learning an explicit or implicit task. The structure mostly associated with explicit learning is the hippocampus, while implicit learning is believed to mainly rely on frontal areas, basal ganglia and the parietal cortex. However, both types of learning can interact with each other depending on the task instructions. Furthermore, tasks that have been learned explicitly can be transformed into an implicit representation after overlearning.
Apart from the tasks explicitness, the involvement of hippocampus and parietal cortex has also been shown to vary depending on the difficulty of a task and its novelty. However, transitions from the involvement of one structure to the other are not yet understood. Using state-of-the-art virtual reality technology and EEG as well as ECoG recordings, we are investigating the changing involvement of hippocampus and parietal cortex during a centerout reaching task under three conditions: Visuomotor adaptation, visuomotor transformation and visuomotor association.

For the visuomotor adaptation, we are introducing a misalignment between visual input (the observed movement of the arm in virtual reality) and the motor output (the movement of the subject's arm in reality). During visuomotor transformation, the subject is instructed to move his / her arm towards, for example reach to the clockwise neighbour of the visual cue. The concept is similar to the adaptation condition but relies on an explicit rule instead of a misalignment. Visuomotor association represents the most explicit condition in our experiment. In this condition, a non-spatial cue (a number word, e.g. "three") is shown and must be associated with one of the possible targets (which are labeled with numbers, e.g. "3").
These three conditions form a transition from implicit (visuomotor adaptation) to explicit learning (association). By altering the strength of the misalignment during the adaptation, using more complex transformation rules ("reach to opposite direction of the cued target") and different association cues (e.g. "Five minus two" instead of "three"), we can alter the difficulty of the task as well. Finally, the amount of training spent on a specific condition of the task is a gradual change in the tasks novelty.
Preliminary results shows that the strength of misalignment in adaptation condition significantly impacts the path length and completion time, indicating that it is indeed a change in the task difficulty.

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Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.02/LL10

Topic: E.04. Voluntary Movements

Title: Effects of distance control practice of lower limb on motor skill learning and transfer in patients with cerebellar disease

Authors: *J.-H. PARK
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Abstract: Cerebellar disorders are characterized by irregular steps, difficulties with inter- and intra-limb coordination, and reduced postural stability. In particular, impaired control of lower limb movement are often major causes of functional disturbances that affect patient's independent activities in daily living. At present, there is a lack of studies on how repeated practice of lower limb movement influences motor learning and transfer in patients with cerebellar disease. The aim of this study was to investigate the effect of distance control practice using lower limb on motor skill learning and generalization to different task conditions in patients with cerebellar disease. Twelve individuals with cerebellar disease (CD) and age- and

sex-matched 12 normal controls participated in the study. Both group practiced reaching to the targets with their right lower limb presented at three distances (5, 10, 15cm) while sitting. Kinematic data were measured to determine scaling of movement accuracy from start to target position. Performance was tested pre- and post-training for retention effect and two learning transfer conditions (horizontal & vertical directions). The results demonstrated that both groups showed significant improvements in 5cm, 10cm and 15cm distances while distance errors of CD patients were higher than normal controls. In addition, there were significant learning transfer effects to new task conditions, but less evident improvement was observed in vertical direction transfer condition in CD group. Taken together, the results from this study suggest that even though the cerebellum is damaged, task-specific motor training is a promising intervention for improving skill learning for distance control of lower limb and motor generalization in patients with cerebellar ataxia.

Disclosures: J. Park: None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.03/LL11

Topic: E.04. Voluntary Movements

Support: ARC Centre of Excellence in Cognition and its Disorders

Title: Interlimb generalization of learned bayesian prior occurs in extrinsic coordinates

Authors: C. L. HEWITSON[1,2], P. F. SOWMAN[1,2], *D. M. KAPLAN[1,2]
[1]Dept. of Cognitive Sci., [2]ARC Ctr. of Excellence in Cognition and its Disorders, Macquarie Univ., Sydney, Australia

Abstract: Recent work suggests that the brain represents probability distributions and performs Bayesian integration during sensorimotor learning. However, our understanding of the neural representation of this learning remains limited. To begin to address this, we performed two experiments. In the first experiment, we replicated the key behavioral findings of Körding and Wolpert (2004), demonstrating that subjects can perform in a Bayes-optimal manner by combining information about their own sensory uncertainty and a statistical distribution of lateral shifts encountered in a visuomotor adaptation task. In the second experiment, we extended these findings by testing whether visuomotor learning occurring during the same task generalizes from one limb to the other, and relatedly, whether this learning is represented in an extrinsic or intrinsic reference frame. We found that the learned mean of the distribution of visuomotor shifts generalizes to the opposite limb only when the perturbation is congruent in extrinsic coordinates,

indicating that the underlying representation of learning acquired during training is available to the untrained limb and is coded in an extrinsic reference frame.

Disclosures: C.L. Hewitson: None. **P.F. Sowman:** None. **D.M. Kaplan:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.04/LL12

Topic: E.04. Voluntary Movements

Support: NINDS R01NS084948

Title: Perception and visuomotor adaptation share the same psychological space

Authors: *C. CAMPAGNOLI, J. A. TAYLOR
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Abstract: Several features of a visual scene can potentially serve as feedback for movement planning. One compelling example of such mechanism is motor adaptation in an error clamp paradigm: in it, participants aim a series of reaching movements at an instructed location, while receiving endpoint feedback at a different location regardless of the actual movement direction. Even though they are told to ignore the feedback, participants gradually bias their reaching movements in opposite direction to that specified by the clamp, as if trying to compensate for an error. This subconscious behavior is commonly referred to as implicit adaptation.
When studying the spatiotemporal unfolding of visuomotor implicit adaptation, it is commonly assumed that the magnitude of the error signal (i.e., the simulated size of the clamp) is somehow accurately estimated by the visuomotor system. However, this statement contrasts with many psychophysical studies showing that spatial perception is often inaccurate. In this study we investigated whether the same visual feature is retrieved from different psychological spaces for motor adaptation and for perception.
We started exploring this problem using a Virtual Reality setup, where we instructed our participants to perform reaching-in-depth movements towards a target. At the beginning of each trial, they viewed a 42 cm wide circular target at a distance of 2 meters, in the middle of the visual field. Participants were asked to throw a virtual cursor at the center of the target, but to ignore the clamped endpoint feedback: regardless of the actual hand's direction, the cursor always hit off the target by a fixed horizontal offset. In a blocked design, two different groups saw the target either alone (No-depth condition) or embedded in a 3D scene (Depth condition). As expected, overall participants showed implicit adaptation in response to a task-irrelevant error clamp. Importantly, the size of the motor compensation was smaller in the Depth condition, although in principle the movement could be planned using only retinal information in both

conditions. Furthermore, these results mirrored those of a perceptual task, which showed that, in the Depth condition, the target appeared overall smaller than in the No-Depth condition. Taken together, these findings suggest that the size of the error clamp was estimated differently depending on the presence or absence of depth information, irrespective of the task. This suggests that perception and adaptation share a common psychological space.

Disclosures: C. Campagnoli: None. **J.A. Taylor:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.05/LL13

Topic: E.04. Voluntary Movements

Support: NIH R01AG041878

Title: Searching for sensitization to visuomotor errors with task-irrelevant clamped feedback

Authors: *J. R. MOREHEAD[1], H. E. KIM[3], D. E. PARVIN[4], R. IVRY[5], M. A. SMITH[2]
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Abstract: Visuomotor adaptation is thought to be driven by errors. Much work has proposed that the motor system may alter its sensitivity to errors over time (Burge, Ernst & Banks, 2008; Zarahn et al.; 2008; Herzfeld et al., 2014). However, the experiments inspiring these proposals did not control explicit aiming strategies, leaving the possibility that the observed behavior may not reflect the implicit recalibration of a visuomotor map. Recent work that did control cognitive aiming strategies has shown that the initial rate of learning increases linearly for errors smaller than 4.5°, before becoming saturated for error sizes larger than 4.5° (Kim et al., 2018). However, after prolonged training, this study showed that asymptotic learning from all error sizes reached a similar magnitude. This conflicts with the predictions of state-space learning models featuring a fixed learning and forgetting rate (Thoroughman & Shadmehr, 2000). For these models, large early differences in learning rate across error sizes would cause substantial differences in the magnitude of asymptotic learning. A way that the motor system could have different early learning rates but also similar asymptotic learning magnitudes across error sizes is that the it becomes sensitized to small errors (< 4.5°) over repeated exposures, eventually delivering the same response that errors larger than 4.5° would evoke, causing asymptotic learning state to be similar across error sizes.
We tested this hypothesis by comparing the asymptotic magnitude of learning between two groups. After a baseline of 40 cycles, the Sensitized group (n=15) had extended exposure (480

cycles) of clamped visual feedback offset by ±2.5° from the reach target. The Unsensitized group (n=20) was first exposed to 320 cycles of clamped feedback offset by ±7.5°, which then changed to ±2.5° for the remaining 160 cycles (counter-balancing offset sign). This afforded comparison of the magnitude of asymptotic learning from a 2.5° error, for a group that was allowed sufficient exposure to become sensitized to the 2.5° error and one that was not. The prediction of the sensitization hypothesis is that the mean hand angle of the Unsensitized group will drop below that of the Sensitized group during the final 160 cycles of the perturbation because the Unsensitized group will have a smaller learning rate. The Unsensitized group dropped to 3.2° below the Sensitized group, but this was not significantly different (p=.31, 95% CIs = [-3.2°,9.6°]). This lack of a difference could indicate that sensitization is not taking place, but our results were underpowered to detect a difference. Therefore, further work is needed to assess the sensitization hypothesis.

Disclosures: J.R. Morehead: None. **H.E. Kim:** None. **D.E. Parvin:** None. **R. Ivry:** None. **M.A. Smith:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.06/LL14

Topic: E.04. Voluntary Movements

Support: NICHD R01 HD075740

Title: Suppression of lateral prefrontal cortex impairs somatosensory working memory

Authors: *A. SIDARTA[1], N. KUMAR[2,1], T. F. MANNING[1], D. J. OSTRY[1,3]
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Abstract: The capacity to maintain in working memory previously performed movements, and their success or failure, presumably plays a substantial role in human motor learning. Indirect evidence in support of this idea comes from a recent study in which we found that motor learning is associated with changes in functional connectivity between second somatosensory cortex (SII) and right BA 9/46 (lateral prefrontal cortex), the latter presumably is important for somatosensory working memory. In the current study, we directly tested the hypothesis that lateral prefrontal cortex is the neural substrate of somatosensory working memory. We used a variant of an *N*-back procedure to assess working memory. On each trial a robotic device displaced the participants arm (without vision of the arm) in a number of different directions (memory set), and this was followed by a test displacement (also without vision) that was used to assess working memory. On half of the trials, the test direction was one of the items in the

memory set, and in the other half it was not. Participants had to indicate whether or not the test movement was from the memory set. Performance was estimated using hits and false alarms. We observed a reduction in the working memory performance following a cTBS protocol to the right lateral prefrontal cortex (BA 9/46). To assess the specificity of the finding, we recruited a control group that received sham cTBS to the same cortical region. The sham stimulation involved similar tactile and auditory effects without the actual stimulation pulses. Given that somatosensory working memory is necessary for reinforcement-based motor learning, our future plan is to test the effect of cTBS directly on motor learning.

Disclosures: A. Sidarta: None. **N. Kumar:** None. **T.F. Manning:** None. **D.J. Ostry:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

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Program #/Poster #: 309.07/MM1

Topic: E.04. Voluntary Movements

Support: WELLCOME TRUST-DBT INDIA ALLIANCE
NICHD R01 HD075740

Title: Somatosensory but not primary motor cortex is involved in the consolidation of motor memory

Authors: *N. KUMAR[1,2], T. F. MANNING[2], A. SIDARTA[2], D. J. OSTRY[2,3]
[1]Indian Inst. of Technol. Gandhinagar, Gandhinagar, India; [2]Dept. of Psychology, McGill Univ., Montreal, QC, Canada; [3]Haskins Labs., New Haven, CT

Abstract: There has been recent interest in the idea that motor learning does not occur in isolation but rather that motor learning involves changes to sensory systems and sensory networks in the brain as well. As an example, previous studies of sensorimotor adaptation have shown that motor learning is associated with a systematic change in the sensed position of the limbs. Consistent with this finding, neuroimaging studies have found learning related changes in both sensory and motor areas of the brain. The neuroplasticity that is seen in sensory systems following motor learning could be driven by corticocortical connections between motor and somatosensory cortex such that motor outflow during learning causes the changes in somatosensory cortex. Another possibility comes from motor learning studies in rats which suggest that plasticity in somatosensory cortex could be a result of its role in processing sensory error information during motor learning. However, it is unknown whether these learning related changes in somatosensory cortex play any role in the consolidation of motor memories developed through motor learning. We test the hypothesis that somatosensory cortex contributes directly to the consolidation of motor memory by using inhibitory transcranial magnetic

stimulation. Participants perform a motor learning task which involved force-field adaptation. Immediately following adaptation, we applied continuous theta-burst transcranial magnetic stimulation (cTBS) to suppress activity in primary somatosensory cortex (S1) with the goal of blocking motor memory consolidation. Subjects returned to the laboratory 24 hours later to test for memory retention. It was seen that stimulation of somatosensory cortex following adaptation greatly reduces retention. Sham TMS to S1 does not interfere with retention, nor is the interference following stimulation of S1 due to the spread of current from S1 to motor cortex (M1). This is shown by applying cTBS stimulation directly to M1. Suppression of M1 does not interfere with retention of motor learning and participants' performance was similar to that of the sham control group. These results suggest that primary somatosensory cortex is involved in the initial consolidation of motor memories developed during sensorimotor adaptation.

Disclosures: N. Kumar: None. **T.F. Manning:** None. **A. Sidarta:** None. **D.J. Ostry:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.08/MM2

Topic: E.04. Voluntary Movements

Support: NIA R01 AG041878

Title: Environmental compliance modulates the rate of motor learning

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Abstract: The motor system has the ability to update subsequent actions based on the error resulting from the current action. The ability to learn from errors in our movements is crucial for motor skill acquisition, and allows for an automatic adjustment, for example, of subsequent saccadic gain following an eye saccade that falls short of its target. While our motor systems have the remarkable ability to not only correct for motor errors by adapting motor output, it can also modulate the rate at which this error-dependent motor adaptation occurs. However, although the relationship between the size of error and the subsequent adaptive response has been extensively studied, less is known about the mechanisms governing how this relationship changes. A greater understanding of these mechanisms may offer deeper insight into the underlying organization of the motor system itself. We have previously reported that the motor system can modulate its learning rate based on environmental consistency. Here we demonstrate that an internal estimate of the physical compliance of an environment is another critical determinant for the learning rate. We used a reaching task where participants were asked to move towards a straight-ahead target, where we dramatically increased the compliance of the

environment by guiding participants' movements through virtual force-channels (FC) in directions that varied from the target direction. These FC trials were implemented as a high-stiffness one-dimensional spring that resisted lateral deviations from a pre-defined straight-line path but had no effect on longitudinal movement. We also introduced a controlled pattern of errors by varying the FC directions in a manner that reflects baseline movement variability. Specifically, the FC directions were drawn from a normal distribution with a standard deviation of 2.6 degrees. Surprisingly, we found a nearly one-to-one relationship between the compliance of the environment and rate of learning from error with a ~12-fold decrease in compliance leading to a ~12-fold increase in the adaptive response. These results suggest that the rate of error-dependent adaptation strongly depends on internal estimates of environmental compliance.

Disclosures: L. Alhussein: None. **A.E. Brennan:** None. **M.A. Smith:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.09/MM3

Topic: E.04. Voluntary Movements

Support: NIH NS095706
NIH 1R01NS078311
ONR N00014-15-1-2312
NSF 1723967

Title: Force production during holding suggests presence of a neural integrator for reaching

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Abstract: "Posture follows movement like a shadow" - Sir Charles Sherrington. As noted by Sherrington, the movements we make are linked to the postures we hold at the end of movement. Although these processes are separated in time, changes in the motor commands that move the limb may affect perception and control of posture. In terms of perception, adaptation to an externally imposed force field leads to a shift in our belief of where our arm is in space. And in terms of control, forces related to movement adaptation linger into holding - curiously, after adapting to a force field, subjects produce unnecessary postural forces at the end of movement. These observations raise the following question: are the processes of moving and holding coupled to one another in pre-motor circuits? To test this idea, we performed a series of force field adaptation experiments. In these tasks, subjects held the handle of a robotic arm and made reaches to peripheral targets. We gradually imposed a force field to perturb reaching movements. However, at the end of movement, the robot clamped the hand at its final position. In this way,

we perturbed the moving system but removed errors related to holding posture. These experimental conditions unmasked a striking relationship between moving and holding: the postural forces at the end of the reach were almost perfectly predicted by the integral of the moving forces that preceded holding ($R^2 = 0.95$). In other words, the motor commands generated to counteract the force field appeared to be integrated into the postural signal that held the arm in place. In a series of tasks where the perturbation conflicted across consecutive movements, we found that these postural forces were specific to the moving forces of the current movement, not the history of prior movements. Moreover, the relationship between postural force and moving force, was independent of the direction, amplitude, and duration of the reach. But was the relationship between moving and holding really captured by mathematical integration? We considered a task where subjects adapted to a force field that had an integral of zero, differing in sign during the first and second halves of the movement. We found that as subjects learned to produce forces during reaching, bringing the integral of their moving forces close to zero, the postural forces vanished. These results demonstrate that the postural system for the arm acts as a mathematical integrator of the forces that the limb produces during movement. Analogous to the brainstem neural integrator of the oculomotor system, there may exist a neural integrator that uses an efference copy of the motor commands during reaching to form the motor commands during holding.

Disclosures: S.T. Albert: None. **R. Shadmehr:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.10/MM4

Topic: E.04. Voluntary Movements

Support: NIH Grant NS092079
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Title: Movement history biases action planning more than action execution

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Abstract: Repeating a specific movement is thought to bias future movements towards the repeated one, a phenomenon referred to as use-dependent learning (UDL). In center-out reaching, UDL is thought to reduce variability at the most frequently practiced target location, but at the cost of a bias towards this location when attempting to reach elsewhere. Here we attempt to determine whether these effects are primarily due to action selection or action

execution biases. Furthermore, given a recent report that reward-based learning may interact with UDL during isometric tasks, we addressed the issue of whether reward modulates UDL during reaching. In experiment 1, we used a reaching task similar to the seminal study on UDL by Verstynen and Sabes (2011). Participants (n=10) were presented with the repeated target location on 88% of trials, with interleaved probes ±30°, ±60°, and ±90° distal to this location for the remaining trials. Online visual feedback of hand position was provided only during reaches to the repeated target. Initial heading angles revealed mean biases towards the repeated target, comparable in size to those reported by Verstynen and Sabes (~15° maximum). However, a finer grained analysis revealed a wide range of reaches during the probe trials, including some directly towards the repeated target. Despite there being no constraints on participants' reaction time (RT), there was a strong inverse relationship between the size of the bias and RT. This suggests that participants initially selected a default movement plan towards the repeated target prior to completion of planning to the probe, eliciting the biased responses, especially when RT was short. In a second experiment, we removed the RT-dependent effects of action selection biases by enforcing a delay of 500 ms before the response, allowing us to examine the effects of reward on the 'pure' UDL execution bias. One group (n=16/group) received rewarding feedback for accurate reaches to the repeated location; the second group never received performance-based feedback. For both groups, no feedback was given for reaches to probe locations. Despite the rewarded group exhibiting a reduced variance around the repeated target, the bias was similar for both groups, a modest 3°-4° across all probes. Thus, these studies point to a much larger role for action selection biases in use-dependent reaching paradigms than previously reported, and also to a negligible effect of rewards on the small UDL execution bias.

Disclosures: H.E. Kim: None. **D.E. Parvin:** None. **R. Ivry:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.11/MM5

Topic: E.04. Voluntary Movements

Support: RBIQ/QBIN Grant RI-05
ANPyC FONCYT: PICT 2015-0844
MINDEF PIDDEF 2014/2017 #17

Title: Time course of structural plasticity induced by different types of motor learning

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Abstract: The nervous system translates new knowledge into long-lasting plastic changes that lead to the formation of memories. To date, the timescale of structural remodelling that accompanies functional neuroplasticity is largely unknown. Magnetic resonance neuroimaging provides us with non-invasive tools to explore structural neuroplasticity in humans. There is wide evidence of changes in grey and white matter structure in the healthy human brain following extensive motor training (< 1 week, Dragansky et al., 2004; Landi et al., 2011; Scholz et al., 2009; Sampaio-Baptista et al., 2014). Animal experiments, however, suggest that structural remodelling due to motor learning is a rapid, dynamic process that can be detected over much shorter timescales (1-3 hours; Fu and Zuo, 2011; Xiao et al., 2016). A recent Diffusion Weighted Imaging (DWI) study has shown that training on a spatial memory task induces a decrease in mean diffusivity (MD) that correlates with N-methyl-D-aspartate (NMDA) dependent astrocyte hypertrophy in the hippocampus (Sagi et. al., 2012; Assaf, 2017). Here, we used DWI to investigate the emergence of early cortical plasticity elicited by a short session of motor learning. To this end, we trained 21 healthy subjects [11 female; age (mean ± SD): 23,6±3,1 years old] in two well-characterized motor tasks, tapping on different neural substrates: motor sequence learning (MSL) and visuomotor adaptation (VMA). DWI images (2×2×2 mm^3, 30 gradient directions, b-value = 1000 s/mm^2, TR=5208 ms, TE=89 ms, FOV=240x240 mm^2) were obtained before, 30 min and 24 hours after training to asymptotic performance (~15 min for MSL and ~25 min for VMA). Prior to the tensor and MD estimation, DWI images were corrected for geometric distortions (Andersson et al., 2003), head motion, eddy currents and b-vector correction (Andersson and Sotiropoulos, 2015). MD maps were non-linearly transformed to MNI152 T1 using ANTs (Avants et al., 2011), and longitudinal MD changes were statistically assessed using the threshold-free cluster enhancement (TFCE) approach of Randomise (Smith and Nichols, 2009; Smith et al., 2004). Learning the MSL task was associated with a significant reduction of MD in the left hippocampus 30 minutes post-learning that returns to baseline levels at 24 hrs. MSL also lowered MD in the fronto-parietal network 30 min post-learning, but this decrement persisted overnight. No significant changes in microstructure were found after learning a VMA task. Our results suggest that acquiring a new motor policy -as in MSL- may involve changes in synaptic efficacy that are not triggered when learning is associated with recalibration of an existing motor policy.

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Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.12/MM6

Topic: E.04. Voluntary Movements

Support: NIH Grant K01AG047926

Title: Role of attention in motor performance on a novel functional upper extremity task: Evidence from aging and implications for motor learning

Authors: P. WANG[1], D. S. PETERSON[2], *S. Y. SCHAEFER[1]
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Abstract: Theories of motor skill learning have long suggested that performing novel tasks requires high levels of attention. We have developed a functional upper extremity motor task that involves reaching, grasping, and object manipulation to study the process of learning more complex, real-world movement, and have validated it against more established upper extremity tasks (i.e., point-to-point reaching). The extent to which this novel motor task involves attentional control has, however, not been established. Thus, the purpose of this study was to test whether participants' performance on a novel functional upper extremity task was related to their dual-task ability. Participants with advancing age were used in this study to maximize the variance in dual-task interference as well as upper extremity motor performance. To minimize any confounds of upper extremity sensorimotor impairment or limitation that may be present in older populations, dual-task ability was measured using the amount of interference in Timed-Up-and-Go test (TUG) under dual-task conditions (i.e., while performing serial subtraction); this assessment has no upper extremity involvement and has been related to cognitive impairment and fall risk in older adults. We hypothesized that more dual-task interference on the TUG would be associated with worse performance on the upper extremity task, even when the upper extremity task was performed without any distraction. Forty-nine community-dwelling adults aged 65 and older performed the functional upper extremity task with both the dominant and nondominant hand as quickly as possible. In the same session, they also completed the TUG under single- and dual-task conditions. Dual-task interference was calculated as the percent difference in time to complete the TUG under single- and dual-task conditions, normalized to the single-task condition. Linear regression indicated that only the nondominant feeding task performance was correlated with dual-task interference (R^2=0.13; p<.05), such that the greater the interference, the worse the performance on the upper extremity task. No relationship was observed when using the dominant hand, suggesting that the task is not novel when performed with the dominant hand and therefore not appropriate for studying skill learning. When performed with the nondominant hand, however, the task has a substantial attentional load and

may be learned with repetitive practice (see Schaefer et al. 2015), validating it as a method for studying motor learning in older adults.

Disclosures: P. Wang: None. **D.S. Peterson:** None. **S.Y. Schaefer:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.13/MM7

Topic: E.04. Voluntary Movements

Support: RBIQ/QBIN RI-05
ANPCyT, FONCyT: PICT 2015 0844
MINDEF, PIDDEF 14/17

Title: Visuomotor adaptation increases the number of spindles associated with slow oscillation during NREM sleep

Authors: A. SOLANO, L. A. RIQUELME, *V. M. DELLA MAGGIORE
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Abstract: It has been suggested that during nocturnal consolidation of hippocampal memories, slow oscillations (SO) facilitate the emergence of sleep spindles, which in turn recruit hippocampal ripples (Staresina et al, 2015). Convergent experimental evidence from human and non-human animals suggests in fact that long-term hippocampal memory measured overnight is associated with an increase in the level of coupling between sleep spindles and slow oscillations (~1Hz) during Non-Rapid Eye Movement (NREM) sleep. Little is known, however, about the presence and relevance of this SO-spindle coupling in non-hippocampal motor memories. To address this issue, we carried out a study in which polisomnographic recordings were obtained from 10 healthy right-handed participants during a night of sleep after performing a visuomotor adaptation task with the right hand. Participants came to the sleep lab three times (familiarization, experimental and control sessions), each separated by one week, and performed the task before and after a full night of sleep. During the experimental session subjects learned to adapt to a 45 deg rotation; during the control session, subjects performed the same task without the perturbation. Sleep recordings were staged according to standard criteria. Spindles and Slow Oscillations were identified using standard detection algorithms in artifact-free NREM sleep segments (Mölle et al, 2011). SO (0.5-1.25Hz) and Spindle (10-16Hz) density and the coupling between Spindles and SO was computed. No differences were found in the sleep architecture across experimental conditions. There were no significant differences in the frequency and duration of spindles across conditions. Yet, we found a significant increase in the density of Spindles in the experimental compared to the control session (Session: $F(1,8)=3.539$, $p=.097$;

Channel: F(10,80)=5.068, p=.001; Session*Chan: F(10,80)=2.164, p=.028). This increment detected in the frontal (FC1) and central (C3, C4) electrodes was associated with the occurrence of SO (RM-ANOVA. Session: F(1,8)=2.410, p=0.159; Channel: F(10,80)=6.673, p=0.001; Session*Chan interaction: F(10,80)=2.310, p=0.019). Our results suggest that the SO-Spindle interaction may not be privative of hippocampal memories, but may reflect a non-specific process underlying consolidation in different memory systems.

Disclosures: A. Solano: None. **L.A. Riquelme:** None. **V.M. Della Maggiore:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.14/MM8

Topic: E.04. Voluntary Movements

Title: The effects of limb-based visual feedback on human's reaching movements

Authors: *F. ZAHED, M. BERNIKER
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Abstract: Subjects in experimental settings have a strong tendency to move their hand along a straight path. Even when large forces are applied to the hand, subjects adapt to the forces by returning to straight stereotyped movements. In standard reaching experiments subjects are seated in front of a monitor where their hand is displayed as a cursor on the screen and the targets are depicted as circles. The persistence for moving the cursor on a straight path made us think that the cursor is bias for straight reaches. We tested this by changing the standard visual feedback to "limb-based" visual feedback, displaying the posture of the subject's arm, and targets as desired limb-postures. Subjects made roughly 25 cm point-to-point reaching movements on the edges of a right triangle. We found that when limb-based visual feedback is provided reaches become curved relative to the standard cursor feedback, suggesting a new control strategy for movements. This suggests that the type of visual feedback used can affect the control strategy for movements.

Disclosures: F. Zahed: None. **M. Berniker:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.15/MM9

Topic: E.04. Voluntary Movements

Support: Wyss Center for Bio and Neuroengineering

Title: Modulation of the task-related functional connectivity during motor adaptation

Authors: *J. C. MIEHLBRADT[1], C. PIERELLA[2], C. GIANG[2], N. KINANY[2], E. PIRONDINI[3], M. COSCIA[4], S. MICERA[2,5]
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Abstract: The importance of cortical coherence during the rehabilitation of motor tasks is still poorly understood. To study this process in healthy subjects, tasks requiring motor adaptation are often used. Here, we evaluated the modulations in the cortical activity associated with a slow or rapid motor adaptation to an altered visual feedback. Healthy participants were asked to perform a three-dimensional, robotic-assisted center-out reaching task, with an inversion of the visual feedback. Initially, among all the possible directions of the workspace only a subset of target directions were presented to the participants. An algorithm running continuously assessed their motor improvement and replaced the targets by new reaching directions when the improvement exceeded a specific threshold. The EEG activity of the participants was recorded before and during the task execution, and we computed the band-specific power and coherence in and between key motor and visual areas. The rate of adaptation to the altered visual feedback, defined as the number of new inserted targets along the practice, distinctively clustered the participants into slow and fast learners. While the fast learners displayed a significant modulation of the beta-band coherence, this phenomenon was not observable in the slow learners. This result highlights the implication of visuomotor correlation in the motor adaptation to an altered visual feedback.

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Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

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Topic: E.04. Voluntary Movements

Support: NIH Grant F31-NS100520
NIH Grant 2R01-NS053606

Title: Generalization of visuomotor skill learning across movement directions

Authors: *P. N. PARMAR[1], J. L. PATTON[2]
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Abstract: Error-feedback plays an important role in the acquisition of motor skills for goal directed movements by facilitating learning of internal models. When error is perceived consecutively across different movement directions during training, it is unclear whether the brain learns an independent internal model for each movement direction or a generalized internal model spanning all movement directions. Our study focused on evaluating how errors perceived across different movement directions facilitate learning. We trained 15 healthy human subjects to reach in six directions in various nonlinear visuomotor distortions. We then tested their learning data against three most probable models: movement-direction-specific model where errors across directions are not shared, generalizing model where the current error is shared across all directions, and mixed model, which was a weighted sum. Our results indicate that the subjects learned 6.25 times more from the error that was observed at a movement direction than neighboring directions. Also, the generalization effect of learning from one movement direction to neighboring directions reduced nearly to zero by 60 degrees away.

Disclosures: P.N. Parmar: None. **J.L. Patton:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

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Program #/Poster #: 309.17/MM11

Topic: E.04. Voluntary Movements

Support: NICHD R01 HD075740

Title: Neural basis for learning novel sensorimotor maps

Authors: *F. T. VAN VUGT[1], Y. ZENG[2], D. J. OSTRY[2]
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Abstract: One of the challenges in a new learning environment is to determine the correspondence between movements and sensory effects: a sensorimotor map. Map acquisition can be studied by monitoring participants as they learn an unknown mapping between previously largely unlinked modalities such as movements and sounds. Several studies have characterised this acquisition process behaviourally but it remains unclear how learning is implemented in the brain. In particular, once a map is acquired, this knowledge then needs to be maintained when the subject no longer engages in the task. In the present work participants learned an audiomotor map in the scanner by making movements to auditory targets using a joystick while their brain activity was measured using functional magnetic resonance imaging (fMRI). Before and after learning resting state brain activity was assessed to track the persistence of information learned during the task. Behaviourally it was observed that participants initially moved at random and then progressively improved their reaching performance, indicating that they were able to learn the mapping. Neural structures involved in the task were defined as those having larger or smaller signal during task than during inter-trial rest and these formed a distributed network comprising cortical primary sensorimotor regions, supplementary motor area, superior parietal lobule, several foci in cerebellum, thalamus and the striatum. Frontal and parahippocampal regions showed lower activity during task than during rest. Changes in functional connectivity between these areas was assessed in subsequent resting state scans in relation to the amount of learning. Taken together, these findings characterise the brain areas that are involved in the earliest stages of learning novel sensorimotor maps and provide a first glimpse into how learned information is maintained when the task is no longer being performed.

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Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

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Topic: E.04. Voluntary Movements

Support: Internal grant of the KU Leuven (STG/14/054)
FWO Grant (1519916N)

Title: Impact of baseline reaching performance on motor adaptation across age

Authors: *K. VANDEVOORDE, J.-J. ORBAN DE XIVRY
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Abstract: While the contribution of cognition to motor adaptation is reduced with aging, older adults usually rely more on cognitive control for motor tasks. At the brain level, this higher reliance on cognitive control is reflected by an age-related over-activation of frontal areas. In the current study, we aimed for reconciling these two opposing findings, the decline of the cognitive component of motor adaptation and the increased cognitive control found in motor tasks. We hypothesized that reaching without visual perturbation (i.e. baseline trials) requires more cognitive control in older adults than in younger ones. As a result, the availability of further cognitive control for the adaptation process is further reduced in older adults, which limits the contribution of cognition to motor adaptation in this population.
To investigate the extent to which the availability of cognitive resources influenced performance in unperturbed reaches, a pre-registered dual-task paradigm was implemented during the baseline of a visuomotor rotation task. In this dual-task paradigm, participants were instructed to perform a reaching task, a cognitive task (Eriksen flanker task), or both tasks concurrently. The difference between performances in the single- and dual-task conditions are used as an indicator of the cognitive cost of reaching during baseline and as predictor for the extent of the cognitive component in the ensuing adaptation period. The cognitive component of adaptation was quantified with a cued motor adaptation experiment (Morehead et al. 2015; Vandevoorde and Orban de Xivry, 2018). We tested 31 young (23 ± 4 years) and 31 older adults (67 ± 4 years). Contrary to our prediction, we did not find a correlation between baseline dual task cost and contribution of cognition to motor adaptation. In older adults, we found a link between baseline reaching accuracy during the single reaching task and visuospatial working memory capacity (WMC) (exploratory analysis).
Our study provides little evidence for the limited resources hypothesis. This may be due to the choice of cognitive task and the fact that both tasks are not really performed in parallel but in series. Yet, given the observed link between unperturbed reaching accuracy and adaptation performance, the theory needs to be tested further with additional experiments.

Disclosures: K. Vandevoorde: None. **J. Orban de Xivry:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

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Topic: E.04. Voluntary Movements

Support: KU Leuven internal grant STG/14/054
FWO 1519916N

Title: Implicit adaptation does not decline with aging as revealed by measures of spontaneous recovery

Authors: *P. HERMANS, Y. LAM, K. VANDEVOORDE, J.-J. ORBAN DE XIVRY
KU Leuven, Leuven, Belgium

Abstract: In motor adaptation, learning is thought to rely on a combination of several processes. Two of these are implicit learning (incidental updating of the sensory prediction error) and explicit learning (intentional to reduce target error). The explicit component is thought to be fast adapting, while the implicit one is slow (McDougle et al, 2015). The dynamic integration of these components can lead to an adaptation rebound, called spontaneous recovery (Smith et al, 2006): the trace of a first, longer learned adaptation reappears after it is extinguished by a shorter period of de-adaptation. The explicit process decays quickly to baseline during the short de-adaptation period, not contributing to the behavior seen afterwards, while the slow implicit process is still decaying from the first adaptation, resulting in the before mentioned adaptation rebound. Trewartha et al. (2014) found that older adults show less spontaneous recovery than their younger controls, indicating impairments in implicit learning. This is in disagreement with evidence suggesting that the implicit component does not decline with aging (Vandevoorde and Orban de Xivry, 2018). In order to clarify this discrepancy, we replicated the force-field adaptation paradigm designed by Smith et al (2006). Twenty-one healthy young (23.4 ± 2.4 years) and thirteen healthy older adults (64.7 ± 4.2 years) completed a long perturbation phase, followed by a short counter-perturbation phase and an error clamp phase, in which feedback was fixed to zero error to elicit spontaneous recovery. Throughout the perturbation phases we interspersed catch trials, which were color cued, to assess the implicit component of adaptation (Morehead et al, 2015). Both groups adapted equally well to the perturbation. Implicit adaptation of the older subjects was indistinguishable from their younger counterparts (young: 5.01 ± 1.47cm, old: 4.21 ± 1.65cm). In addition, the extent of spontaneous recovery was also similar across groups (young: -0.99 ± 0.86 N, old: -1.08 ± 1.47 N). Implicit adaptation and spontaneous recovery were found to be correlated (Pearson r= 0.53; p=0.0006). Our results reconcile previous studies by showing that both spontaneous recovery and implicit adaptation are unaffected by aging.

Disclosures: P. Hermans: None. **Y. Lam:** None. **K. Vandevoorde:** None. **J. Orban de Xivry:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.20/MM14

Topic: E.04. Voluntary Movements

Support: JSPS Grant 16J02485
JSPS Grant 17H00874

Title: Motor practice under transcranially induced variable brain states improves the retention of motor memories

Authors: *M. TAKEMI, D. NOZAKI
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Abstract: Humans can learn new motor skills through trial and error, producing a memory that will be recalled the next time. However, this memory is temporary, and the skill gets close to the baseline with the passage of time. Thus, a fundamental issue in motor learning is how to better retain the memories. Previous studies that examined familiar tasks such as ball throws revealed the advantage of variable practice over constant practice in retention of motor memory (Kerr and Booth 1978; Shea and Kohl 1991), but its neural underpinnings remain unclear mostly due to the complexity of the learning processes. Here, using an arm-reaching task in a velocity-dependent force field (FF) and transcranial direct current stimulation (TDCS), we indicated that the benefit of variable motor practice stems from the variability of sensorimotor cortical activities during learning period.

36 participants were assigned to one of the three conditions. One condition applied four different TDCSs to the sensorimotor cortex in which current flowed anterior-to-posterior, posterior-to-anterior, medial-to-lateral, and lateral-to-medial directions relative to the central sulcus during FF learning. The others used one or two of the four TDCSs throughout the learning period. Following the FF learning, all participants performed reaching movements in a channel in which errors were absent with sham TDCS. The results showed that the decay of motor memories, quantified using the force exerted against the channel in the last 10 trials, was less in the participants who were exposed to FF with multi-pattern TDCS than those exposed with single- and double-pattern TDCS. The task performance at the end of the learning period and the learning rate were not different between the conditions. Moreover, a follow-up experiment, which tested the effects of the four TDCSs on the recollection of motor memories with 20 participants, demonstrated that the memory was most reinstated when TDCS intervention during FF learning and the channel test was matched. The amount of the memory reinstatement was not associated with TDCS-induced changes in the corticomotor excitability, assessed using electromyographic responses of transcranial magnetic stimulation.

The present results provided causal evidence that the TDCSs targeting sensorimotor cortex manipulated brain states involved in the formation of motor memories and thus enabled to tag a motor memory to multiple cortical activation patterns. Variable brain states motor practice, mediated by externally applied electric fields, may help to compose a more robust representation of the task, resulting in facilitation of the memory stability.

Disclosures: M. Takemi: None. **D. Nozaki:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.21/NN1

Topic: E.04. Voluntary Movements

Title: Variety of target position in force-field reaching task affects retention of the motor skill

Authors: *T. OGASAWARA, M. TAKEMI, D. NOZAKI
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Abstract: Movement variability is widely thought of the inevitable consequence of stochastic nervous system function (Churchland et al., Neuron 2006) and often deemed as an unwanted characteristic of motor performance. However, a recent study has shown that higher levels of task-relevant intrinsic movement variability related to faster error-based learning to adapt movements in novel physical environments (Wu et al., Nat Neurosci 2014). We inferred from this study that artificial manipulation of the task-relevant variability may benefit motor learning. Yet no one has systematically tested how the extrinsically imposed movement variability affects different aspects of motor learning, such as learning rate, the amount to be learned, and retention of the motor memory.
In this experiment, 50 participants performed 110 reaching movements under a velocity-dependent curl force field (FF) while holding a robotic manipulandum. They were divided into five experimental groups. One group had a single visual target to be reached, which was shown 10 cm forward from the start of the movements. In the other groups, 11 visual targets uniformly distributed in the range of ±2.5°, 5°, 10°, or 20° from the front target were used for the training (10 reaches for each target). The targets distributed within different ranges enabled to artificially manipulate the task-relevant movement variability. Following the FF learning, all participants performed 50 reaching movements to the front target in a channel in which errors were absent. The results showed that motor memories, quantified using the intercept of the exponential curve that was fitted to the peak force in the last 50 channel trials, remained well when the target position varied within ±5°. The amount of memory at the end of FF learning and the learning rate was not different between the groups.
Why did the target variability facilitate retention of the motor memory?Neurons are recruited differently every trial even when one intended to repeat a constant motor act(Churchland et al., Neuron 2006). The variability of reaching targets may further increase the variety of the firing neurons, some of which are hardly activated during a constant motor act. We speculated that optimal level of the additional variability in targets allows to involve residual neurons in motor learning and thus to compose redundant neural representation of the learned skills.

Disclosures: T. Ogasawara: None. **M. Takemi:** None. **D. Nozaki:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.22/NN2

Topic: E.04. Voluntary Movements

Support: JSPS Grant 16J02485
JSPS Grant 17H00874

Title: Looking for a sign of failures: Reaching error triggered by slowing down of movement in the preceding trials

Authors: *T. KOBAYASHI, M. TAKEMI, D. NOZAKI
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Abstract: Even in well-practiced motor skill, we cannot repeatedly perform the movement without variability that sometimes makes unexpected motor errors. For example, a professional baseball player who can pitch with high repeatability and precision often threw the ball to the location to which he did not aim (Chaisanguanthum et al., 2014). Previous studies have suggested that movement variability is associated with the neural activities during the preparatory period in dorsal premotor cortex and primary motor cortex (Churchland et al., 2006; Haar et al., 2017). These findings lead to the possibility that we can predict the occurrence of failures from neural activity. In fact, specific patterns of the electroencephalographic activity were observed 100−1000 ms before the movement onset only in the failure trials (Babiloni et al., 2008; Bediou et al., 2012). However, it has not been fully investigated how and why such a failure action and the associated brain activity pattern arise. Do they suddenly arise or is there any sign beforehand? In the present study, we examined this question using a reaching movement adaptation paradigm. 15 healthy adults were trained to reach toward a forward target (movement distance: 10 cm) under the presence of rightward velocity-dependent force field. They performed 440 trials consisting of baseline phase without the force field (trials 1−20), adaptation phase with the force field (trials 21−420) and washout phase removing the force field. We evaluated a lateral deviation (LD) from the straight path between the target and the starting position at the peak hand velocity as a performance index and found that, even for the final 300 trials in the adaptation phase in which the sufficient practice had been completed, the LD varied among trial-to-trial and sometimes exhibited greater magnitude. Failure trials (FTs) were defined as the trials in which the top 5% of the LD was observed. The state space model for motor adaptation (Thoroughman & Shadmehr, 2000) predicts greater LD (i.e., failure trials) should follow smaller LD, but there was no significant change in the LD in the up to 5 trials before the FT. Neither a significant change in the reaction time was observed. The only behavioral sign associated with the FTs was the peak velocity, which gradually decreased from 2 trials before the

FT. These results were substantially unaffected if the definition of FT was changed (e.g., top 3 and 10%). Our results suggest that movement failures do not suddenly happen and there is a sign of the failure observed in the prior trials. Our approach may pave the way to investigate how failures happen and the underlying neuronal mechanisms.

Disclosures: T. Kobayashi: None. **M. Takemi:** None. **D. Nozaki:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.23/NN3

Topic: E.04. Voluntary Movements

Support: OGS
NSERC-CREATE

Title: Do movement sequences and consequences facilitate dual adaptation to opposing visuomotor rotations?

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Abstract: When planning movements, the human central nervous system (CNS) can actively compensate and adapt to two or more distinct perturbations simultaneously ("dual adaptation") though this process only occurs when each visuomotor map is associated with a sufficient contextual cue. Not all contextual cues are effective at facilitating dual learning and only more "intrinsic" or motor-based cues tend to be integrated by the CNS. More recently It has been shown that lead-ins, follow-throughs, or even a sequence including both, can facilitate learning of opposing force-field perturbations. Here, we investigate whether movement sequences require an active component or if a visual consequence is sufficient in facilitating dual adaptation of opposing visuomotor rotations. Using a virtual reality paradigm, participants manipulated a projected hand-cursor using a digitizing tablet in a semi-dark room with an opaque board occluding visual feedback of the hand. In the sequence experiment, participants experienced opposing rotations (30° clockwise (CW) or 30° counter-clockwise (CCW)) within the same experimental block, each associated with a distinct sequence (i.e. hand reaches to the left or right of the primary target to a secondary target). To explore whether a passive visual consequence was sufficient, in the follow-up experiment each rotation was associated with a target consequence (i.e. target moves to the left or right secondary target). In the final experiment, the secondary target cued the perturbations but no action was required to achieve it. To compare the extent of dual learning, two more groups each learned a single rotation with the same previous

sequence-rotation association. Lastly, in a secondary task immediately following training, all groups received additional training where we brought awareness to the cursor-movement discrepancy. In these tasks, participants were instructed to include or exclude any strategy they formed to compensate for the perturbed hand-cursor. Across all experiments, in the training condition, participants either completed CW trials only, CCW trials only, or both interleaved within the same block ("dual group"). We find that both movement sequences and consequences sufficiently but weakly facilitate dual adaptation showing small reach aftereffects in the expected directions. Static visual cues did not lead to dual learning. Together these findings show whether active movement sequences and passive consequences are incorporated into motor planning and execution, and can thus facilitate dual learning of opposing visuomotor rotations.

Disclosures: M.N. Ayala: None. **D.Y. Henriques:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.24/NN4

Topic: E.04. Voluntary Movements

Support: DFG HA 6861/2-1
NSERC

Title: The fast and slow process differ with feedback but not age

Authors: *J. E. RUTTLE[1], B. M. 'T HART[2], A. STÄUBLE[3], T. EGGERT[4], D. Y. HENRIQUES[5]
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Abstract: Motor control is integral for quality of life. Importantly, the motor system can adapt to alterations in visual feedback, to ensure consistent, accurate movements. One prominent model, the two-rate model (Smith et al., 2006), proposes that a fast and slow process, which respond differently to errors in movement, combine to create changes in motor output, including those seen during rotated visual feedback training (McDougle et al., 2016). Specifically, the two-rate model can explain a "rebound" effect observed in error-clamp trials in some perturbation schedules. However, how these two processes contribute to motor adaptation with different visual feedback and in different age groups is still unclear. First we change how errors are shown to participants who learned to reach with a visuomotor rotation of 45º by giving them either terminal or continuous feedback. In continuous feedback the cursor was shown throughout, but

in terminal feedback it only appeared at the end of the reach. The same participants completed both feedback conditions with different rotations in separate areas of the work space and in counterbalanced order to prevent interference. As expected, reaches with continuous feedback were best modeled with a two-rate model of motor learning. On the other hand, we found that terminal feedback reaches were best modeled with a single process, which follows from the lack of a rebound. We also tested if age affects visuomotor adaptation when the rotation is introduced abruptly or gradually over the course of 60 trials, by testing a group of younger (under 35 yrs.) and older (over 55 yrs.) participants. We found no effect of either speed of rotation introduction or age with no interaction between measures; the magnitude of the rebound was similar. In other words, it appears the balance of fast and slow processes is comparable in abrupt and gradual rotation introduction paradigms regardless of age. Simulations suggest that changing the perturbation schedule could lead to larger differences in reach deviations in the error clamp phase between abrupt and gradual conditions, or different age groups, but this remains to be tested. Our results highlight the viability and benefits of within-subject paradigms for testing models of motor learning and may improve the design of motor-learning experiments.

Disclosures: J.E. Ruttle: None. **B.M. 't Hart:** None. **A. Stäuble:** None. **T. Eggert:** None. **D.Y. Henriques:** None.

Poster

309. Voluntary Movements: Reaching Control: Motor Learning: Human II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 309.25/NN5

Topic: E.04. Voluntary Movements

Support: NSERC
DFG HA 6861/2-1

Title: Proprioception and prediction do not optimally integrate in hand localization

Authors: *B. M. 'T HART[1], M. N. AYALA[2], D. Y. HENRIQUES[3]
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Abstract: Knowing where your limbs are, is important for planning and controlling movements. Limb position also takes a central role in optimal feedback control paradigms when evaluating movements to update internal models. When people are asked to localize their unseen hand after a movement, they have two non-visual signals available: predicted sensory consequences, based on an efference copy of the motor command, and felt hand position, or proprioception. People could combine these two signals in a maximum likelihood estimate which would have higher reliability than each signal individually, evident as a lower variance. While we can’t measure

hand location estimates based on predicted sensory consequences in isolation, we can measure hand location estimates based on the two signals combined (lower variance) and based on proprioception alone (higher variance). In a previous paper (’t Hart & Henriques, 2016) we found no evidence of maximum likelihood estimation as the variance of the responses was approximately equal. However, there were very few trials, and a relatively small group of participants, potentially obscuring effects. Here we have almost triple the data per participant in 84 younger participants. In this larger dataset there is again no evidence of maximum likelihood estimation: the variance of responses in the two hand localization tasks is equal. In sum, it seems that the brain does not create a maximum likelihood estimate integrating predicted sensory consequences with actual sensory information the same way it would integrate two sensory signals. Perhaps it is optimal to either keep both predicted and actual sensory information separately available, or combine the signals in a different way.
We use this larger dataset to explore some other issues as well. In a group of older participants (N=24, age: 55+) we can test if proprioceptive acuity decreases with age. Furthermore, we can probe if weaker proprioceptive priors lead to larger training-induced recalibration of proprioception, or if the variance of pre-training no-cursor reach directions can better predict training-induced changes on any measures.

Disclosures: B.M. 't Hart: None. **M.N. Ayala:** None. **D.Y. Henriques:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.01/NN6

Topic: E.04. Voluntary Movements

Support: Whitehall Foundation Research Grant 2017-05-71

Title: Adaptations of motor cortex activity in the planning and execution of sensory selection

Authors: K. ARULJOTHI, *E. ZAGHA
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Abstract: What neural mechanisms enable us to respond to certain stimuli while ignoring others? To address this question, we developed a lateralized whisker detection task, in which mice are trained to respond to stimuli in one whisker field (target) and ignore stimuli in the opposite whisker field (distractor). In expert mice, we used widefield GCaMP6 Ca2+-sensor imaging to observe activity in target and distractor, sensory and motor cortices simultaneously. For both target and distractor stimuli, sensory responses rapidly emerged in primary somatosensory cortex. On hit trials (responses to target), we observed rapid and robust propagation of activity into motor cortex preceding the response, which was significantly

stronger in the target-aligned versus distractor-aligned motor regions. Additional evidence suggests that asymmetric motor cortex activity is a task-dependent adaptation for sensory selection. First, stronger activation of target-aligned motor cortices was also observed preceding spontaneous responses and responses to the distractor, and therefore is not dependent on sensory inputs. Second, stronger activity in the target-aligned motor cortices was present during the inter-trial even before stimulus onset. These data contrast with recordings in naïve or anesthetized mice, in which activity is highly symmetric across hemispheres. Overall, these recordings demonstrate task-dependent adaptations of motor cortex activity in the planning and execution of goal-directed behavior.

Disclosures: K. Aruljothi: None. **E. Zagha:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.02/NN7

Topic: E.04. Voluntary Movements

Support: Whitehall Foundation Research Grant 2017-05-71

Title: Functional plasticity of motor cortex in a lateralized whisker detection task

Authors: *B. ZAREIAN[1], Z. ZHANG[2], E. ZAGHA[1,2]
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Abstract: Recent studies have reported diverse and contradictory roles for motor cortex in motor control, including motor learning, execution, initiation and inhibition. One possible explanation for these discrepancies is that the function of motor cortex may differ under different task conditions. We wanted to test the extent to which motor cortex function is task-dependent, even within the same individual. Therefore, we developed a Go/NoGo whisker detection task, in which mice were trained to respond to stimuli in one whisker field (target) and ignore stimuli in the opposite whisker field (distractor). In expert mice, we used optogenetic methods to test the functional output of motor cortices aligned either to the target or distractor representations. Additionally, we tested two major types of layer V pyramidal neurons, within both whisking and licking motor regions. We observed significant differences in the functional outputs of target-aligned and distractor-aligned motor regions. Notably, in the distractor-aligned motor cortices, we observed on-off responses, which was not observed in target-aligned motor cortices or naïve animals. Our results highlight the capacity for motor cortex to undergo extensive and asymmetric functional plasticity with task learning. Furthermore, these findings argue that motor cortex may mediate multiple aspects of motor control, depending on the contingencies of the task.

Disclosures: B. Zareian: None. **Z. Zhang:** None. **E. Zagha:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

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Topic: E.04. Voluntary Movements

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Title: Investigating kinesthesia in the primate somatosensory cortex

Authors: *R. DARIE[1], D. A. BORTON[2,3,4]
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Abstract: Motor control is a dynamic feat that humans perform seamlessly across diverse and changing environments. Rich kinesthetic feedback concerning the state of one's limbs is a necessary condition for fluid motor function. Understanding the neural code for kinesthesia could inform the design of afferent prosthetic interfaces that communicate such feedback to the nervous system. However, efforts in this direction have been restricted to the upper limb representation and the problem remains unsolved. We propose to close this knowledge gap by recording broadband neural signals from the hindlimb area of primary somatosensory cortex (S1) in an awake, behaving, nonhuman primate engaged in a kinesthetic categorization task.
We have trained a nonhuman primate to sit in a standard primate chair while its foot is secured to a motorized manipulandum with one circular degree of freedom. On each trial, the manipulandum displaces the foot to a predetermined target position. By pressing one of two buttons (two alternative, forced choice) the animal indicates whether the displacement was greater than 90 degrees in magnitude. As expected, the animal's performance is proportional to the difference between the target angle and the reference. In the case of touch perception, somatosensory cortical spike timing and cortical spike rate carry complementary information. We hypothesize that similar mechanisms are at play for kinesthesia. To test this hypothesis, we have recorded and analyzed the activity of neural features (i.e. changes the firing rate and timing of cortical action potentials) evoked by the hindlimb displacements during the task at a single neuron level and at a population level. Simultaneously, we have measured the positions of anatomical landmarks using a motion capture system. We hypothesize that it is possible to decode kinematics from the firing rate of somatosensory cortical neurons. Furthermore, information about a stimulus might be present in the response of a neural population, but not

used by higher order regions to drive behavior. Therefore, our analysis seeks to identify the sensory responses relevant to the behavioral outcomes: we have constructed neurometric curves based on rate and timing neural features and compared them to psychometric response curves.

Disclosures: R. Darie: None. **D.A. Borton:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

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Program #/Poster #: 310.04/NN9

Topic: E.04. Voluntary Movements

Support: Department of Veterans Affairs, Center for Neurorestoration and Neurotechnology

Title: Motor cortical correlates of obstacle avoidance during locomotion in non-human primates

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Abstract: Humans have the remarkable ability of walking without cognitive effort, yet can smoothly and quickly adjust the trajectory of their legs in response to environmental cues, such as obstacles along one's path. It has been shown in animal models that the spinal cord is capable of generating the base muscle activation patterns necessary to perform locomotion through central pattern generators; however supraspinal regions are still required to carry out precise, volitional limb movements. Primary motor cortex (M1) is one such region, yet how M1 seamlessly weaves voluntary limb movements into the ongoing locomotor rhythm during walking in primates is still an open question. Here, we employed an obstacle avoidance paradigm using rhesus macaques to investigate the role of motor cortex in voluntary control during locomotion. Animals were trained to perform three different movement tasks inside a treadmill enclosure. First, they were trained to walk on a treadmill at 2.5km/h. Next, animals were trained to step over an obstacle (3"x2"x17") moving toward them at a speed of 2.5km/h from a stationary, standing position. These two tasks were designed to decouple the neural correlates of autonomous and voluntary movements. Finally, animals were trained to step over the moving obstacle while walking on the treadmill at 2.5km/h. This task integrates the voluntary motion into the underlying locomotion movements. Animals were then implanted with 96-channel Utah-type arrays (Blackrock Microsystems, Utah) in M1 which were connected to a wireless neural recording headstage streaming extracellular activity from untethered animals as they performed the above tasks. Simultaneously, joint kinematics of the hindlimb were obtained using a video tracking system (Simi Motion, Germany). Animals carried out similar movement strategies to avoid the obstacle while stationary compared to while walking. Here, we discuss preliminary

results elucidating the role of motor cortex during primate locomotion. These results could also have implications for the development of hind-limb brain-machine interfaces.

Disclosures: D.Y. Xing: None. **D.A. Borton:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

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Topic: E.04. Voluntary Movements

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Title: The supplementary motor area, but not motor cortex, produces neural trajectories consistent with a network that can autonomously generate long-timescale sequences

Authors: *A. A. RUSSO[1], R. KHAJEH[1], S. R. BITTNER[1], S. PERKINS[2], J. CUNNINGHAM[1], L. ABBOTT[3], M. M. CHURCHLAND[3]
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Abstract: It has been hypothesized that the supplementary motor area (SMA) contributes to motor sequence generation while motor cortex (M1) is primarily concerned with the current motor output. We translated this hypothesis into a dynamical systems framework and examined its predictions. We defined a 'sequence-generating network' as one able to autonomously generate long-duration outputs based on minimal guiding inputs. In contrast, we defined a 'pattern-generating' network as producing outputs more complex than its inputs, while still relying on inputs for timing information. We considered data recorded from monkeys trained to produce rhythmic sequences: 1,2,4, or 7 revolutions of a hand-pedal.
Networks were trained to produce 4- and 7-cycle outputs – a simplified version of the empirical task. A sequence-generating network received a pulse input (different for 4- vs. 7-cycles) and generated the desired output, stopping at the appropriate time, with no further inputs. Network trajectories resembled a spiral, with 4- and 7-cycle sequences involving separated trajectories. These features allowed the network to 'know' whether it was on a 4- or 7-cycle trajectory, and where it was within each trajectory. We trained a pattern-generating network to produce the same output, but with a 'go-pulse' and a 'stop-pulse' 4 or 7 cycles later. This network produced a

limit-cycle that repeated, almost identically, until terminated by the stop-pulse. Thus, the pattern-generating network did not, on its own, retain knowledge regarding which sequence it was generating or where it was within that sequence. We refer to this lack of information as 'trajectory confusion'.
SMA and M1 population trajectories resembled, respectively, sequence- and pattern-generating networks. SMA trajectories avoided trajectory confusion: different sequences and different cycles within each sequence were distinct. M1 showed considerable trajectory confusion: trajectories followed a repeating orbit until the sequence was terminated. We quantified trajectory confusion via an index that is high when two trajectory segments are similar yet lead to dissimilar future trajectories. Trajectory confusion was much lower in SMA.
To further explore computational implications of the differences between SMA and M1, we trained networks to internally follow the empirical neural trajectories, with no aid from guiding inputs. In the presence of noise, networks were stable only when generating the low-confusion SMA trajectories. Thus, SMA neural trajectories, but not M1 trajectories, are consistent with a network that can generate long time-scale sequences with minimal reliance on guiding inputs.

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Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

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Title: Preparation of movement sequences in motor cortex

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Abstract: Before movement, population activity within motor cortex establishes a preparatory state from which movement-related dynamics evolve. Converging evidence argues that this

preparatory process is essential and universally present. Yet our understanding of preparatory activity derives largely from the study of solitary point-to-point movements while most real-world movements occur within sequences. Are sequences prepared as a single 'chunk', or does preparation for subsequent movements occur as the current movement unfolds?
We trained a monkey to perform individual reaches and sequences of two reaches. We recorded from 140 single neurons in motor cortex. We considered two hypotheses: first, sequences might be prepared as a single 'chunk'. Second, reaches might be prepared sequentially, with preparation of the second occurring during execution of the first. These hypotheses make divergent predictions. Consider neural activity when reaching to target A alone, versus A then B. If preparation is chunked, sequence AB should be prepared differently from A alone. If preparation is sequential, there should be little difference in preparation before A begins. Instead, during sequence AB, there should then be a second epoch of preparation during reach A, in anticipation of reach B.
Behavior suggested use of a chunking strategy: sequences were highly practiced and unfolded rapidly and accurately. However, the neural data strongly supported sequential preparation. To isolate preparatory activity, we defined a five-dimensional 'preparatory subspace' based on neural activity during a delay-period. This subspace became strongly occupied once the target(s) were presented. Activity within this subspace depended primarily on the first target, regardless of the presence or direction of a second reach. Among conditions that shared the same first movement, the mean Euclidean distance was 13% of that between conditions with different first movements.
The sequential preparation hypothesis predicts that preparation for the second movement must occur during the first. This was indeed the case. For conditions with only one reach, preparatory subspace occupancy rose following target onset, remained high during the delay, fell as the movement began, and remained low. For sequences, the same pattern was observed, but preparatory occupancy did not stay low. Instead, occupancy re-emerged ~30 ms after initiation of the first movement, reaching a peak 67% as large as during the delay. These results do not rule out chunking in regions upstream of motor cortex, but demonstrate that even rapid and well-learned sequences are subserved by sequential preparation in motor cortex.

Disclosures: A.J. Zimnik: None. **M.M. Churchland:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.07/NN12

Topic: E.04. Voluntary Movements

Support: National Institute of Neurological Disorders and Stroke (NINDS) Javits Award NS25074

Department of Veterans Affairs, Rehabilitation Research & Development Service
DARPA REPAIR (N66001-10-C-2010)

Title: LFP signature of an optimal preparatory subspace in primate reaching and grasping motor networks

Authors: *J. B. HYNES, C. E. VARGAS-IRWIN, J. P. DONOGHUE
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Abstract: Emerging views in systems neuroscience regard motor cortical circuits as dynamical systems that combine sensory information with internally generated signals in order to compute activity patterns that drive spinal motor circuits. In this view, each behaviorally-relevant movement is associated with a specific preparatory neural 'state' (a collective pattern of activity across neurons) that represents the initial phase in a cascade of states (or a neural trajectory (NT)) that ultimately generates movement (Shenoy, 2013). However, little is known about the computations that might drive a neural population to a given preparatory state. Here we examine the relationship between local field potentials (LFPs) and single unit ensemble activity during movement preparation to gain insight into the network computations underlying preparatory state dynamics. We used a state-space analysis framework (Vargas-Irwin, 2015) to examine neural activity in macaque primary motor and dorsal/ventral premotor cortex recorded during the preparation of reach-and-grasp actions cued using a set of instructions (one of two objects and a colored light indicating grip-type) followed by a go signal. The instructions were presented in two different temporal orders (sequential or simultaneous) in order to generate different sets of neural dynamics during the movement planning phase. Analysis of the two experimental conditions revealed distinct NTs associated with the different cue presentation orders. However, activity patterns for both conditions tended to converge to a common preparatory state prior to movement onset. For the sequential condition, the common state was reached around 400ms after the onset of the final instruction cue (1.6 s before the go signal). The simultaneous trials converged onto the same state at a wider range of latencies, reflecting variations in reaction time. In both conditions, the common neural preparatory state coincided with a large negative deflection in the LFP resembling the macroscopic n400 signal observed in frontal and parietal EEG during the semantic integration of representations into working context. We argue that the n400 observed in our data reflects computational processes associated with integrating cue information into the working motor plan at the neural population level. Our results provide support for the 'optimal subspace' hypothesis and suggest that the evolution of population activity to a final preparatory state for a given movement is associated with a general principle of network computation announced by an n400-like field potential.

Disclosures: J.B. Hynes: None. **C.E. Vargas-Irwin:** None. **J.P. Donoghue:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.08/NN13

Topic: E.04. Voluntary Movements

Support: NIH/NINDS Grant NS025074

Title: Stability of single-unit and ensemble-level tuning in primate primary motor and premotor cortex through extensive practice of a motor skill

Authors: *K. PAROO[1], C. E. VARGAS-IRWIN[1], L. FRANQUEMONT[1], J. P. DONOGHUE[1,2]
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Abstract: Brain networks underlying the formation of a conditional arbitrary association ndergo substantial changes early in learning, when behavior is erratic yet rapidly improving. Research in sensory learning has found that activity distributed across many neurons becomes consolidated into a smaller subset of more highly specialized cells. Neurons that carry low levels of stimulus information bifurcate into a small subset with high information and a larger subset with little to no information. However, little research has been done test whether these same changes occur in motor cortex in response to skill learning. Additionally, a skill can continue to be practiced after one has achieved a high level of behavioral performance. It is an open question whether networks underlying the skill continue to evolve more compact and efficient representations as practice continues. Here, we test whether motor cortex evolves into a sparse network with few highly selective neurons following extensive practice of a motor skill. Two rhesus macaque monkeys were trained to reach and grasp objects with two possible grips. A colored light cued the grip for each trial, and another light subsequently cued the monkey to move. We recorded neural activity of populations of neurons in MI, PMd, and PMv using microelectrode arrays (Blackrock Microsystems). Each monkey learned this core task for at least one year before we introduced variations such as reversing the order of cues or delivering both cues simultaneously. All data presented here come from trials of the core task that were interspersed with variation trials during a period of three to four months after the year in which the monkeys achieved proficiency at the core task. After the year of training, nearly half of all MI neurons, and a third of premotor neurons, exhibited selective firing for grip-object combinations during the task. Nearly all neurons in all three areas exhibited some kind of task response. Population analyses reveal that while information in MI is more broadly distributed than in premotor areas, significant decoding is still only achieved with ensembles of dozens of neurons. These results suggest that primary and premotor areas of primate cortex do not evolve toward a compact or sparse representation of task features, despite a lengthy training period and high behavioral

accuracy. This may be an intrinsic feature of a learning function in motor cortex, or it may be due to the learning of novel tasks that occurred contemporaneously with the continued practice of the well-learned task.

Disclosures: K. Paroo: None. **C.E. Vargas-Irwin:** None. **L. Franquemont:** None. **J.P. Donoghue:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.09/NN14

Topic: E.04. Voluntary Movements

Support: CIHR MOP 53339

Title: Premotor cortex contributes to the planning of visually-guided gait modifications in the cat

Authors: *T. NAKAJIMA[1], N. FORTIER-LEBEL[2], N. YAHIAOUI[2], T. DREW[2]
[1]The Res. Ctr. for Brain Function and Med. Engin., Asahikawa Med. Univ., Asahikawa, Japan; [2]Univ. Montreal, Montreal, QC, Canada

Abstract: We have tested the hypothesis that the cat premotor cortex (PMC) contributes to the visuomotor transformations implicated in the planning of gait modifications. We recorded single unit activity from 136 cells localized within areas 6iffu and 4δ of the ventral bank of the cruciate sulcus, lying caudal and medial to the primary motor cortex (area 4ɤ), while cats walked on a treadmill and stepped over an obstacle that advanced towards them. We found a rich variety of discharge patterns including limb-independent cells that discharged several steps in front of the obstacle regardless of whether the limb contralateral or ipsilateral to the recording site was the first to step over the obstacle. Other cells showed step-related changes in discharge patterns related to the contralateral limb when it was the first (lead) limb to step over the obstacle. Such cells discharged either in the steps leading up to the step over the obstacle or during the step over the obstacle. Another class of neurons discharged only, or primarily, when the contralateral limb was placed in front of the obstacle prior to the step over the obstacle by the ipsilateral limb. We also found a mediolateral gradient in the characteristics of neuronal activity within the ventral bank in which a majority of neurons in the medial portion of the PMC were limb-independent while step-related cells were more prevalent in the lateral portion. We propose that the population of cells within the PMC in the ventral bank of the cruciate sulcus contributes to the temporal evolution of a planning process that transforms global information of the presence of an obstacle into the precise spatio-temporal limb adjustment required to negotiate that obstacle.

Disclosures: T. Nakajima: None. **N. Fortier-Lebel:** None. **N. Yahiaoui:** None. **T. Drew:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.10/NN15

Topic: E.04. Voluntary Movements

Support: This work was supported by the CIHR (grant MOP 53339)

Title: Long trains of stimulation applied to the cat's premotor cortex during locomotion modify gait

Authors: *N. FORTIER LEBEL, T. DREW
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Abstract: The premotor cortex is known to play a significant role in the planning and execution of visually-guided movements. However, in the context of natural locomotion, the contribution of this area remains poorly understood. In the current study, we used long trains of intracortical microstimulation (ICMS; 200 ms trains of 0.2 ms pulses at 330Hz) to examine the influence of several regions of the cat's premotor cortex to the structure of the locomotor cycle during treadmill walking. Using glass-insulated tungsten microelectrodes, a total of 120 sites were stimulated at 1.5-2 times the threshold for movement in one chronically-instrumented, unrestrained animal. ICMS was applied both at rest and during all phases of the step cycle in areas 6aα/β, and 6aγ, as well as in area 4γ (the cat's primary motor cortex). We identified stimulation effects by recording both movement kinematics and the electromyographic activity evoked in multiple muscles of the fore- and hindlimbs. Stimulation in area 4γ evoked responses primarily in the contralateral forelimb or hindlimb, depending on the site of the stimulation (forelimb or hindlimb representation). The most common effect was an increase in swing duration and amplitude (for stimulation during swing) with or without a reset of the step cycle (for stimulation during stance). Stimulation in different sites produced different limb geometries during swing. Similar effects were observed upon stimulation of area 6aγ, although often accompanied by movements of the head. In contrast, stimulation of area 6aα/β evoked more complex patterns that frequently involved all four limbs, and often included a curtailment of the contralateral forelimb swing phase. While the stimulation responses were generally incorporated into the gait, some sites produced strong bilateral hindlimb responses that interrupted locomotion. The results show that the premotor cortex of the cat can exert a strong influence on locomotion and that some areas may make an important contribution to interlimb coordination. Such effects may be particularly important for coordinating limb activity when walking over uneven terrain.

Disclosures: N. Fortier Lebel: None. **T. Drew:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

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Topic: E.04. Voluntary Movements

Support: NIH Grant K99 NS101127

Title: Neural activity during corrective, precise arm movements displays cyclic dynamics

Authors: *A. G. ROUSE
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Abstract: Many voluntary movements have been shown to have common neural population activity that is cyclic. This cyclic activity appears as a condition-independent, circular trajectory in the neural space. This cyclic activity has been observed in not only inherently cyclic movements like locomotion but also single, point-to-point reaching movements. Most reaching studies, however, have focused on consistent, overlearned movements with few errors or corrective movements.

To examine the common neural activity during corrective movements, monkeys were trained to use a joystick to reach to 8 peripheral targets of varying sizes in a precision center-out task. The smaller targets required significant precision, often with corrective movements. The subjects were required to acquire and hold the final target for 500-600ms. If the subjects left the target during the final hold, they were allowed to make a corrective movement (without going back to the center) to re-enter and successfully hold the target and complete the trial.

In initial analysis, firing rates were averaged separately for both initial as well as corrective movements. These condition-independent averages were computed for all trials regardless of target or movement direction. jPCA was performed on both the initial movements and corrective movements to identify the two neural dimensions with the most rotational activity. We observed that the initial and corrective jPC subspaces were largely overlapping. Additionally, the neural trajectories of both the initial and corrective movements followed a similar circular path and aligned to the onset and offset of movement.

The phase of the jPCs was next examined for its relationship to the corrective movements. We observed consistent phase alignment of the neural activity with the corrective movement back to the target. In some cases, corrective movements involved multiple peaks in speed and we observed that each was typically accompanied by additional cycles of neural jPCs. In each of the 1st, 2nd, and 3rd cycles of corrective movements, there was a significant relationship between the jPC phase and the peak speed of movement. Finally, we found evidence that the brain state at the time of target exit as defined by jPC phase was predictive of how long the subject took to

make the corrective movement back to the target.
These results suggest that the corrective movements were not performed using a continuously updating model where feedback is used to constantly adjust the hand towards the target. Rather, the results support a pulsatile or cyclic model where discrete submovements are made toward the target.

Disclosures: A.G. Rouse: None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.12/OO1

Topic: E.04. Voluntary Movements

Support: NIH/NINDS grant: R01 NS 082865

Title: Neurons in somatosensory and motor cortices encode hand postures, not joint velocities

Authors: *J. GOODMAN, JR, A. S. LEE, E. V. OKOROKOVA, A. K. SURESH, N. G. HATSOPOULOS, S. J. BENSMAIA
Univ. of Chicago, Chicago, IL

Abstract: Despite the remarkable complexity of our hands, we effortlessly use them to grasp and manipulate objects. To achieve dexterous object manipulation requires not only a sophisticated motor system to move the hand but also a sensory system to provide sensory feedback - proprioceptive and tactile - about the consequences of those movements. While some progress has been made to understand the neural basis of touch in somatosensory cortex, much less is known about the neural basis of hand proprioception. To fill this gap, we simultaneously record time-varying joint kinematics of the hand - measured using a camera-based motion tracking system - and neural activity from somatosensory and motor cortices of rhesus macaques - using chronically implanted electrode arrays - as they perform natural grasping movements and are subjected to passive hand movements. We find that somatosensory representations of kinematics are very similar to their motor counterparts, with spiking activity preferentially encoding the postures (not the velocities) of multiple joints spanning the entire hand. Preferential encoding of hand posture stands in stark contrast to models of kinematic encoding of the shoulder and elbow, where velocities are preferentially encoded. Moreover, we observe similar response properties in somatosensory and motor cortices during both active and passive movements of the wrist and digits. We conclude that hand shaping via movements of the digits and wrist relies on different neural mechanisms than does hand transport via movements of the arm.

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Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

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Program #/Poster #: 310.13/OO2

Topic: E.04. Voluntary Movements

Support: F32 NS093721-01
RO1 NSO35103

Title: Parallel motor pathways in the neocortex of tree shrews and monkeys

Authors: *M. K. BALDWIN[1], L. A. KRUBITZER[2]
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Abstract: The current study is part of an ongoing project focused on understanding the organization and function of frontoparietal networks in mammals and how these pathways were elaborated in primates. Previous work from our lab, using long duration intracortical stimulation techniques, has shown that evoked movements can be elicited from both frontal motor cortical areas (i.e. primary motor and premotor cortex), posterior parietal cortex (PPC), as well as somatosensory cortical areas in both tree shrews (Baldwin et al., 2017) and macaque monkeys (Baldwin et al., 2018). Other studies in primates have shown that evoked movements from stimulation within PPC rely on the integrity of M1 (Stepniewksa et al., 2014; Cooke et al., 2015). Thus, when M1 is inactivated, movements from PPC cannot be evoked suggesting that M1 serves as a gateway for motor commands from PPC. However, little is known about how primary somatosensory cortex functions in the frontoparietal network. In the current set of studies, primary motor cortex was reversibly inactivated using cooling techniques while stimulating somatosensory and posterior parietal cortical areas in both New World titi monkeys, and tree shrews, one of the closest living relatives to primates. When M1 was inactivated, evoked movements could not be elicited from matched movement domains within PPC; similar to previous findings in New World monkeys and prosimians. However, evoked movements from stimulation of the primary somatosensory area (3b) were unaffected by M1 inactivation in both titi monkeys and tree shrews. These findings suggest that 3b is part of a parallel pathway from which movements can be generated; and this pathway does not rely on the integrity of M1. Therefore, primary somatosensory cortex does not simply provide sensory feedback for the frontoparietal motor network, but has the capacity to be involved in the generation of motor movements independent of motor cortex.

Disclosures: M.K. Baldwin: None. **L.A. Krubitzer:** None.

Poster

310. Voluntary Movements: Cortical Planning and Execution: Neurophysiology: Animal I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 310.14/OO3

Topic: E.04. Voluntary Movements

Support: R01 NS 082865

Title: Decoding hand kinematics from neuronal populations in primary motor and somatosensory cortices during grasping

Authors: *E. OKOROKOVA[1], J. GOODMAN[1], S. LEE[1], G. TABOT[2], A. RAJAN[4], N. G. HATSOPOULOS[1], S. J. BENSMAIA[3]
[2]Organismal Biol. and Anat., [3]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL; [4]Epigenetics, Quadrant Biosci., Syracuse, NY

Abstract: The hand, a complex effector comprising dozens of degrees of freedom of movement, endows us with the ability to flexibly, precisely, and effortlessly interact with objects. The neural circuits that mediate manual dexterity in primary motor (M1) and somatosensory (S1) cortices have received comparatively less attention than have those that mediate proximal limb control. The goal of this project is to assess the degree to which hand kinematics can be reconstructed from the activity of neural populations in M1 and S1. To this end, we measure time-varying hand kinematics using a camera-based motion tracking system and simultaneously record the responses evoked in M1 and S1 using chronically implanted electrode arrays while a monkey grasps objects that vary widely in shape and size. We then evaluate our ability to decode hand kinematics from M1 and S1 responses. We find that both neuronal populations yield high decoding performance. Interestingly, hand postures (joint angles) are better decoded than are hand movements (joint angular velocities) from both M1 and S1, in contrast to what has been observed for proximal limb kinematics. Results from this decoding analysis suggest differences between the neural representations of the proximal and distal limb. Furthermore, we show that signals from sensorimotor cortex can support the dexterous control of an anthropomorphic robotic hand using a brain-machine interface.

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Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 311.01/OO4

Topic: E.04. Voluntary Movements

Support: NIH R01 MH111417

Title: Size of the spatial correlation between ECoG and fMRI activity

Authors: *G. PIANTONI[1], D. HERMES[1,3], N. F. RAMSEY[1], N. PETRIDOU[2]
[1]Brain Ctr. Rudolf Magnus, [2]Ctr. of Image Sci., Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [3]Stanford Univ., Stanford, CA

Abstract: Electrocorticography (ECoG) is widely employed to accurately identify the seizure focus as well as the location of brain functions to be spared during subsequent surgical resection in patients with drug-resistant epilepsy. Increasingly, this technique has become a valuable tool to investigate the detailed neurophysiology of human brain functions. Functional MRI (fMRI) is used for similar purposes at a much larger scale but the neural underpinnings of the measured Blood-Oxygen Level Dependent (BOLD) signal are not well understood. ECoG can be used to elucidate this, but since the different modalities exhibit different spatial and temporal features, research would benefit from being able to correlate across modalities. A major issue complicating this is the unknown spatial extent of BOLD signal generated by neuronally active foci. Each grid electrode is thought to record from the cortical area directly underneath the contact but the size of a corresponding BOLD response is unknown. An estimate of this measure would be highly beneficial to cross-modal research (eg neurovascular coupling).
We compared the high-frequency broadband (HFB) activity recorded with ECoG while patients (n=8) performed a motor task (quantified as r-squared), with the activity maps measured with fMRI at 3 Tesla for the same task prior to surgery. For both the preoperative fMRI and ECoG sessions, patients were asked to flex and extend their thumb or all the fingers of one hand for 30 seconds, followed by a rest period of 30 seconds, four or five times. Electrodes covered large parts of one hemisphere and were spaced 1 cm apart. The research was approved by the local institutional review board.
Channels exhibiting low signal or artifacts were rejected and signals from remaining electrodes were referenced to the common average. Subsequently we computed HFB activity in the range between 65 and 95 Hz and compared it between the task periods and the rest periods for each electrode. The fMRI pipeline consisted of realignment, gray-matter segmentation, and general linear model regression . No smoothing was applied. We correlated HFB power change measured with ECoG with the fMRI BOLD percent signal change in the area around each electrode. This latter measure was quantified by applying a 3D Gaussian kernel of varying width

(sigma between 1 mm and 12 mm) to the fMRI maps including only gray-matter.
We confirmed previous reports that HFB activity can explain up to 40% of the BOLD percent change at 3T. Further, we found that the best kernel size across subjects was between 6 and 8 mm. These results suggest that ECoG electrodes are best compared to 3T fMRI with a kernel width of 6-8 mm for crossmodal research.

Disclosures: G. Piantoni: None. **D. Hermes:** None. **N.F. Ramsey:** None. **N. Petridou:** None.

Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 311.02/OO5

Topic: E.04. Voluntary Movements

Support: Netherlands Organisation for Scientific Research (Vici grant)

Title: Changes in corticospinal excitability reflect hand preferences for reaching during whole-body motion

Authors: L. OOSTWOUD WIJDENES[1], S. C. WYNN[1], B. ROESINK[1], D. J. L. G. SCHUTTER[1], L. P. SELEN[1], *W. MEDENDORP[2]
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Abstract: An important aspect in the planning of a reaching movement is deciding which hand to use. While this decision is affected by various factors (incl. handedness, task demands, distance to the reach goal), we recently showed that this decision also depends on whether the body is stationary or in motion (Bakker et al. 2017). More specifically, we showed that acceleration of the body, but not velocity, affects the decisions of hand choice. The neural correlate underlying this observation is not known. Here, using single-pulse TMS, we investigated the excitability of left M1 during a hand selection task under sinusoidal whole-body translations, imposed by a vestibular sled. At eight possible motion phases, subjects had to reach, freely choosing either their left or right hand, to a target presented at one of 35 possible directions (reach trials) or received a short magnetic pulse to their left M1, in the absence of a target and reach (TMS trials). While experiments are still underway, we have now collected data in 8 subjects. As a measure of hand selection bias in the reach trials, we determined the target direction that resulted in equiprobable right/left hand choices, using an adaptive approach. While hand choice was biased towards the dominant hand, this choice bias was modulated by the acceleration signal, replicating our earlier findings. During the TMS trials, we measured MEP amplitudes from the lateral triceps of the right arm as an indicator of corticospinal excitability. We found that MEP amplitudes were dependent on the phase of the motion, following a similar

modulation of the behavioral choice bias. Our findings so far suggest that whole-body motion affects corticospinal excitability, thereby biasing upcoming hand choices in an acceleration dependent manner.

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Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 311.03/OO6

Topic: E.04. Voluntary Movements

Support: FWO Post-doc Fellowship for J. Gooijers
Brains Unlimited Pioneer Fund

Title: Delineation of effector-specific representations in M1 using ultra-high resolution (7T) imaging

Authors: *J. GOOIJERS[1], A. KAAS[2], A. ROEBROECK[2], S. P. SWINNEN[1]
[1]KU Leuven, Leuven, Belgium; [2]Cognitive Neurosci., Maastricht Univ., Maastricht, Netherlands

Abstract: It is generally accepted that a coarse topographical representation of body parts is present in the primary sensorimotor cortex (M1-S1)**[1]**. As to finer-grained representations, i.e. single digits, there is less consensus. Although separate center-of-mass coordinates per digit have been observed, these representations also show overlap**[2]**. Considering these ambiguous findings, the spatial resolution at which the topography is studied might be key. Using ultra-high field (7T) MR scanning, our goal is to determine if increased spatial resolution allows us to more finely delineate digit representations in M1-S1.
Right-handed participants (N=16, age ~24 yrs, 7 male) performed a finger-tapping task. They were instructed to tap one of ten fingers for 20-sec at 1.5Hz. These 20-sec tapping trials were repeated 6 times per finger across 4 runs. Tapping performance was recorded by MR compatible force sensors. Functional images were acquired using a 7T Siemens scanner (32-channel head coil; 1.25 mm isotropic resolution). Functional data were analyzed using GLM with a separate regressor for each finger convolved with a HRF (BV 20.6). Estimates were used to calculate distance measures.
See *Fig.1* for finger representations in M1-S1 superimposed on high-resolution anatomical images. Differential activations are shown, i.e., one finger against other fingers of the same hand.Note that an increased spatial resolution reveals significant peak voxels using differential contrasts (i.e. increased sensitivity to pick-up finger-specific activations). Regarding the thumb, activations are found laterally in M1-S1 (influence of draining veins to be explored). Regarding

all fingers of the left hand, the differential contrast maps of some of the participants show a medial to lateral order for the little/ring, middle/index and thumb. The dissimilarity between activation patterns, measured for each finger pair (Mahalanobis distance), should confirm these results. ROI-based analyses will be performed to separate M1 & S1.
Acknowledgements: We thank J Diedrichsen for assistance with apparatus design

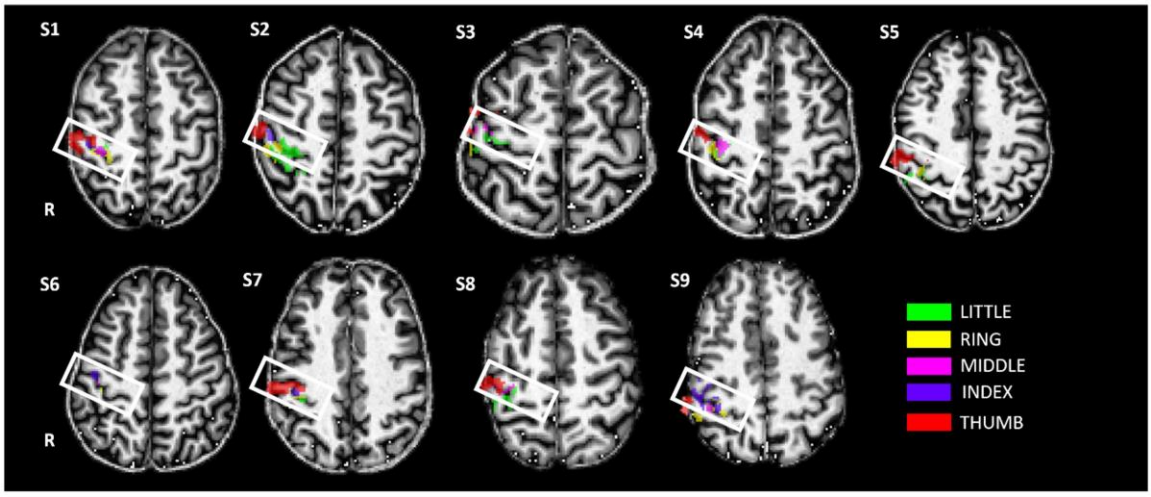

Figure 1. *Individual finger representations in sensorimotor cortex in right hemisphere for left hand tapping. Example subjects are presented. Red: activation in response to tapping of the thumb. Purple: activation in response to tapping of the index finger. Pink: activation in response to tapping of the middle finger. Yellow: activation in response to tapping of the ring finger. Green: activation in response to tapping of the little finger. Activations within the white rectangle largely represent sensorimotor cortex (M1/S1).*

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Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 311.04/OO7

Topic: E.04. Voluntary Movements

Support: CIHR Grant MOP-125915

Title: Cognitive-motor integration performance and its association with white matter integrity in females

Authors: J. M. HURTUBISE[1], *D. J. GORBET[2], L. E. SERGIO[3]
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Abstract: In everyday reaching tasks we often look towards the target we are reaching for. This type of visuomotor transformation is considered "standard" visuomotor mapping. However, reaching movements where the eye and hand are incongruent - "non-standard" mapping - are also common in our daily life. These decoupled eye-hand coordination tasks require cognitive-motor integration (CMI), where rules dictate the relationship between perception and action[1,2]. Previous work has shown an association between poor performance on CMI tasks and decreased white matter integrity in individuals at risk for dementia[3]. The aim of this study is to examine whether such a relationship also exists in individuals with post-concussion syndrome (PCS) [4]. **Methods:** Twenty-six female participants are included in this study; 13 with PCS, with symptoms persisting for 6 months or greater at the time of examination, and 13 age-matched healthy control participants with no self-reported history of concussion. Participants completed 2 visuomotor transformation tasks; one requiring standard mapping (reaching directly to visual targets) and one requiring non-standard mapping (reaching on a different spatial plane relative to visual targets and with 180° rotated visual feedback). In addition diffusion weighted images were acquired. Fractional anisotropy (FA) values were extracted from white matter tracts for analysis of correlation with composite scores of movement timing, trajectory, and corrective movement production. **Results:** No significant differences were detected between the two groups of participants on either performance or white matter integrity. However, there was a significant overall relationship between white matter integrity and CMI task performance. In the non-standard condition, there was a significant relationship between the trajectory performance score and the FA of the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF). Furthermore, there was a significant association between the corrective movement score and FA of the IFL, IFOF, superior longitudinal fasciculus (SLF), and corticospinal tract (CST). In all regions, worse performance was associated with decreased FA. There were no associations between FA in any tract and any of the performance scores in the standard condition. **Conclusions:** The results of this study suggest that decreases in white matter integrity may underlie impaired performance in cognitive-motor integration. [1]Wise et al. *Can J Physiol Pharmacol* (1996) [2]Sergio et al. *Cortical Mechanisms of Vision.* (2009) [3]Hawkins et al. *Journal of Alzheimer's Disease* (2015) [4]Tator et al. *J Neurosurg (2016).*

Disclosures: J.M. Hurtubise: None. **D.J. Gorbet:** None. **L.E. Sergio:** None.

Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

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Title: Exploring changes in motor network physiology and complexity with HD-tDCS and fMRI

Authors: *S. LEFEBVRE[1], K. JANN[2], A. SCHMIESING[1], K. ITO[1], M. JOG[2], N. SCHWEIGHOFER[3], D. J. J. WANG[2], S.-L. LIEW[1]
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Abstract: ***Introduction*** Transcranial direct current stimulation (tDCS) applied to the primary motor cortex (M1) may be an effective tool to modulate motor cortex excitability. However, recent studies have demonstrated significant inter-individual variability in behavioral and neurophysiological changes following M1 tDCS. We hypothesized that stimulating another target, (dorsal premotor cortex; PMd) with high-definition tDCS (HD-tDCS) might modulate brain excitability and motor network complexity more reliably than M1 tDCS.
Methods 46 healthy participants were randomized into 3 groups (left M1, left PMd or sham) in this double-blind study. A 7-minute resting-state fMRI scan was acquired before and after a 7 min HD-tDCS (1mA) session to explore changes in network complexity using a multiscale entropy (MSE) measure, which examines the regularity of biological signals across a range of temporal scales. Changes in cortical excitability were measured before and after tDCS using motor evoked potentials (MEP). fMRI data were linear-drift detrended and noise-corrected using white-matter, CSF, and motion-parameters as regressors. MSE computations used a pattern matching threshold of 0.5 and a pattern length of 2. In total 20 coarse-sampled scales and four regions of interest (L M1, R M1, L PMd, R PMd) were investigated.
Results No significant differences in cortical excitability were found between PMd and M1 groups, which were then combined into one "active stim" group for excitability analyses. A two-way RM-ANOVA, with factors group (active stim, sham) and time (pre, post), showed a marginal increase in cortical excitability (measured by peak-to-peak MEP amplitude) following HD-tDCS (group*time $F(1,43)=2.6$, $p=0.11$; post-hoc tests: *active stim post > sham post* $t(43)=2.3$, $p=0.03$. The weak significance of these results reflects the strong inter-individual variability in groups; only 50% of participants responded to M1 tDCS, versus 73.3% to PMd tDCS.
The MSE analysis showed significant changes after tDCS. In the PMd group, MSE increased in the L PMd (group*time $F(2,43)=7.5$, $p=0.002$, post-hoc tests *PMd post > PMd pre* $t(43)=4.1$, $p>0.001$) and in the R PMd (group*time $F(2,43)=3$, $p=0.06$, post-hoc tests *PMd post > PMd pre* $t(43)=2.2$, $p=0.03$). In the M1 group, MSE showed a marginally-significant increase in the L M1 (group*time $F(2,43)=2.5$, $p=0.09$; post-hoc tests *M1 post > M1 pre* $t(43)=1.68$, $p=0.09$). Overall, MSE changes were stronger in the PMd than M1 group.
Conclusion PMd HD-tDCS may modulate motor network neurophysiology and complexity more robustly than M1 HD-tDCS. In addition, multiscale entropy may be a sensitive marker of changes following noninvasive brain stimulation.

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Poster

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Topic: E.04. Voluntary Movements

Support: KAKENHI 17K01618

Title: Effect of the viewpoint on motor learning and brain activity

Authors: *H. KADOTA, S. SAWADA
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Abstract: Humans can perform appropriate behavior under conditions different from their own viewpoint, such as remote operation, through engineering innovation. In this study, we investigated the effect that different view point environments had on motor memory and brain activity. First, participants performed reaching task with force field learning. This task was carried out from a frontal viewpoint or a right viewpoint. The viewpoints were counterbalanced between participants. The first (from the frontal/right viewpoint) and the second (from the right/frontal viewpoint) blocks were set as the baseline. The third block (the frontal/right viewpoint) had a clockwise velocity-dependent force field. This block was set as learning. The fourth (the right/frontal viewpoint) and fifth (the frontal/right) blocks were set as washout (null force field) to verify the presence of an after-effect and to cause participants to forget the memories that they had learned. The results indicate that motor learning occurred regardless of the viewpoint. Moreover, after-effects were shown at the washout when a viewpoint was converted. This result suggests that the two viewpoints have both a shared motor memory and independent motor memories. Next, we conducted fMRI experiment to identify the neural correlates of the different process from the frontal and the right viewpoint. The participants performed reaching tasks with MRI compatible joystick from either the frontal viewpoint or the right viewpoint. Each participant participated in ten sessions, each consisting of six 20-s blocks. Each session was composed of two resting blocks (the first and the last) and two frontal and two right viewpoints blocks (the order of viewpoint was counterbalanced between participants). The fMRI result showed that the posterior parietal cortex activated during the right viewpoint compared with the frontal viewpoint, whereas there was no significant activation during the frontal viewpoint compared with the right viewpoint. This area appears to be involved to the transformation of visual information from right viewpoint to motor output for reaching movements. The difference of brain activity may contribute to the motor memory depending on the viewpoint.

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Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

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Title: Receptor architecture of the macaque monkey superior parietal lobule

Authors: D. IMPIERI[1], K. ZILLES[2], M. NIU[2], L. JANKOVIC-RAPAN[2], C. GALLETTI[1], *N. PALOMERO-GALLAGHER[2]
[1]Dept. of Biomed. and Neuromotor Sci., Univ. of Bologna, Bologna, Italy; [2]Res. Ctr. Juelich, Juelich, Germany

Abstract: The macaque monkey superior parietal lobule (SPL) is part of a neuronal network involved in the integration of information from visual and somatosensory cortices for execution of reaching and grasping movements. The cytoarchitecture of areas V6, V6Ad, V6Av, PE, PEc, PEci and PGm of the SPL has been described, but little is known about their receptor architectonic organization, although receptor analyses not only provide information concerning brain structure, but also crucial insights into its functional organization.
We applied quantitative in vitro receptor autoradiography to analyze the distribution patterns of 15 different receptors for glutamate, GABA, acetylcholine serotonin, dopamine and adenosine in the SPL and adjoining cortex, as well as in the primary visual, somatosensory and motor areas of four adult male *Macaca fascicularis* monkeys. For each area, mean (averaged over all cortical layers) receptor densities were visualized as a receptor fingerprint of each area. Multivariate analyses were conducted to detect clusters of areas according to the degree of (dis)similarity of their receptor organization.
Differences in regional and laminar receptor distribution patterns confirm the location and extent of areas V6, V6Ad, V6Av, PE, PEc, PEci and PGm as found in cytoarchitectonical and functional studies. Receptor densities are higher in supra- than in infragranular layers of SPL areas, with the exception of kainate, M_2 and adenosine receptors, which reach highest values in layers V-VI. The hierarchical cluster analysis (Figure 1) shows a principal segregation of SPL areas from the primary sensory cortices. Areas PE, PEc, PEci and PGm cluster with posterior cingulate area 31. Area V6Av clusters with visual V6, and V6Ad with MIP and somatosensory area 2. These results are in accordance with the fact that V6Av contains more cells responsive to visual stimuli than does V6Ad, whereas the opposite holds true for cells responsive to

somatosensory stimuli. They further emphasize the special receptor architecture of posterior parietal areas involved in reaching and grasping.

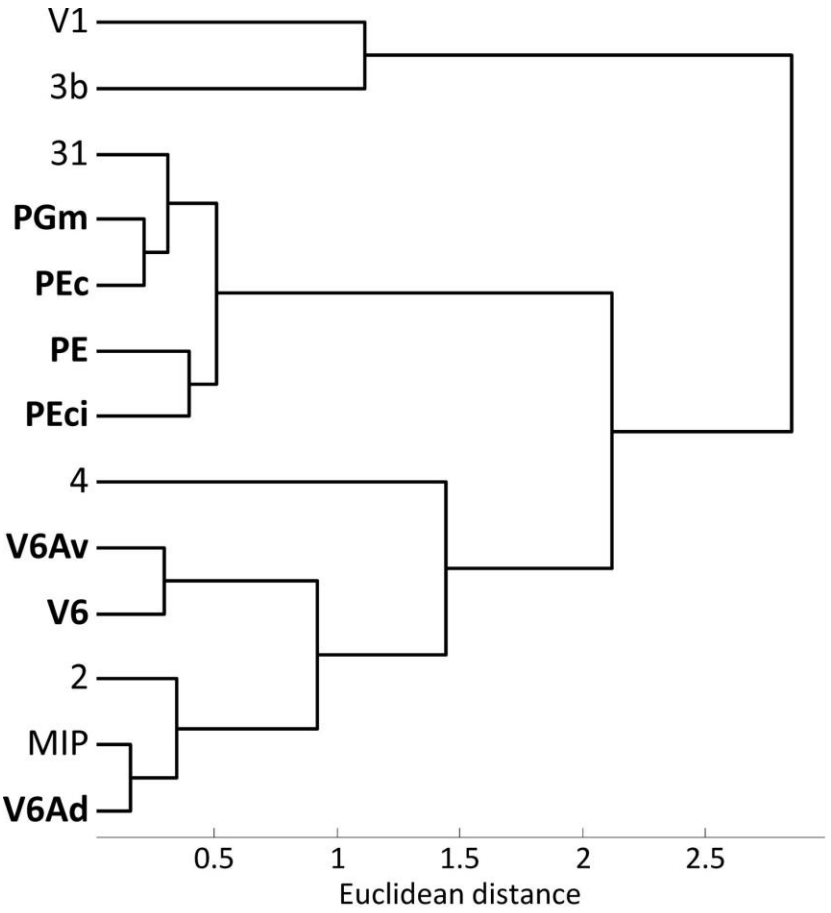

Figure 1: Hierarchical cluster analysis of the receptor fingerprints of areas of the macaque superior parietal lobule (bold font), as well as of the primary visual (V1), somatosensory (3b), and motor (4) areas, and of somatosensory area 2, cingulate area 31 and intraparietal area MIP.

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Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

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Topic: E.04. Voluntary Movements

Support: National Institutes of Health R03HD087481
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Title: Test-retest reliability of corticospinal tract integrity in chronic stroke

Authors: *A. F. LEWIS, M. K. MYERS, J. HEISER, M. B. KOLAR, J. C. STEWART
Univ. of South Carolina, Columbia, SC

Abstract: Stroke often results in damage to the corticospinal tract (CST) that correlates with motor deficits. Fractional anisotropy (FA) of CST is often used to quantify the extent of damage to the motor system, predict motor outcomes, and investigate response to intervention. However, the stability of FA is unknown. The purpose of this study was to examine the test-retest reliability of corticospinal tract FA using two different methods. Eighteen participants with chronic stroke (mean age 59.2 years, months post-stroke 45.4, UE FM score 42.9) underwent diffusion tensor imaging (DTI) on the same MRI scanner 4 days apart. All images were preprocessed in FSL. Two methods for determining CST FA were analyzed. In the manual-based method, a single researcher hand drew masks of the CST at the level of the cerebral peduncle (3 slices). In the template-based method, a standard sensorimotor area tract template (S-MATT) of the CST was transformed into native space. Investigators were blinded to participant and day of data collection in both methods. FA was extracted and reliability was determined by calculating an intraclass correlation (ICC) and minimal detectable change (MDC). As expected, mean FA was significantly lower in the ipsilesional CST compared the contralesional CST ($p<0.02$) and FA ratio (ipsilesional/contralesional FA) values were <0.93 across days. For the manual-based method, FA on Day 1 correlated with FA on Day 4 in both the ipsilesional CST ($r=.698$; $p=.012$) and contralesional CST ($r=.730$; $p=.007$). Moderate reliability was found for ipsilesional CST FA (ICC=.696; MDC=.072) and contralesional CST FA (ICC=.707; MDC=.069); FA ratio was slightly more reliable (ICC=.773; MDC=.101). For the template-based method, FA on Day 1 correlated with FA on Day 4 in both the ipsilesional CST ($r=.967$; $p<.001$) and contralesional CST ($r=.910$; $p<.001$). Excellent reliability was found for ipsilesional CST FA (ICC=.966; MDC=.013) and contralesional CST FA (ICC=.910; MDC=.014); FA ratio was slightly more reliable (ICC= .986; MDC=.015)). FA correlated with UE FM in the manual-based method ($r=.868$; $p<.001$) but not the template-based method ($r=.380$; $p=.180$). The results of this study indicate that both a manual-based and template-based approach are reliable measures of CST FA across days. The template-based approach showed higher reliability than the manual-based approach; however, the validity of this method in capturing CST accurately is unclear (FA did not correlate with motor impairment). The ICCs and MDCs reported here may be useful for future research that aims to predict motor outcomes using CST FA values or report changes in CST FA values over time or in response to intervention.

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Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 311.09/OO12

Topic: E.04. Voluntary Movements

Support: IBS-R015-Y1-2018-a00

Title: Dissociation of neural substrates for motor planning and execution in learning multiple visuomotor mappings

Authors: *S. KIM, K. LIM
Neurosci., Inst. of Basic Sci., Suwon, Korea, Republic of

Abstract: Previous behavioral studies have shown that humans can simultaneously adapt movements to multiple visuomotor mappings after extensive practice. Motor planning, not motor execution, has been known to play a critical role in separating multiple interfering motor tasks and motor memory formation. However, it remains unclear how the human brain represents distinct motor planning and execution for multiple visuomotor mappings. To address this issue, we designed a fMRI experiment in which motor planning and execution can be dissociated during learning multiple visuomotor mappings. Specifically, subjects first adapt to two conflicting visuomotor rotations with different movements and then later with identical movements but different plannings. Finally, subjects make different movements without rotations, by which we can control the effect of motor execution. We reported distinct neural substrates revealed by multivoxel activity pattern analysis (MVPA) for motor planning and execution in learning multiple visuomotor mappings. We also discuss how the pattern separation can account for experienced interference between the mappings, which decreases as a course of learning.

Disclosures: S. Kim: None. **K. Lim:** None.

Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

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Topic: E.04. Voluntary Movements

Support: Canadian Institute of Health Research

Title: Interactions between auditory and motor networks during command-driven actions

Authors: *D. GALE[1], C. H. HONDA[1], I. S. JOHNSRUDE[2], J. R. FLANAGAN[1], J. P. GALLIVAN[1]
[1]Queen's Univ., Kingston, ON, Canada; [2]Psychology / Comm Sci. Disorders, Univ. of Western Ontario, London, ON, Canada

Abstract: While following verbal commands seems effortless in everyday tasks, this belies the complexity of multisensory and motor-related processing occurring in underlying neural systems. Research in rodents and primates has provided critical insights into how the brain transforms visual information into motor-related commands, yet remarkably little is known at the neural level about how incoming auditory commands are similarly used to guide goal-directed behaviour. Here, using functional magnetic resonance imaging (fMRI) and a verbal command-following task that guided different hand movements, we examined neural interactions between human auditory and motor systems. Participants learned to map two nonsense verbal commands to either a right- or left-handed reach-to-grasp movement; the mapping of which switched throughout the experiment, allowing us to disentangle neural activity related to the verbal command from the motor response associated with that command. We hypothesized that representations of the verbal commands in auditory regions might be flexibly shaped by the motor responses cued by those commands. To explore this hypothesis at a network level, we performed task-based functional connectivity analyses between several auditory and motor regions during the task, which showed that the functional coupling of auditory and motor regions increased within the hemisphere guiding the upcoming grasping action. Within auditory regions, multivoxel pattern analysis and dimension reduction techniques were used to reveal time-varying changes in pattern information and low-dimensional neural states, respectively, influenced by the motor effector used. Together, this study provides a first glimpse into the highly dynamic and intertwined nature of auditory and motor networks during natural communicative behaviour, while offering promising avenues for future work examining interactions cognitive and motor systems.

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Poster

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Topic: E.04. Voluntary Movements

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RFBR grant no. 16-04-01883

Title: Stability of cortical muscle representations: TMS motor mapping test-retest study

Authors: *V. MOISEEVA[1], M. NAZAROVA[1], P. NOVIKOV[1], E. IVANINA[1], K. KOZLOVA[1], V. NIKULIN[1,2]
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Abstract: Cortical mapping with transcranial magnetic stimulation (TMS) is a promising approach for non-invasive investigation of the motor cortex in humans. However, apart from the parameters reflecting general corticospinal excitability, e.g., resting motor threshold (RMT) and mean amplitude of the motor evoked potentials, the reproducibility of other TMS motor maps metrics remains controversial or unknown. We studied a test-retest reliability of TMS cortical maps corresponding to multiple hand muscles. We took into account both standard size parameters such as map`s areas as well as novel parameters such as intricate muscle-specific excitability profiles.
The study included 18 young healthy right-handed male volunteers. We used MRI-navigated TMS to stimulate left motor cortex in two mapping sessions separated by 5-10 days. For the mapping we used a grid of 53-58 points each being stimulated in a pseudo-random order five times. Second day TMS session was an exact repetition of the first day session. An analysis was performed using custom-made software TMSmap (http://tmsmap.ru/). We used intra-class correlation coefficient (ICC) to assess reliability of map areas, volumes and the extent of the different muscles overlap. For the quantative comparison of the cortical excitability profiles of individual muscles we utilized earth mover's distance metrics (EMD).
We found that RMT remained the same across two testing sessions in all but two subjects in whom it changed by one percent. ICC for the same muscle representation could be considered as good (0.73-0.85) for areas, moderate for the extent of the different muscles maps overlap (0.7) and poor (0.45-0.49) for volumes. An average shift for hotspots was ~10 mm and for centers of gravity it was ~3 mm. When assessing individual excitability profiles, we found significantly smaller normalized EMD (higher reproducibility) for the same muscle representations across days than for the different muscle representations across days ($P<0,0001$).
The obtained results provide evidence that not only general excitability but also other specific features including standard characteristics (areas, volume) and even excitability profiles of the cortical muscle representation can be reliably traced with TMS motor mapping. This in turn indicates that the existence of the complex TMS cortical representations doesn't simply indicate stochastic fluctuations in the corticospinal excitability during TMS mapping procedure but rather demonstrates a possibility to probe with TMS cortical organization reflecting intricate descending projections relating to specific muscles.

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Poster

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Support: German Research Foundation (DFG), project STR 1146/9-1
SFB/TRR 135 project A3
International Research Training Group IRTG 1901 "The Brain in Action"

Title: The role of the interaction between action generation and hand identity in self-other distinction

Authors: *L. UHLMANN, M. PAZEN, B. VAN KEMENADE, T. KIRCHER, B. STRAUBE
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Abstract: The feeling that a seen hand movement can be attributed to one's own action is in part based on a match between the incoming sensory information and predictions about the sensory consequences of the action. Matches should occur if the hand movement was self-generated (i.e., active) and if the moving hand was recognized as one's own hand. It has been shown that sensory consequences caused by active movements are attenuated perceptually and neurally. It is still unclear, however, how predictive processes interact with afferent signals relaying the identity of a seen hand in order to coordinate self-other distinction. Thus, we conducted an fMRI study in which we investigated whether the sensory consequences of active and passive hand movements are processed differently depending on whether one's own or someone else's hand is seen. In the experiment, 24 healthy participants (14 female, aged 20-35 years) were instructed to detect temporal delays between active or passive hand movements and a visual feedback displaying a correspondingly moving hand on a computer screen. To execute a hand movement, participants had to grab the handle of a custom-made movement device while performing an extension and a flexion of their right wrist. In passive trials, the movement device moved automatically so that the participant's hand was moved passively. Furthermore, either the participant's own or someone else's hand was displayed as feedback. Importantly, the movement trajectories of the seen hand always corresponded with the actual hand movement. These manipulations allowed us to disentangle movement-related effects (e.g., who is triggering the movement) from effects due to visual characteristics (e.g., whose hand is moving), which both contribute to self-other distinction. On the neural level, passive movements elicited a stronger BOLD-response in parietal and frontal areas than active movements. Moreover, an interaction between action generation and hand identity was found in the precuneus and the angular gyri, suggesting that self-referred processing was modulated by sensory predictions accompanying active movements. In addition, taking the precuneus as seed region, a stronger functional

connectivity (PPI) with the middle occipital lobe as well as the left precentral and postcentral gyrus was found for passive movements, as compared to active movements, indicating that a loss of self-agency is processed in a wide network including motor and sensory areas. We assume that efferent signals involved in action generation processes and afferent signals relaying the identity of the seen hand interact in order to differentiate between self and other.

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Poster

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Program #/Poster #: 311.13/OO16

Topic: E.04. Voluntary Movements

Support: University of Houston
Guangdong Provincial Work Injury Rehabilitation Center

Title: Single trial investigation of flash-cued hand clenching through scalp EEG and source localization

Authors: *Y. ZHANG[1], T. T. NGUYEN[2], T. POTTER[1], R. G. GROSSMAN[3]
[2]Biomed. Engin., [1]Univ. of Houston, Houston, TX; [3]Neurosurg., Houston Methodist Hosp., Houston, TX

Abstract: Voluntary motor activity is a complex task that been a focus of study for many decades. Of particular interest are the cortical dynamics that support motor reactions and the role of the readiness potential, which appears before subjects report the decision to move.
In this experiment 5 healthy subjects were recruited to perform a visually-cued hand clenching. Subjects were seated in a comfortable chair in front of a laptop computer and a 64 EEG cap was placed on their head, with the FT10 channel sacrificed to measure EMG. Participants were asked to squeeze their hand for ~10 seconds whenever the screen flashed white, without straining or counting the time. Under the experimental paradigm, the screen displayed a green background screen with white flashes occurring every ~25 seconds. Data were collected across 30 total trials at a 1 kHz sampling rate. Signals were band-pass filtered from 0.5-50 Hz and ICA was applied to remove ocular and motion artifacts. T1 structural MRI data was also collected from each subject and Freesurfer software was used to create subject-specific models. Source imaging was then performed using the sLORETA algorithm and signals were analyzed at the scalp and electrode layers. Single trial results were examined at the supplementary motor area (SMA) and motor cortex (MCx), along with their associated EEG channels (Cz and C3).
Scalp EEG at the Cz location showed an increase in alpha activity that began ~50 ms after the

flash and ended ~50 ms before hand squeezing. This activity was comprised of two peaks: one exclusive to the alpha band and a broader activation spanning from ~0.5-10 Hz. A gradually increasing positive potential can be seen to peak ~350 ms after stimulus flash, which deflects to a negative peak at the time of hand squeezing. Cortical activity showed a spike of activity that aligned with stimulus perception, followed by a quiescent period and a second peak ~50ms before hand clenching. EEG activity at the C3 electrode showed a negative peak (3-12 Hz) occurring ~100 ms after stimulus onset, with a positive deflection occurring ~250 ms before hand clenching. Source imaging revealed a peak in activity immediately after stimulus onset that matched with EEG (0.5-12 Hz), with a second peak rising largely in the alpha band ~100 ms after clenching. Despite maintaining the clenching, no further peaks in activity remarkable peaks were observed after the initial response.
Results revealed activity in the SMA and MCx that was associated with the readiness potential and motor response. While EEG responses were generally seen as broad, slow waves, cortical responses instead showed distinct spiking activity that related to both stimulus perception and movement.

Disclosures: Y. Zhang: A. Employment/Salary (full or part-time):; University of Houston. **T.T. Nguyen:** A. Employment/Salary (full or part-time):; University of Houston. **T. Potter:** A. Employment/Salary (full or part-time):; University of Houston. **R.G. Grossman:** None.

Poster

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Support: T32 GM008471-22
NIH RO1NS18338
NIH PO1NS058901
NIH 1R21NS103098-01

Title: Mesoscopic imaging of the mouse cerebral cortical network dynamics during spontaneous behavior

Authors: *S. WEST[1], L. S. POPA[1], R. E. CARTER[1], G. CHEN[1], J. D. ARONSON[1], L. GHANBARI[2], S. B. KODANDARAMAIAH[2], T. J. EBNER[1]
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Abstract: The brain performs complex computations involving large networks that span across multiple cortical and subcortical structures. However, study of these processes is difficult, as the recording of neuronal activity is often limited spatially or temporally. Using CAD design and 3D

printing, we fabricated optically clear, geometrically conformant cranial prostheses that chronically replace a large portion of the dorsal mouse cranium without inducing tissue deformation of the cerebral cortex. These prosthetic windows allow for wide field-of-view (approximately 4 x 4 mm) for optical imaging of the majority of the dorsal cerebral cortex at 1x magnification. By implanting these windows in Thy1-GCaMP6f mice expressing the Ca^{2+} indicator GCaMP6f in Layer II/III and Layer V pyramidal neurons, we imaged cerebral cortical Ca^{2+} activity in awake animals (50 Hz acquisition) with high spatial resolution (35 x 35 µm pixel size). After recovery from surgery and acclimatization to experimental setup, the animals were recorded during multiple sessions, typically 10 trials each 50 s in duration, over several months. During imaging sessions, the mice were head-fixed under a single-photon fluorescent microscope (Nikon AZ-100), on a low friction, disk treadmill. Simultaneously with imaging, motor behaviors including locomotion, grooming, and whisking were recorded using-high speed cameras at either 50 Hz or 200 Hz. Behavioral motion was tracked using a computer vision segmentation and SURF tracking algorithm. Additionally, locomotion distance and speed were monitored by sensors on the treadmill. Mesoscopic Ca^{2+} imaging of the dorsal cerebral cortex revealed a widespread and dynamic nature of neuronal activity even during quiescent periods. During a trial, different regions of the cerebral cortex are active at various times with a strong tendency for homotopic cortical regions to be active bilaterally. These complex spatial and temporal activity patterns were analyzed using spatial independent component analysis (ICA), segmenting the cortical surface into spatially distinct cortical domains. Typically, 10-20 independent components were identified in a trial that, in aggregate, cover the entire dorsal cortex. Individual components tend to reflect functional domains (i.e. barrel or motor cortex) and are consistent across trials and days. Several of the components are present at all times, while others depend on the behavioral state of the animal. We are able to quantify cortical activity as patterns of activation that occur on a mesoscopic scale across the brain. These patterns are dynamic over time and reflect the variation in cortical function with behavioral states.

Disclosures: S. West: None. **L.S. Popa:** None. **R.E. Carter:** None. **G. Chen:** None. **J.D. Aronson:** None. **L. Ghanbari:** None. **S.B. Kodandaramaiah:** None. **T.J. Ebner:** None.

Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 311.15/OO18

Topic: E.04. Voluntary Movements

Support: McGovern Institute Neurotechnology (MINT) fund
NIH Grant 1R21NS103098-01
NIH Grant 3R21 NS103098-01S1

Title: Craniobot: An open source robotic neurosurgery platform for automated craniotomies in small animals

Authors: M. L. RYNES[1], L. GHANBARI[2], J. J. HU[1], D. SOUSA SCHULMAN[3], M. LAROQUE[3], G. JOHNSON[3], G. SHULL[1], *S. B. KODANDARAMAIAH[4,1]
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Abstract: Over the last decade, a plethora of tools have been developed for neuroscientists to interface with the brain. Implementing these tools requires precise removal of sections of the skull to access the brain. These delicate cranial microsurgical procedures need to be performed on sub-millimeter thick bone without damaging the underlying tissue and therefore, require significant training. Automating some of these procedures would not only enable more precise microsurgical operations, but also democratize use of advanced neurotechnologies. We have developed the Craniobot, a cranial microsurgery platform that combines automated skull surface profiling with a computer numerical controlled (CNC) milling machine to perform a variety of cranial microsurgical procedures in mice. The Craniobot utilizes a low force contact sensor to profile the skull surface and uses this information to perform micrometer-scale precise milling operations within minutes. The Craniobot's custom contact sensor was able to detect the surface of the mouse's skull precise to 6 μm for 97.4% of measurements (n = 6 mice, 192 points each mouse). Data acquired from surface profiling was successfully used to perform microsurgical procedures for demonstration purposes, including skull thinning and polishing for optical access, skull excisions for glass coverslip implantations, and pilot holes for skull anchors. The Craniobot is built using off-the-shelf components for under $1000 and is controlled using open-source CNC programming software.

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Poster

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Program #/Poster #: 311.16/PP1

Topic: E.04. Voluntary Movements

Support: NIH RO1NS18338
NIH PO1NS058901
T32 GM008471-22
NIH 1R21NS103098-01

Title: Functional interactions within the mouse cerebral cortical network during spontaneous behavior

Authors: *L. S. POPA, Mr[1], S. WEST[1], R. E. CARTER[1], G. CHEN[1], J. D. ARONSON[1], L. GHANBARI[2], S. B. KODANDARAMAIAH[2], T. J. EBNER[1]
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Abstract: Understanding both brain function and pathology at a system level rests on understanding the multitude of interactions between structures defined by specific behavioral roles. However, the sheer complexity of the brain as well as the dynamic nature of the functional interactions require new investigative approaches. One of these experimental paradigms is longitudinal mesoscopic imaging of cellular Ca^{2+} signals. We deployed this approach in the dorsal cerebral cortex of behaving mice, using chronic implants of morphologically conformant, optically clear, 3D printed skull prostheses in Thy1-GCaMP6f mice expressing a Ca^{2+} indicator in neurons. This method allows repeated imaging of large cortical areas (~16 mm^2) at 50 Hz during 50 s trials over months simultaneously with high-speed imaging of behavior. We used independent component analysis (ICA) to functionally segment the imaged cerebral cortical area, obtaining on average 13 ± 3 spatial independent components, excluding movement artifacts. We used a second ICA step to extract six independent time courses for each spatial independent component that characterize their temporal evolution. For further analyses, we retained only the time courses with a relative high stability score (iq > 0.75). Within a trial, the population of stable time courses cluster in groups with high similarity (correlation coefficient > 0.7). The clustering of time courses is highly dependent on the behavioral state of the mouse (preparing to walk, walking, or resting after walk). To better understand the functional interactions between the spatial independent components, we used conditional, multi-variate Granger causality. This allowed us to measure the directed interactions between selected groups of time courses, conditional on the presence of the rest of the time courses extracted within the same trial. The interacting groups were selected based on being extracted from one spatial component. To determine the interaction timing, the target time courses were shifted relative to the rest of the time courses in 20 ms steps over a ±5 s time window. The Granger analysis was repeated at each time shift. We determined that the interactions between independent components are highly dependent on the behavior state of the mouse. We also determined that long range interactions between independent components over extended time spans (up to ± 5s) are very common, even during fast motor behavior epochs. One of the more intriguing findings is that the interaction between the same independent components can be repeated at multiple times, spanning the whole ± 5s time window investigated.

Disclosures: L.S. Popa: None. **S. West:** None. **R.E. Carter:** None. **G. Chen:** None. **J.D. Aronson:** None. **L. Ghanbari:** None. **S.B. Kodandaramaiah:** None. **T.J. Ebner:** None.

Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

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Program #/Poster #: 311.17/PP2

Topic: E.04. Voluntary Movements

Support: NIH Grant R01 CA189665

Title: Therapeutic and neurophysiological effect of combining physical and mental practice in breast cancer survivors

Authors: *S. H. SALEH[1], D. ALLEXANDRE[1], A. HOXHA[1], G. H. YUE[1,2]
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Abstract: Breast cancer survivors often experience physical weakness due to the effect of treatment, which limits their ability to participate in high effort physical training. We hypothesize that combining submaximal physical practice with motor imagery (MI) at maximum voluntary contraction (MVC) can have significant therapeutic and neurophysiological effect on cancer weakness without inducing fatigue. This was tested on the right hand (High Mental Effort, HME) in breast cancer survivors by evaluating its effect on muscle strength, and cortical activation during an MVC and a submaximal (20% of MVC) task. Effect of HME was compared to a control group who received physical training only (Low Mental Effort, LME) and another who received no training (CTR). To date, 6, 5 and 5 female cancer survivors were randomly assigned to the HME, LME and CTR group respectively. The HME and LME group participants completed 5 weekly training sessions for 5 weeks. Baseline measures included MVC of right hand and fMRI cortical brain activation measures. An MRI-compatible Biopac force transducer was used to acquire and provide real-time visual feedback of the handgrip force in the scanner. In scan 1, subjects were provided with visual cues to squeeze a handgrip sensor up to the 20% MVC target (PercMVC). In scan 2, subjects were instructed to perform a MVC. 10 trials were acquired for each task (10 seconds each with 12 to 16 seconds of rest in between). fMRI data were preprocessed using conventional methods in FSL. Neural correlates of each experiment task were analyzed using simple regression analysis, and between sessions comparison was performed using mixed-effects ANOVA. Results show changes in neural correlates of percMVC and MVC tasks in the HME and LME groups and no changes in the CTR group. In the HME group, results show increased activation in contralateral sensorimotor cortex during MVC task after training and more focal activation during percMVC task. Similar changes in sensorimotor activation were shown for both the LME and HME groups during the percMVC task while no significant activation change was observed during the MVC task. The percent change in MVC after training is similar in all groups. In conclusion, these preliminary data show that even though no difference in strength improvement could be observed, combining MI and physical training

resulted in higher neuromodulatory effect than performing physical training alone. Future effort will include additional analyses of connectivity and muscular activity and additional data from newly enrolled participants to increase statistical power and help better understand the therapeutic and neurophysiological effect of HME versus LME and CTR.

Disclosures: S.H. Saleh: None. **D. Allexandre:** None. **A. Hoxha:** None. **G.H. Yue:** None.

Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

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Program #/Poster #: 311.18/PP3

Topic: E.04. Voluntary Movements

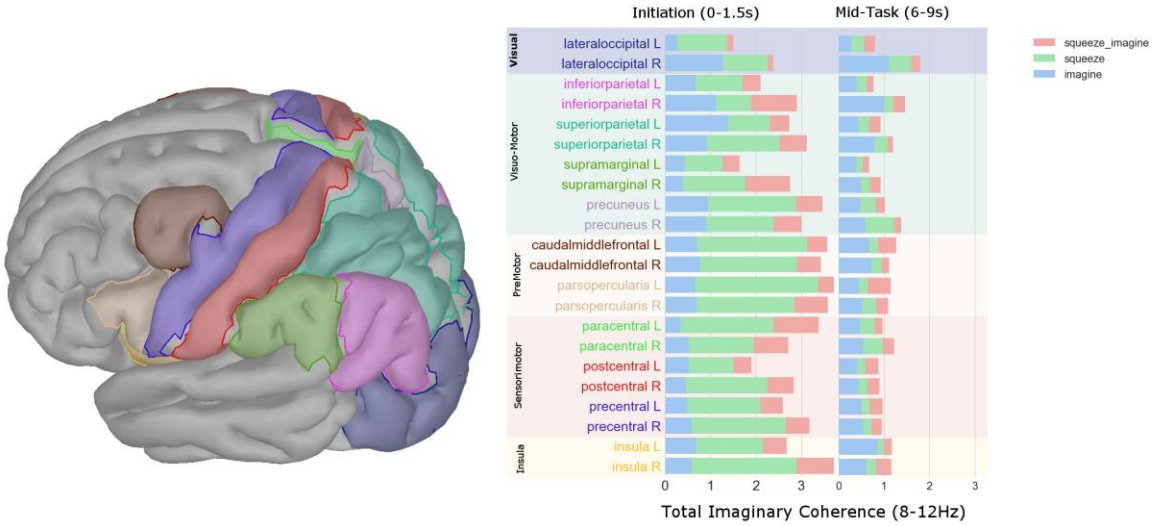
Support: NIH/NCI grant R01CA189665

Title: EEG source-space connectivity during motor imagery versus motor practice in breast cancer survivors

Authors: *D. ALLEXANDRE, A. HOXHA, V. SHENOY, S. H. SALEH, G. H. YUE
Kessler Fndn., West Orange, NJ

Abstract: Background: The underlying premise for the therapeutic benefit of motor imagery is that it engages the same motor-related cortical regions than those during the actual motor task. This study examines the potential benefit of combining motor imagery with submaximal motor contraction in breast cancer survivors with muscle weakness by investigating its neural correlates using an EEG source-space connectivity analysis. Method: In a randomized mixed design, 10 right handed breast cancer patients were asked to (1) perform series of actual submaximal right hand handgrip contractions (Squeeze Exercise; SE) at 20% of their maximal voluntary force (MVF), or (2) imagine contracting their handgrip at their MVF (Imagine Exercise; IE) or (3) combine SE and IE conditions by performing handgrip contractions at 20% MVF while imagining and urging the handgrip muscles to contract maximally (Squeeze+Imagine Exercise; SIE). After computing EEG source localization time series from 22 motor related region of interests using the sLORETA inverse modeling technique, connectivity was estimated using the imaginary coherence in the alpha band (8-12Hz) during the initial and static phase of each handgrip contraction trial. Results/Discussion: Motor execution shows strong brain connectivity across all regions in the initiation phase; most evident in the premotor and sensorimotor regions. This connectivity subsequently diminished during the static phase suggesting that maintaining a steady state contraction does not require strong interregional interactions. Although connectivity was lower in IE than SE during the initiation phase, it intensified and consequently became greater than SE during the static phase, thus keeping the regions strongly engaged without physical exertion. Stronger connectivity was also observed in SIE during the sustained phase but

to a lesser extent than SE, possibly due to challenges in engaging in a dual task. In summary, SE and SIE showed strong brain connectivity in the visuo-motor network, providing support for their benefit as low exertion therapeutic approaches.



Disclosures: D. Allexandre: None. **A. Hoxha:** None. **V. Shenoy:** None. **S.H. Saleh:** None. **G.H. Yue:** None.

Poster

311. Voluntary Movements: Cortical Planning and Execution: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 311.19/PP4

Topic: E.04. Voluntary Movements

Support: New Jersey Commission on Brain Injury Research (CBIR15MIG004)

Title: Understanding the neural dynamics of Traumatic Brain Injury participants during the lower limb balance dysfunction task: An EEG source-space connectivity study

Authors: *V. SHENOY HANDIRU[1,2], A. HOXHA[3], S. SALEH[3], G. YUE[3,2], D. ALLEXANDRE[3]
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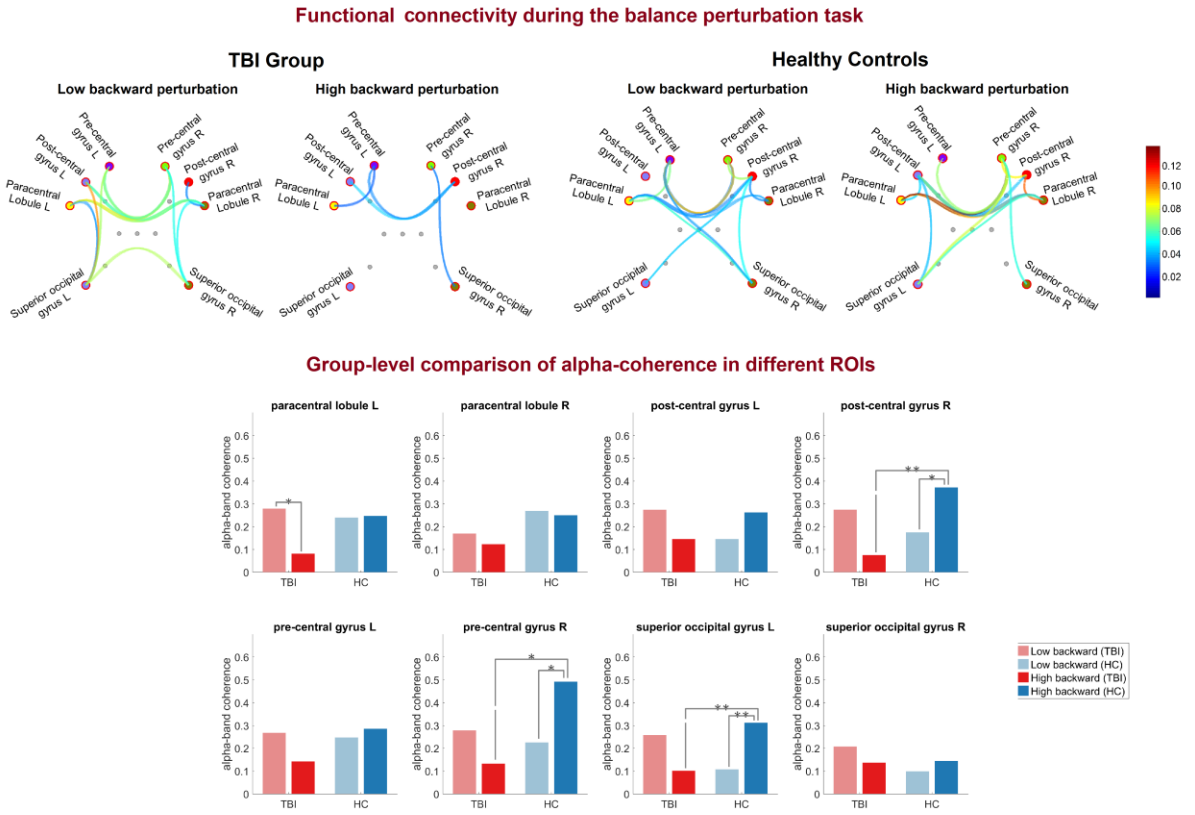
Abstract: Background: Traumatic brain injury (TBI) patients often suffer from long term balance problems, the cause of which remains poorly understood. To elucidate the underlying mechanism of the deficit, an EEG based connectivity analysis was performed on the neural

response to balance perturbation. **Method:** Brain activity (64 ch Brainvision EEG system), lower limbs muscle activity (EMG) and center of pressure (COP) were collected from 4 TBI and 4 age-matched healthy control (HC) participants while they stood on a balance platform (NeuroCom Inc). The platform was subjected to ~100 unpredictable forward or backward 4s long perturbations at low (1cm) and high (4cm) amplitude sinusoidal displacements at 0.5Hz. After computing EEG source-space time series using sLORETA, imaginary coherence based functional connectivity (FC) between motor-related regions of interest (ROIs) was estimated in the alpha band (8-12Hz) during the first 1.5s of the perturbation. Weighted node degree (WND) values defined for a given ROI as the sum of its coherence values with other ROIs were then compared between groups and conditions using ranksum test. **Results:** The TBI group had balance deficit compared to HC (mean Berg Balance test score of 49 vs 56, p=0.02). As shown in the figure, there was an overall increase in WND-based FC for HC group for the high (vs. low) backward perturbations reaching significance (or trend toward) for the superior occipital gyrus (**, p<0.05), and post- and pre-central right gyri (*, p<0.1). Surprisingly the TBI group shows an opposite trend, leading to significantly greater (or trend toward) FC in postcentral and superior occipital gyri (**, p<0.05) and precentral gyrus (*, p<0.1) in HC compared to TBI for the high backward perturbation. **Conclusions:** The inability for the TBI group to increase brain connectivity in response to a more challenging high perturbation task (as the HC group do), may be a contributor to the balance deficit. Future efforts will include more participants and study the correlation of COP and muscle response with connectivity results to further interpret our results.



Disclosures: **V. Shenoy handiru:** A. Employment/Salary (full or part-time):; RUTGERS BIOMEDICAL HEALTH SCIENCES. **A. Hoxha:** None. **S. Saleh:** None. **G. Yue:** None. **D. Allexandre:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

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Program #/Poster #: 312.01/PP5

Topic: E.05. Brain-Machine Interface

Support: DARPA BTO HAPTIX SPAWAR Pacific Contract No. N66001-15-C-4017
NSF Award No. ECCS-1533649
NSF GRFP Award No. 1747505

Title: Expanding the reach of upper-limb prosthetics: Restoring sensorimotor function after complex regional pain syndrome, long-term hand disuse and an elective transradial amputation

Authors: ***J. A. GEORGE**[1], M. R. BRINTON[1], T. S. DAVIS[2], M. D. PASKETT[1], D. T. KLUGER[1], C. C. DUNCAN[3], D. T. HUTCHINSON[4], G. A. CLARK[1]
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Abstract: The long-term goal of these studies is to provide intuitive, dexterous motor control of, and biomimetic sensory feedback from, an advanced prosthetic hand after prior amputation in humans. Here we report on a unique case-study in which an individual with Complex Regional Pain Syndrome (CRPS) and multi-year disuse of their intact hand underwent an elective transradial amputation, received neural and intramuscular electromyographic (iEMG) implants simultaneously, and then subsequently controlled an advanced prosthesis (e.g., DEKA LUKE arm; HANDi Hand). During amputation, three Utah Slanted Electrode Arrays (USEAs; Blackrock Microsystems) were implanted into the residual nerves (distal median, proximal median and ulnar) and 32 iEMG recording electrodes (Ripple, LLC) were implanted into the residual forearm muscles. Sensory percepts were evoked by passing current through USEA electrodes (biphasic, 100-200 μs, 1-18 μA pulses at 5-50 Hz), triggered by the experimenter or by sensors on the prosthetic hand. Motor intent was decoded from neural and iEMG recordings using two different motor-decode algorithms: a modified Kalman filter (mKF) and a convolutional neural network (CNN). Despite prior multi-year hand disuse, during the first post-amputation assessment, the participant successfully achieved 8-degree-of-freedom (DOF) proportional control via the mKF with modest, tolerable pain. In contrast, a pre-amputation study with surface EMG was limited to 3 DOFs and involved debilitating pain. USEA-evoked sensory percepts had low detection thresholds (e.g., 4-7 μA) and provided the participant with the first functional, non-painful sensory hand experience since CRPS onset. EMG signal and motor-

decode capabilities improved over time. Motor-decode performance was also increased with a novel training paradigm involving extended hold-times at the end point of each DOF. The relative performance of the two motor-decode algorithms varied according to the performance metric: the CNN had fewer unintended movements ($p < 0.05$), whereas the mKF provided significantly better control over intended movements ($p < 0.05$). Altogether, this work highlights progress in motor-decode algorithms and provides novel insights from a unique case-study. Future investigations using selective USEA stimulation to generate well-controlled afferent activity may help elucidate the underlying mechanisms of CRPS. Ultimately, the ability to restore non-painful sensorimotor function demonstrates that neuromyoelectric prostheses can also benefit CRPS individuals after hand amputation.

Disclosures: J.A. George: None. **M.R. Brinton:** None. **T.S. Davis:** None. **M.D. Paskett:** None. **D.T. Kluger:** None. **C.C. Duncan:** None. **D.T. Hutchinson:** None. **G.A. Clark:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

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Program #/Poster #: 312.02/PP6

Topic: E.05. Brain-Machine Interface

Support: NSF Grant DGE 1106400
SRC STARnet
SRC JUMP

Title: A robust emg-based hand gesture classifier controlling a 3d-printed bionic arm actuator

Authors: *A. MOIN[1], A. ZHOU[1], A. RAHIMI[2], S. BENATTI[3], A. MENON[1], S. TAMAKLOE[1], J. TING[1], N. YAMAMOTO[1], Y. KHAN[1], F. BURGHARDT[1], L. BENINI[2,3], A. C. ARIAS[1], A. ARAUJO[4], J. M. RABAEY[1]
[1]Dept. of Electrical Engin. and Computer Sci., Univ. of California, Berkeley, Berkeley, CA; [2]ETH Zurich, Zurich, Switzerland; [3]Univ. of Bologna, Bologna, Italy; [4]Univ. Politécnica de Madrid, Madrid, Spain

Abstract: Modern actuated prostheses for upper-limb loss patients provide many degrees of freedom (DOF) and mimic natural limbs well, but robust, multi-DOF control of such devices has not yet been achieved. Electromyography (EMG) signals based on patients' intact muscle activity may be used as control signals, but most available algorithms employ very simple encoding and mapping of EMG features to actuation of few DOFs. Modern machine learning methods can be used to classify gestures and movements from EMG features, but their accuracy is degraded by variance in signal properties due to changing electrode placement, arm position, and other contextual variations.

We present an end-to-end system for classifying finger/wrist movements and gestures using EMG recordings from a flexible, printed, high-density electrode array. Raw signals are digitized right at the electrode array and wirelessly transmitted to a base-station. They are then encoded and classified using a brain-inspired hyper-dimensional computing algorithm operating on 10,000-element random vectors. Because of the high-dimensionality of the vectors, classification performance is very robust to noise and context changes. Hyper-dimensional computing also offers fast, incremental learning, allowing for a minimal initial training dataset and quick model updates for learning new contexts. We achieve ~95% accuracy in classifying 25 common finger/wrist movements and gestures, with little accuracy degradation between different arm positions and wear sessions.
The classified gestures are wirelessly sent as a set of commands to be actuated on a 3D-printed prosthetic arm. The arm is based on HACKberry open-source bionic hand design with some modifications in order to accommodate more DOFs. Two servomotors for wrist (elevation and azimuth), one for thumb, one for index, and one for the rest of the fingers are used to mimic flexion, extension, and combination movements on the prosthesis.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Program #/Poster #: 312.03/PP7

Topic: E.05. Brain-Machine Interface

Support: DARPA BTO SPAWAR Pacific Contract No. N66001-15-C-4017
NSF Award No. ECCS-1533649

Title: Development of a portable take-home system for control of advanced prostheses

Authors: *M. BRINTON[1], E. L. BARCIKOWSKI[5], T. S. DAVIS[2], M. D. PASKETT[1], J. G. NIEVEEN[3], D. T. KLUGER[1], J. A. GEORGE[1], C. C. DUNCAN[4], D. J. WARREN[1], G. A. CLARK[1]
[1]Bioengineering, Univ. of Utah, Salt Lake City, UT; [2]Neurosurg., Univ. of Utah, Salt Lake Cty, UT; [3]Electrical Engin., [4]Physical Med. and Rehabil., Univ. of Utah, Salt Lake City, UT; [5]Ripple, Salt Lake City, UT

Abstract: This work documents the first portable neuromyoelectric prosthetic interface capable of providing intuitive, dexterous, high degree-of-freedom, motor control to amputees, with potential expansion to include neural stimulation for sensory feedback. A mobile processing unit

(Nomad; Ripple, LLC) was used to record 96 neural and 496 differential, electromyographic (EMG) channels (from 32 single-ended electrodes); perform optimal channel selection; estimate user intent using a modified Kalman filter; and communicate that intent to an advanced six degree-of-freedom prosthetic arm (DEKA LUKE arm). Participants in the study included (a) two healthy volunteers with 32 surface EMG electrodes applied to the skin near forearm muscles and a bypass-socket to support the DEKA arm; and (b) a recent upper-limb amputee with prior complex region pain syndrome (CRPS) and long-term hand disuse (George et al., SFN 2018). To begin the decode training, the users simply pressed a button and then mimicked preprogrammed movements of the DEKA arm with their own phantom or intact hand while the Nomad recorded neural and EMG signals. In less than 15 minutes, the decode training was complete and control of the prosthetic was automatically transferred to the participant. Intact participants used the system to complete dexterity tasks in the lab (e.g., Box and Block Test, SHAP). In preparation for future take-home trials, lab personnel successfully operated the system at home to perform activities of daily living (e.g., don a sock, use scissors, open jars, sweep floor, fold towel). The amputee participant used both EMG and neural inputs (median nerve) to control the arm in a laboratory setting. The system can acquire neural and EMG signals, calculate differential EMG pairs, decode motor intent and communicate with the DEKA arm in less than 2ms, faster than the threshold for perceived delay. The system can be programmed to provide position or velocity control of the wrist and digits. For post-hoc analysis of a take-home trial, the DEKA arm stores the length of time each degree of freedom moved, the velocities at which they moved and the amount of compliance experienced. This work represents a major step toward the development and commercialization of advanced neuromyoelectric prostheses.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Program #/Poster #: 312.04/PP8

Topic: E.05. Brain-Machine Interface

Support: NIH Grant 5R01EY015545-12
Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech
Boswell Foundation

Title: Representation and performance of multiple effectors in closed-loop cortical control recorded from a single array in human posterior parietal cortex

Authors: *C. Y. ZHANG[1], T. AFLALO[1], D. OUELLETTE[2], E. ROSARIO[3], N. POURATIAN[4], R. A. ANDERSEN[5]
[1]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA; [2]Casa Colina Hosp. and Centers for Healthcare, Pomona, CA; [3]Res. Inst., Casa Colina Hosp. and Centers For Healthcare, Pomona, CA; [4]Univ. of California Los Angeles, Los Angeles, CA; [5]BBE, Calif Inst. of Technol., Pasadena, CA

Abstract: Recently, our lab has found "partially mixed selectivity" in human posterior parietal cortex (PPC), a method of encoding information enabling multiple variables to be represented in a shared substrate (Zhang et al., 2017). Here, we study this structure and how it behaves in a closed-loop cortical brain-machine interface (BMI). Recordings were made from a 4x4 mm electrode array implanted in the anterior intraparietal area (AIP) of a human tetraplegic patient. We examined the representations of imagined or attempted movements of the left or right hand, comparing how the structure of the representations are preserved between BMI calibration (training) and closed-loop control (online). We also assessed the control performance of the different movement conditions in a one dimensional cursor control task. We found that all four movement conditions were feasible for BMI control. The structure of the representations was largely preserved between training and online control, generalizing from training to online control and vice versa. Furthermore, of the four tested movement conditions, attempted movements of the right (contralateral) hand performed best in online BMI control, with the relative performance differences predictable from offline analyses. Our results demonstrate that the overlapping mixed representations previously found in offline analysis are still meaningful and accessible during BMI control. This result indicates that the large number of variables found in the partially mixed encoding structure of a small patch of human PPC can be still decoded and used for BMI control.

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Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

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Topic: E.05. Brain-Machine Interface

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Title: Separability of neural population structures in human motor cortex during gross and fine upper limb movements

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Abstract: A fundamental question in neuroscience is how neural activity in the primary motor cortex (M1) drives ongoing movements. Recent evidence suggests that populations of neurons produce coordinated activity patterns in order to generate arm movements, but it remains unclear how these population structures behave to drive selective movement in different parts of the arm and hand. Here we examined whether gross and fine upper limb movement tasks are driven by similar structures of population-wide activity patterns in human sensorimotor cortex.
We conducted intracortical recordings from two 88-channel microelectrode arrays, implanted in medial/lateral areas of M1 in a human participant with a C5-motor/C6-sensory incomplete spinal cord injury (limited arm use, paralyzed hand), while the participant viewed and engaged with cyclic movement tasks. Gross (shoulder, elbow, wrist, whole hand) and fine (five individual finger) movements were presented on a computer monitor in separate task-specific blocks, and the participant was instructed to attempt to perform each movement in time with the viewed actions (0.5 Hz). We defined a neural state space by performing principal component analysis (PCA) on binned firing rates, and examined the trajectory of the population's trial-averaged time-series activity through this space during different movements.
We found that the neural state oscillated rhythmically between separate regions of neural space during the two phases of each movement (e.g. flexion/extension). In the space defined with activity from both arrays together, the general shape and location of these trajectories varied significantly between movements, with gross movements spread out and fine movements closer together. Analyzing each array separately revealed that neural trajectories from the medial and lateral array were more separable during gross and fine movements respectively, as predicted by somatotopy. Despite this bias, each array's activity also displayed similar dynamics during both movement types. This provides preliminary evidence of a common neural mechanism for encoding gross and fine movements.
We found that the coordinated activity of neural populations in M1 produced highly structured trajectories through neural space. Within each movement, neural activity moved cyclically between different neural states which varied with the movements' phases. The similarity in population structures across cortical areas and movement types suggests that population activity in M1 may be coordinated at a large spatial scale, acting less as a set of spatially distinct representations and more as a unified dynamical system.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Topic: E.05. Brain-Machine Interface

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Title: Biomimetic intraneural sensory encoding enhances sensation naturalness, tactile sensitivity and manual dexterity in a bidirectional prosthesis

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Abstract: The lack of sensory feedback during grasping is a very important limitation of current hand prostheses, which affects their everyday usability. In the last years several research groups have demonstrated that nerve stimulation by implantable peripheral nerve interfaces can be reliably used to restore sensory feedback to upper limb amputees. They have shown that direct neural stimulation of peripheral nerves can effectively provide tactile information to the amputees, controlling the sensation intensity by modulating either the amplitude or the frequency of the injected stimuli. However, efforts are still necessary to identify encoding strategies converting tactile information into neural stimulation patterns capable of eliciting percepts that are both felt as natural and effective for prosthesis control. In this study, we compared the naturalness and efficacy of a set of encoding strategies based on biomimetic (model-driven) frequency modulation, amplitude modulation, or combinations of both. Such strategies were used to deliver neural stimulation to a trans-radial amputee implanted with intraneural electrodes (*TIMEs*). Frequency modulation was based on a biomimetic model (*TouchSim*) able to reproduce nerve activation patterns of the multifaceted mechanics of the skin and mechano-transduction. It was perceived as more natural, while amplitude modulation enabled better performance in tasks requiring fine identification of the applied force. Notably, hybrid encoding strategies involving both amplitude and frequency modulation were able to convey at least as much information as the amplitude modulation (for the completion of tasks), and were perceived at least as natural as the frequency modulation. The hybrid strategies improved the gross manual dexterity of the subjects during functional tasks while maintaining high manual accuracy. They also improved

the level of prosthesis embodiment and reduced abnormal body perceptions of the phantom limb ("telescoping"). Encoding strategies based on the combination of biomimetic frequency modulation and amplitude modulation are able to provide highly sensitive and natural percepts and should be preferred in bidirectional prosthesis use.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Topic: E.05. Brain-Machine Interface

Title: Modeling neural ensemble dynamics in motor cortex leads to improved EMG decoding of multiple muscles in goal-directed reaching tasks

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Abstract: Mounting evidence demonstrates that the activity of large ensembles of neurons in primary motor cortex (M1) reflects network level phenomena: lawful "dynamics" that dictate how activity evolves over time. We recently demonstrated a deep learning tool, Latent Factor Analysis via Dynamical Systems (LFADS), that uses artificial neural networks to uncover dynamics from neural ensemble activity on a single-trial, moment-by-moment basis. We previously found that LFADS is able to uncover dynamics from ensemble activity in M1 during structured motor tasks (highly stereotyped reaches, consistent task timing, a single starting position), and further, that modeling dynamics dramatically improved our ability to decode reaching kinematics. Here we aimed to test the extent to which uncovering ensemble dynamics in M1 might also improve decoding the more dynamically complex EMG activity underlying reaching, and whether M1 dynamics could also be modeled during tasks that lacked consistent structure. We analyzed simultaneously recorded spiking activity of ~90 neurons and electromyographic (EMG) activity from 10 muscles, from a monkey performing two separate tasks: (a) a center out task with a single starting position and 8 fixed target locations and (b) a random target task with variable starting positions and rapid sequential movements to capture a series of targets in random locations spanning the workspace. First, we analyzed activity during the center-out task, testing whether, by modeling ensemble dynamics, LFADS could infer neural firing rates that were more informative about EMG activity than a standard method (Gaussian

smoothing of the spiking activity). We compared the methods by using simple, cross-validated, least-squares linear regression to map firing rates onto EMG activity. We used small bin sizes (4ms) and no temporal history to determine how predictive the inferred rates were about EMG activity on a moment-by-moment basis. LFADS produced firing rate estimates that improved EMG decoding accuracy over Gaussian-smoothed spiking for all recorded muscles (quantified via R^2; improvements ranged from 7-32%). Next we analyzed neural activity from the random target task. Its less structured design ensured a large variety of movements and pacing, with no repeating sequences of movements. Despite the lack of task structure, LFADS uncovered dynamics from the M1 ensemble activity, allowing it to infer firing rates that improved (6-42%) decoding accuracy for all recorded muscles. Our results offer more evidence of the critical role of M1 ensemble dynamics in commanding movement, and may provide important new insights into the generation of muscle activity.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Topic: E.05. Brain-Machine Interface

Support: NSF GRFP
ONR

Title: Neural control strategies of a kinematically redundant brain-machine interface

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Abstract: Natural learning of motor skills involves the coordination of our body's numerous, redundant degrees of freedom (DOF) to achieve goals such as controlling joints in our arm to reach an endpoint target**.** Some motor control studies have shown that while this control is reliable, the reach trajectories are variable, with inconsistent joint angle combinations. This suggests that there may be an optimal control policy where goal-relevant dimension errors are corrected while task-irrelevant dimensions are tolerated. However, how motor cortex generates and refines these neural commands for kinematically redundant control is not well-understood. Understanding how the brain controls these high degrees of freedom may be important in designing neuroprostheses with multiple actuators. To examine this question, we previously

studied how subjects learned to control a 4-DOF virtual limb using BMI. Neural activity was recorded from motor cortex of two rhesus macaques and decoded into joint angle velocity commands for each of the four joints. Subjects were instructed to complete a center-out task to eight different targets, and movements were constrained to a 2D plane, thereby creating the kinematic redundancy. Over training, the reach times for both animals decreased with joint angle variability increasing over sessions. In this study, we find neural correlates of refined control that improve the subjects' performance. Using linear regression, we find that in both animals, past state space information drives future neural commands to the decoder. In particular, the performance in both animals was highly correlated with how representative neural activity reflected past joint angle velocities. Interestingly however, the joint angle velocities were not the most predictive states for the neural activity, but only acted as performance correlates. Our results indicate that while neural activity became increasingly more decoder-relevant (i.e. pertaining to joint angle velocities), both subjects seemed to generate more neural patterns correlated to other task-relevant variables (e.g. endpoint position, joint angle, etc). This suggests that even if the control variables imposed by the BMI are not analogous to natural reaching, embodiment of a multi-DOF prosthesis might still occur over sessions, with joint angle velocities become represented in the neural activity in addition to the endpoint kinematics. Future work will elucidate how control of kinematically redundant neuroprostheses can be generalized or embodied by subjects.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Title: Optimizing parameters for model-based control of prosthetic limbs

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Abstract: Electromyographic (EMG) signals from residual extrinsic hand muscles can be used to control prosthetic hands. Clinically available systems typically use one of two algorithms for control: pattern recognition, in which predetermined prosthetic movements or states are commanded based on recognizing patterns of activity across multiple EMG sensors, or direct control, in which EMG activity directly controls output for a given degree of freedom (DOF). Both approaches face challenges in taking full advantage of modern prosthetic hands that can control individual fingers.In order to address some of the challenges of existing control schemes, we have created a biomimetically inspired, dynamic model of the hand with Hill-type muscle actuators, that estimates joint torques and solves forward dynamics of the hand to generate movement. Here we describe an optimization approach to determine the impact of different intramuscular EMG to muscle activation signal transformations to drive the model and use the same approach to test the effect of different model joint stiffnesses, for which experimental data are lacking.In 14 able-bodied subjects, intramuscular electrodes were acutely placed in the extrinsic hand muscles, including individual compartments of the finger muscles. Subjects performed single and multi-DOF movements of the fingers and wrist while EMG activity and hand kinematics were recorded. The contribution of muscle activity to total finger and wrist joint torques were estimated using inverse dynamics in MuJoCo simulation software using recorded kinematics as input and assuming internal finger joint stiffnesses ranging from 0.01 to 0.1 N/rad. EMG activity was converted to activation using a high-pass filter at 100 Hz, rectification, and then low-pass filtering with cutoff frequencies ranging from 1-10 Hz. This set of activation signals were passed to the musculoskeletal model to calculate simulated joint torques. Summed root-mean-square error between the stimulated torques and inverse torques was minimized using an optimizer that varied a per-channel activation scaling term. In preliminary results for a single subject, we found that using a low-pass filter at 8 Hz and setting the joint stiffness to 0.01 N/rad reduced total torque error by 34% compared to our previously used values of 0.1 N/rad and a 10 Hz. We plan to continue this approach to further test feature extraction and processing to create a robust model-based controller for prosthetic hands.Funding: Research was sponsored by the U.S. Army Research Office and the Defense Advanced Research Projects Agency (DARPA) and was accomplished under Cooperative Agreement Number W911NF-15-2-0016.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Title: Clinical training platform for ECoG-based motor BCI control of multi-degrees of freedom effectors

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Abstract: In the field of neuroprosthetics, one of the major challenges is the development of a Brain Computer Interface (BCI) system for a chronic use in clinical applications with high performance of decoding to control a large number degrees of freedom. The challenge of chronic recording of the brain activities was addressed by the CEA/LETI/CLINATEC with the development of a wireless 64-channels ECoG recording implant WIMAGINE [1]. Moreover, innovative ECoG signal decoding algorithms (tensor-based multimodal algorithms [2] and multi-state hybrid algorithms [3]) was achieved to perform the decoding, by the subject's brain activity, of complex effectors such as a 4-limbs exoskeleton.
One other challenge is the training of patients to perform mental tasks of upper or lower limbs movements. To do that, a BCI training platform has been developed to allow the training of patients whether in a clinical environment or at home. This BCI training platform is composed of a software dedicated to record ECoG signal from WIMAGINE implants and a real-time BCI decoding software and an another software to control the 4-limbs exoskeleton or virtual effectors (such as 3D avatar and serious games). Several virtual environments with different levels of difficulties was developed to allow a gradual training of the patient to control each degrees of freedom necessary to pilot, ultimately, a 4-limbs exoskeleton.
Finally, to allowing the model creation in real time (calibration step), a dedicated software based on adaptive algorithms [4] was performed.
In conclusion, this BCI training platform was achieved to be used during a clinical trial [5] whose the goal is to demonstrated that a tetraplegic patient can control, after training, a 4-limbs exoskeleton thanks to his brain activity monitoring and decoding.
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[2] Eliseyev, A., and Aksenova T.. "Penalized multi-way partial least squares for smooth trajectory decoding from electrocorticographic (ECoG) recording." PloS one 11.5 (2016): e0154878.
[3] Schaeffer, M.C. and Aksenova T.. "Switching Markov decoders for asynchronous trajectory reconstruction from ecog signals in monkeys for bci applications." Journal of Physiology-Paris

110.4 (2016): 348-360.
[4] Eliseyev, A. , et al. "Recursive Exponentially Weighted N-way Partial Least Squares Regression with Recursive-Validation of Hyper-Parameters in Brain-Computer Interface Applications." Scientific reports 7.1 (2017): 16281.
[5] https://clinicaltrials.gov/show/NCT02550522

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Poster

312. Brain-Machine Interface: Reaching Movements

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Program #/Poster #: 312.11/PP15

Topic: E.05. Brain-Machine Interface

Title: A novel brain-machine-interface system for severely impaired stroke patients

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Abstract: Rehabilitation studies leveraging brain-machine interface (BMI) technology have demonstrated clinical improvements with systems where changes in decoded brain activity coincide with peripheral feedback through the movement of an orthosis. In these systems, the decoded movement intention from brain signals is translated into movement of the peripheral orthosis, giving patients feedback about their brain activity. This allows them first to refine their neural activity patterns to be more specific for a given movement, and second leverages the endogenous sensorimotor learning system to link these neural signals and the activation of the peripheral nervous system. So far, studies have been limited to linking patterns from non-invasively acquired brain signals to single movements such as only grasping or only reaching. One challenge with using non-invasive brain signals in these systems is the low number of movements that can be reliably decoded on a single-trial basis. This restriction limits the

feedback available to the patient about how to refine their neural activity patterns, as well as the number of trained movements these systems can reinforce. Thus, one way to improve upon current state-of-the-art is to use a neural recording modality that allows for accurate, single-trial decoding of greater number of movements, and deliver feedback of these decoded movement intention signals through an orthosis with multiple degrees of freedom.
Hemiplegic stroke patients may not exhibit overt movements, but some patients have subthreshold muscular activations during intended movements that can be detected with surface electromyography (EMG). Such activity can be used to discriminate differing movement intentions.
In this work, we present a novel brain-machine interface rehabilitation system for hemiplegic chronic stroke patients that leverages a temporarily implanted intracortical multi-electrode array and a seven degree-of-freedom arm and hand orthosis. Previous work has demonstrated successful use of neural signals acquired from implanted multi-electrode arrays for closed-loop control of multi degree-of-freedom robotic arms. Further, we introduce a novel method of shared control of the orthosis where decoded neural activity signals are fused with decoded movement intention signals from surface EMG. This fusion is hypothesized to accelerate the formation of the neuro-muscular link by reinforcing the co-activation of motor-related neural circuits and target muscles. We demonstrate the usability of this system with a severely paralyzed chronic stroke patient.

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Poster

312. Brain-Machine Interface: Reaching Movements

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Title: Interference of overt movements with BCI control in a human with tetraplegia

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Abstract: Brain computer interfaces (BCI) bypass spinal cord injuries (SCI) by translating motor cortical signals into command signals for computer cursors or robotic arms. After cervical SCI, overt movement is retained above the level of the injury. Ideally in these cases, people could successfully coordinate both overt and BCI movements. In moving towards this goal, we investigated whether the neural representation for overt movement overlapped with BCI movement such that it would interfere with BCI performance. We found that arm movements both ipsilateral and contralateral to the array interfered with BCI performance, with contralateral arm movements causing more interference.

We recorded neural activity from motor cortex (M1) using intracortical arrays in a 31-year-old human male participant with tetraplegia who retained some bilateral arm movement. While at rest, he observed a 1D cursor moving towards left and right targets. After observation, we trained an optimal linear estimator decoder to translate neural activity into horizontal cursor velocity. We then tested his BCI cursor performance (1) with his arms at rest or (2) while he made ipsilateral or contralateral arm movements to the right or left. Arm movements were performed in alternating order for each successive target so that the movements were not associated with the randomized target order.

While his arms were at rest, the BCI cursor's initial movement was towards the target in 95% of trials. However, both ipsilateral and contralateral arm movements interfered with BCI decoding performance. Initial cursor movement was towards the target in 47% of contralateral arm trials and 80% of ipsilateral arm trials. To determine if the neural activity reflected these performance results, we grouped the overt movement trials in two ways, either by BCI target direction or by overt movement direction. A Naïve Bayes neural classifier correctly predicted the movement direction for 100% of contralateral movements and 98.7% of ipsilateral arm movements. However, the classifier predicted the BCI target direction better during ipsilateral arm movements (92.9%) than during contralateral arm movements (57.8%). These classification results are consistent with the performance results. Taken together, these results indicate that contralateral, and to a lesser extent, ipsilateral arm movements overlap with the neural representation of BCI movements.

For future work, we will investigate whether changes to BCI calibration and decoding can minimize the impact of overt movements on BCI control. This will further propel research towards a BCI that can augment overt movements to jointly achieve a motor goal.

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Poster

312. Brain-Machine Interface: Reaching Movements

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UW Institute for Neuroengineering (UWIN), Washington Research Foundation

Title: Restoring forelimb movement after spinal cord injury with cortical-local field potential control of epidural spinal stimulation

Authors: *S. SAMEJIMA[1,5,6,7], A. KHORASANI[8,1], A. BOISSENIN[1], N. M. TOLLEY[1], V. RANGANATHAN[2,6], J. R. SMITH[2,3,5,6], C. T. MORITZ[1,4,5,6,7]
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Abstract: Our goal is to restore voluntary control of forelimb function after spinal cord injury (SCI) via an artificial connection from the brain to spinal cord. This approach includes recording from multi-channel intracortical electrodes and using a computational model to extract the intention to move the forelimb. This intention to move can then be used to control stimulation of electrodes on the spinal cord. To accelerate clinical translation, we deliberately selected both recording and stimulation methods with potential for near-term use in human subjects. This included intracortical Local Field Potentials (LFP) that provide more stable movement-related information and require less power for hardware implementation compared to single unit spike sorting and decoding. We also selected epidural stimulation of the spinal cord surface as it evokes natural fatigue resistant contractions and synergistic movement similar to intraspinal stimulation. Animals were trained to press a lever for liquid reward. We used a Canonical Correlation Analysis (CCA) filter to predict the animals' movement intention from 16-channel LFP recorded from forelimb region of primary motor cortex. After several weeks of cortical recording, the animals received a lateralized contusion on the right side of spinal segment C4 and an epidural implant on the right side of spinal segment C6. We then decoded motor command

from recorded LFPs after SCI to continually control the amplitude of epidural stimulation delivered to the spinal cord below the injury. LFP-controlled epidural stimulation produced significantly larger lever displacements when the stimulation was on compared to trials with no stimulation. Here we demonstrate the effectiveness of closed-loop continuous control of epidural spinal cord stimulation based on LFP signals recorded from motor areas of the brain after spinal contusion injury, with substantial advantages as a platform for clinical translation.

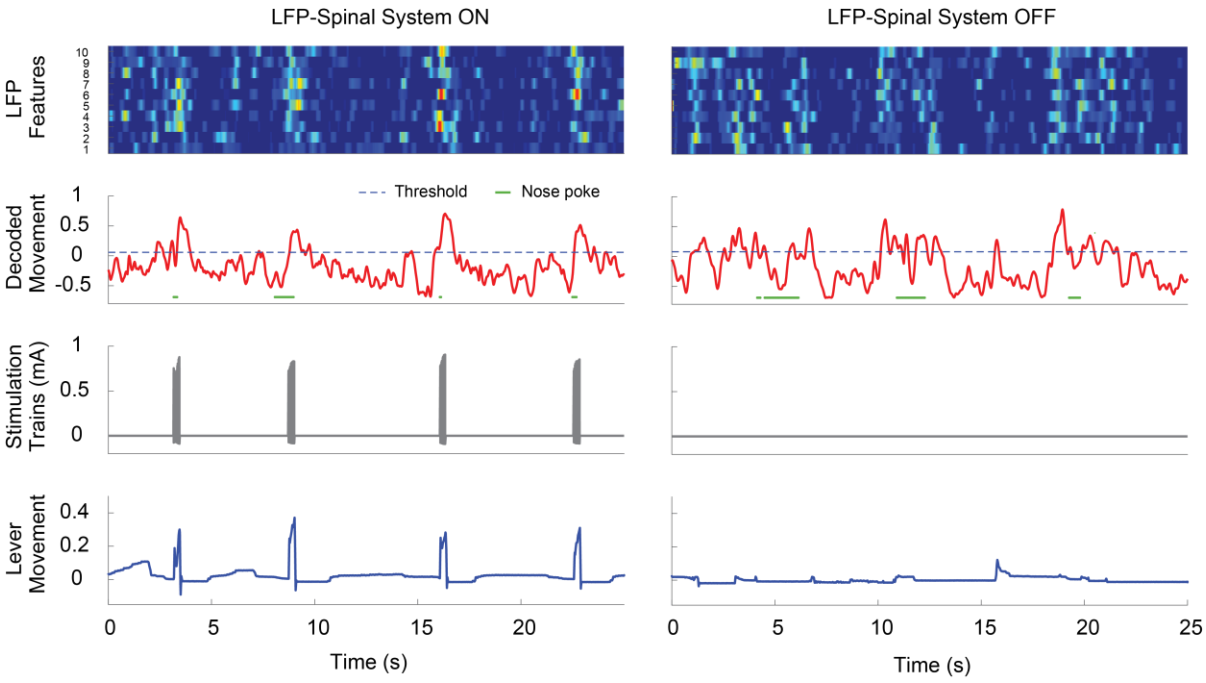

Figure. LFP decoder performance, Epidural Stimulation Trains and the forelimb lever push performance during stimulation on and off.

Disclosures: S. Samejima: None. **A. Khorasani:** None. **A. Boissenin:** None. **N.M. Tolley:** None. **V. Ranganathan:** None. **J.R. Smith:** None. **C.T. Moritz:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 312.14/PP18

Topic: E.05. Brain-Machine Interface

Support: NIH Grant 5R01EY015545-12
NIH Grant U01NS098975
Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech
Boswell Foundation

David Geffen Scholarship

Title: Coordinate frames in human cortex during an imagined reaching task

Authors: *M. JAFARI[1], T. AFLALO[1], S. KELLIS[1], S. CHIVUKULA[1], M. ARMENTA SALAS[1], L. BASHFORD[1], H. JO[1], E. ROSARIO[2], D. OUELLETTE[2], K. PEJSA[1], B. LEE[3], N. POURATIAN[4], C. LIU[3], R. A. ANDERSEN[1]
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Abstract: Cortical neural prosthetics decode intention related activity from populations of cortical neurons to enable direct neural control of external assistive devices. This study aims to understand how different cortical areas encode planning and execution related intention activity across four brain areas recorded in two human subjects with tetraplegia implanted with chronic arrays as part of a neural prosthetic clinical trial. Recordings were made in the region of ventral premotor cortex (PMv), supramarginal gyrus (SMG), and primary somatosensory cortex (S1) in subject FG and the anterior intraparietal cortex (AIP) of subject NS. We used a delayed-reach paradigm in which we systematically varied hand, eye and target position in order to determine the reference frame encoding of reach intentions during planning and execution epochs. A trial consisted of the subject fixating their gaze and imagining their hand at one of four possible locations, followed by target presentation with a delay, and a subsequent imagined reach to the cued target. We used gradient analysis (Pesaran et al., 2006) to determine the relationship between neural firing and behavioral variables. This design allowed us to characterize whether the target of a reach is coded, as a function of brain area and task epoch: relative to the direction of gaze (eye-centered), the position of the hand (hand-centered), relative to the position of eye, hand, and target specifying the differences in locations (relative), or body/world centered. We recorded from 441 (PMv), 982 (SMG), 654 (S1), and 421 (AIP) units across 4-6 sessions. We found 27%, 24%, 20%, and 7% of units tuned during the delay and 6%, 15%, 17%, 17% during the go epoch for PMv, SMG, S1, and AIP ($p < 0.05$, FDR corrected), respectively. Population level gradient analyses during the delay epoch showed a relative reference frame coding in SMG and S1, PMv showed tuning to hand relative to target, and AIP had a very small proportion of tuned units to hand relative to gaze and hand relative to target. These coordinate frames shifted during the execution epoch with all brain areas coding mostly for hand relative to the target (hand-centered). These results demonstrate that: 1) reference frame encoding for some areas vary across epochs, 2) S1 displays significant levels of tuning during the delay and execution epochs, and 3) during the execution phase all areas code the intended movement in hand-centered coordinates.

Disclosures: M. Jafari: None. **T. Aflalo:** None. **S. Kellis:** None. **S. Chivukula:** None. **M. Armenta Salas:** None. **L. Bashford:** None. **H. Jo:** None. **E. Rosario:** None. **D. Ouellette:** None. **K. Pejsa:** None. **B. Lee:** None. **N. Pouratian:** None. **C. Liu:** None. **R.A. Andersen:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 312.15/PP19

Topic: E.05. Brain-Machine Interface

Support: DFG Emmy Noether grant KL 2990/1-1

Title: Temporal stabilized arm movement for efficient neuroprosthetic control by individuals with tetraplegia

Authors: *I. IOSSIFIDIS[1], M. A. HUSSAIN[2], C. KLAES[3]
[1]Computer Sci., Ruhr West Univ. of Applied Sci., Müelheim an der Ruhr, Germany; [2]Ruhr West Univ. of Applied Sci., Mülheim an der Ruhr, Germany; [3]Biol., Ruhr Univ. Bochum, Pasadena, CA

Abstract: The generation of discrete movement with distinct and stable time courses characterizes each human movement and reflect the need to perform catching and interception tasks and for timed action sequences, incorporating dynamically changing environmental constraints. Several lines of evidence suggest neuronal mechanism for the initiation of movements i.e. in the supplementary motor area (SMA) and the premotor cortex and for movement planning mechanism generating velocity profiles satisfying time constraints.
In order to meet the requirements of on-line evolving trajectories we propose a model, based on dynamical systems which describes goal directed trajectories in humans and generates trajectories for redundant anthropomorphic robotic arms. The analysis of the attractor dynamics based on the qualitative comparison with measurements of resulting trajectories taken from arm movement experiments with humans created a framework able to reproduce and to generate naturalistic human like arm trajectories.
This framework for robust incorporation of fluctuating sensor information, but control of movement time is usually restricted to rhythmic motion and realized through stable limit cycles. The present work uses a Hopf oscillator to produce discrete motion and formulates an on-line adaptation rule to stabilize total movement time against a wide range of disturbances. This is integrated into a dynamical systems framework for the sequencing of movement phases and for directional navigation. With only three parameters the presented framework is able to generate temporal stabilized (timed) discrete movements, dealing with disturbances and maintaining an approximately constant movement time.
The approach is demonstrated within a simulation task in a virtual reality environment as well as with a real anthropomorphic robotic arm (KUKA Lbr aiwa). In addition we aim to replace the robotic manipulator by an exoskeleton for the upper body which will enable the patients to move his or hers own limbs, which would complete the development of a real neuroprosthetic device

for every day use.
In the current study we will implant two 96-channel intracortical microelectrode arrays in the primary motor and the posterior parietal cortex (PPC) of an individual with tetraplegia. In the training phase the parameters of the dynamical systems will be tuned and optimized by machine learning algorithms. Rather controlling directly the arm movement and adjusting continuously parameters, the patient adjust by his or hers thoughts the three parameters of the dynamics, which will remain almost constant during the movement.

Disclosures: I. Iossifidis: None. **M.A. Hussain:** None. **C. Klaes:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 312.16/PP20

Topic: E.05. Brain-Machine Interface

Title: Decoding trajectory of a robot arm viewed in simulation from ecog recording

Authors: *J. A. PALMER[1], M. HIRATA[2]
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Abstract: Recent progress in Brain Machine Interface (BMI) research using signals from subdural electrocorticographical (ECoG) arrays implanted over primary motor cortex has demonstrated the potential for successful decoding of participant's arm or hand movement. Concurrent advances in wireless implantable electrode technology are further shortening the gap between existing systems and real functioning rehabilitative neural prosthetics for use by patients with motor system disorders. However the long-term stability and effectiveness of BMI technologies depends crucially on the stability and effectiveness of the feature extraction and decoding algorithms used to translate the neural signals into behavioral commands. Given the limited density and coverage of ECoG channel arrays, it is critical to reliably extract as much of the available information as possible. While some success has been achieved using channel-based features, we have recently shown that improvement may be gained by first applying the Independent Component Analysis (ICA) method to the ECoG channel data to separate and isolate relevant cortical signals. We present results of application of ICA to ECoG data for the derivation of features for BMI applications and comparison to standard approaches. We discuss the interpretation of the ICA features and suggest directions for future improvements.

Disclosures: J.A. Palmer: None. **M. Hirata:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 312.17/PP21

Topic: E.05. Brain-Machine Interface

Support: NRF Grant 2016M3C7A1904988

Title: Networking properties of primary motor cortical neurons can predict decoding performance of upper limb movements in advance

Authors: *M.-K. KIM[1], J.-W. SOHN[2], S.-P. KIM[3]
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Abstract: Brain-machine interfaces (BMIs) for upper limb movement restoration rely on motor cortical circuits coordinating complex arm movements. As BMI decoding performance can vary across days or sessions due to the variation of the recordings of motor cortical neurons, it is important to understand how decoding performance changes with certain properties of the ensemble of neurons. Generally, it is plausible to predict decoding performance by assessing how well neuronal activities encode kinematic information, which requires both neuronal and kinematic data. Yet, it is desirable to estimate decoding performance even before a session starts with no kinematic information so that one can flexibly adjust decoder types or the amount of training in advance. To this end, we examined the networking properties of primary motor cortical (M1) neurons during a pre-session period, where the subject did not begin an arm movement task, to find if these could provide predictive information about decoding performance on the same day (or session). We analyzed networking patterns within M1 neurons of a primate (a Rhesus macaque) during the pre-session periods of seventeen different sessions. The linear Kalman filter was used to decode M1 ensemble firing rates into 3D velocity, and decoding accuracy was calculated as correlation coefficient between predicted and actual movements. We adopted the graph theory to quantitatively assess networking properties. As a result, we found that M1 networking properties could predict across-session performance of 3D velocity decoding. Specifically, an increase in the global clustering coefficient of M1 network led an increase in decoding performance. The result suggests that the M1 networking properties before the session starts can predict decoding performance in BMIs to restore upper limb control.

Disclosures: M. Kim: None. **J. Sohn:** None. **S. Kim:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 312.18/PP22

Topic: E.05. Brain-Machine Interface

Support: Neurological Institute, The Ohio State University

Title: Neural features of intrinsic error recognition in human motor cortex during intracortical brain-computer interface use

Authors: C. DUNLAP[1], N. SKOMROCK[2], H. TRIVEDI[2], N. ANNETTA[2], M. SCHWEMMER[2], S. COLACHIS IV[2], G. SHARMA[2], D. FRIEDENBERG[2], P. D. GANZER[2], *M. A. BOCKBRADER[3]
[1]Biomed. Engin., Ohio State Univ., Columbus, OH; [2]Battelle Mem. Inst., Columbus, OH; [3]Physical Med. & Rehabil., Ohio State Univ. Col. of Med., Columbus, OH

Abstract: Introduction: Brain-computer interface (BCI) performance may be improved by using task-outcome related cerebral activity as input to neural decoding algorithms. Our group has recently shown detectable changes in neural firing rates in the motor cortex of a tetraplegic participant using a BCI coupled with a functional electrical stimulation (FES) orthotic following mismatches between motor intent and muscle activation. In this subsequent study, our objective is to determine if a similar error signal is present while the participant plays a guitar video game without audio or visual feedback. Methods: A 27-year-old man with C5 ASIA Impairment Scale category A traumatic spinal cord injury was recruited from the Reanimation in Tetraplegia clinical trial (ClinicalTrials.gov NCT01997125), an ongoing Phase I/II study for an investigational, intracortical BCI interfaced with an 130-electrode, transcutaneous, forearm FES orthotic. The intracortical microelectrode array implanted in his left primary motor cortex allowed for online recording of neural activity and decoding with machine-learning algorithms. The participant was instructed via a visual cue at specified time intervals to think about flexing his index, middle, or ring finger to press the buttons of a guitar game controller. Single unit activity during the cueing intervals was categorized to one of four groups based on neural decoder performance: correct, incorrect, or no movements, and a class for movements that were not sustained long enough to meet the criteria for any other class. Spikes were binned at 100ms intervals aligned by the start of the cueing window, summed across all channels of the array, and averaged across trials of the same classification. Results: Of 159 trials analyzed, the participant's performance is as follows: 25.2% correct, 8.0% incorrect, 35.2% no movement, and 31.4 % where erratic decoder behavior could not sustain movement. Average firing rates for all classes peaked between 1 and 1.5 seconds after the cue was presented to the participant. The missed cue class had the lowest average firing rate following the initial peak, and the incorrect class had an

additional peak in firing approximately 2 seconds after the start of the cue which was not observed for any other class. Conclusion: These preliminary results suggest that in the absence of performance feedback, intrinsic error recognition during a guitar video game is sufficient to elicit an error signal in the primary motor cortex. Future work aims to increase the sample size and to determine if an increasingly distinctive error signal is present when real-time feedback is given to the participant.

Disclosures: C. Dunlap: None. **N. Skomrock:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **H. Trivedi:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **N. Annetta:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **M. Schwemmer:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **S. Colachis IV:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **G. Sharma:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **D. Friedenberg:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **P.D. Ganzer:** A. Employment/Salary (full or part-time):; Battelle Memorial Institute. **M.A. Bockbrader:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; MicroTransponder, Inc.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 312.19/QQ1

Topic: E.05. Brain-Machine Interface

Support: DARPA and SSC Pacific
Revolutionizing Prosthetics
Neilsen Foundation
UPP Academic Foundation

Title: Neural signal stabilization improves human intracortical BCI control

Authors: *A. J. HERRERA[1,5], A. D. DEGENHART[1,2,5], W. E. BISHOP[6,5], E. R. OBY[1,2,5], E. C. TYLER-KABARA[1,3,4,9], S. M. CHASE[7,5], A. P. BATISTA[1,2,5], B. M. YU[7,8,5], J. L. COLLINGER[4,1,5,10]
[1]Bioengineering, [2]Systems Neurosci. Ctr., [3]Neurosurg., [4]Physical Med. & Rehabil., Univ. of Pittsburgh, Pittsburgh, PA; [5]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [6]Machine Learning, [7]Biomed. Engin., [8]Electrical and Computer Engin., Carnegie Mellon Univ., Pittsburgh, PA; [9]McGowan Inst. for Regenerative Med., Pittsburgh, PA; [10]DVA, Pittsburgh, PA

Abstract: Brain-computer interfaces (BCIs) allow people with severe motor deficits to control a variety of end effectors using only their neural signals. However, a major obstacle to the clinical adoption of BCI technologies is neural recording instabilities (Downey et al., 2018), which degrade performance until recalibration is performed. This places a burden on the user by requiring them to stop using the BCI in order to perform a recalibration procedure. Here, we show that by extracting a stable representation of neural activity from unstable neural recordings, human BCI control can be sustained across days without the need for recalibration.

We stabilize neural activity by extracting a consistent low-dimensional representation of population activity from different sets of neurons. Previous work in non-human primates (NHP) has found that neural population activity resides in a low-dimensional space (Sadtler et al., 2014). Given recordings from neural populations that are different but have some neurons in common, this space can be identified in a consistent manner (Bishop et al., 2014). Neural activity represented in this stable space can then be used with a fixed decoder that translates neural activity into BCI command signals, eliminating the need for recalibration (Degenhart et al., 2016).

We used neural signal stabilization over a 4-week period while a human participant performed a 2D BCI cursor movement task. Neural signals were recorded from microelectrode arrays implanted in the motor cortex of a 31-year old male participant with tetraplegia. On the first day of the experiment, we determined the initial parameters of the stabilizer and fixed parameters of the decoder using a standard calibration procedure. The neural signal stabilizer was then turned on and run continuously. Parameters of the stabilizer were updated every 16 trials to compensate for recording instabilities. On subsequent sessions, BCI control began with the final stabilized BCI from the previous session. At the end of each session, we retested the fixed decoder estimated on the first day. For each of 9 test sessions, we compared BCI performance using the final stabilizer update to that of the fixed decoder. Across experiments, trial completion times and angular error obtained with stabilization were significantly better than those obtained with the fixed decoder.

Our results provide a preliminary demonstration that neural signal stabilization allows BCI performance to be maintained across multiple weeks. Future work will explore the robustness of the stabilized BCI during both higher dimensional tasks, such as prosthetic arm control, and across different control contexts during human BCI use.

Disclosures: A.J. Herrera: None. **A.D. Degenhart:** None. **W.E. Bishop:** None. **E.R. Oby:** None. **E.C. Tyler-Kabara:** None. **S.M. Chase:** None. **A.P. Batista:** None. **B.M. Yu:** None. **J.L. Collinger:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 312.20/QQ2

Topic: E.05. Brain-Machine Interface

Support: NIH R01NS092626

Title: Neural modulation in other cortical areas while a BCI is controlled with M1 units

Authors: *Z. LIU[1], M. H. SCHIEBER[2]
[1]Biomed. Engin., [2]Neurol. and Neurosci., Univ. of Rochester, Rochester, NY

Abstract: The development of brain-computer interfaces (BCI) that use spike recordings for input has made use primarily of neural recordings from the primary motor cortex (M1). Previous work has revealed that the firing rates of many M1 units not directly involved in controlling the BCI (non-BCI units) nevertheless vary in relation to BCI performance. We investigated whether non-BCI units in cortical areas other than M1 also modulate while a BCI is controlled with M1 units.

We trained two monkeys (*Macaca mulatta*) to perform an 8-target center-out task using a joystick to control a cursor. In each trial, the monkey first acquired a center target and then one of the 8 peripheral targets shown on a computer screen. Each monkey then learned to perform the same task with a BCI that drove cursor velocity through linear decoders using the firing rates of 4 M1 units, each acting in one of four cardinal directions (left, right, up, and down). Once subjects achieved stable BCI performance, we recorded the spike activity of non-BCI units simultaneously in 6 cortical areas—M1, dorsal premotor cortex (PMd), ventral premotor cortex (PMv), primary somatosensory cortex (S1), the anterior intraparietal area (AIP), and dorsal posterior parietal cortex (dPPC)—as the monkey first performed the center-out task using the joystick and then performed the same task using the BCI.

Off-line, modulation depth during BCI performance was calculated for each single- or multi-unit with significant cosine tuning ($p<0.05$). More than 80% of non-BCI units in M1 and in PMd but less than 50% of units in PMv and in AIP were modulated significantly during the BCI task. Meanwhile, 60% to 80% of units in S1 and in dPPC were modulated significantly. The modulation depth of such units also varied among cortical areas (Kruskal-Wallis test, $p<0.05$). Followup tests indicated the modulation depth of non-BCI units in M1 was significantly greater than that of units in PMv, or in AIP; and the modulation depth of units in PMd was significantly greater than that of units in PMv, in AIP, or in dPPC. Interestingly, the modulation depth of units in S1 was significantly greater than that of units in PMv.

Our findings demonstrate that non-BCI units in many cortical areas are modulated significantly while M1 units control a BCI, with the number of modulated units and their modulation depth varying among areas. Whether such modulation outside of M1 reflects responses to visual inputs, efference copy, or causally drives M1 activity during BCI control is as yet unknown. We suggest that control of a BCI using M1 neurons may require a network extending well beyond M1.

Disclosures: Z. Liu: None. **M.H. Schieber:** None.

Poster

312. Brain-Machine Interface: Reaching Movements

Location: SDCC Halls B-H

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Topic: E.05. Brain-Machine Interface

Support: Grossman Center for the Statistics of Mind
Searle Scholars Program
Sloan Foundation
Simons Foundation
McKnight Foundation
NIH DP2 NS083037
NIH CRCNS R01NS100066

Title: Decoding sustained cyclic movements from low-dimensional neural states

Authors: *S. M. PERKINS[1,2], K. E. SCHROEDER[2,3], Q. WANG[1], M. M. CHURCHLAND[2,3,4,5]
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Abstract: Decode algorithms for brain-machine interfaces allow impressive two-dimensional cursor control. Successful decode algorithms do not attempt to decode descending commands for muscle activity, but rather exploit the statistically robust covariance of firing rates with hand velocity. However, because that relationship is unlikely to be fundamental, it may not generalize well. Different types of movements may thus require exploitation of different statistical relationships.
Here we focus on decoding rhythmic neural activity during a cycling task where a monkey advances through a virtual environment by rotating a hand-pedal forward or backward. A 96-dimensional vector of firing rates, recorded from motor cortex, was summarized in a low-dimensional neural state space. We previously reported that, in the dominant two dimensions, forward and backward cycling involve trajectories that rotate in the same direction, rather than reversing. Thus, the most robust statistical relationship is not a straightforward covariance of neural activity and hand velocity. Yet other reliable statistical relationships were found. First, movement onset was preceded by a translation of the neural state from a region occupied when stationary to one occupied during cycling. Second, during steady-state cycling the neural state traced roughly circular rhythmic trajectories. Third, circular trajectories occupied different subspaces during forward versus backward cycling.
We leveraged this structure by implementing a hidden Markov model to convert the state translation into a binary move/stop command. We used a Kalman filter (which captured neural

dynamics) to denoise the neural state in the two rotational planes. We computed the difference in angular momentum between the forward and backward planes, leading to commands for the direction and magnitude of motion through the environment.
During online control, the monkey initiated movements via the decoder and stopped on or close to instructed targets in the majority of trials. These decoded movements were in the direction instructed by the task in 89.1%±0.3% (SEM) of individual 1 ms samples from 1933 brain control trials. To better understand the decoder's performance, we performed an offline analysis of 1560 arm control trials. The move/stop command was correctly decoded in 88.6%±0.2% of samples. Peak cross correlation between the decoded velocity and actual velocity on each trial was 0.811±0.004, with a decode lag of 112±5 ms. Thus, although our decode approach bore little resemblance to most prior approaches, it performed well because it was tailored to the statistical regularities within the present application.

Disclosures: S.M. Perkins: None. **K.E. Schroeder:** None. **Q. Wang:** None. **M.M. Churchland:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 313.01/QQ4

Topic: E.07. Rhythmic Motor Pattern Generation

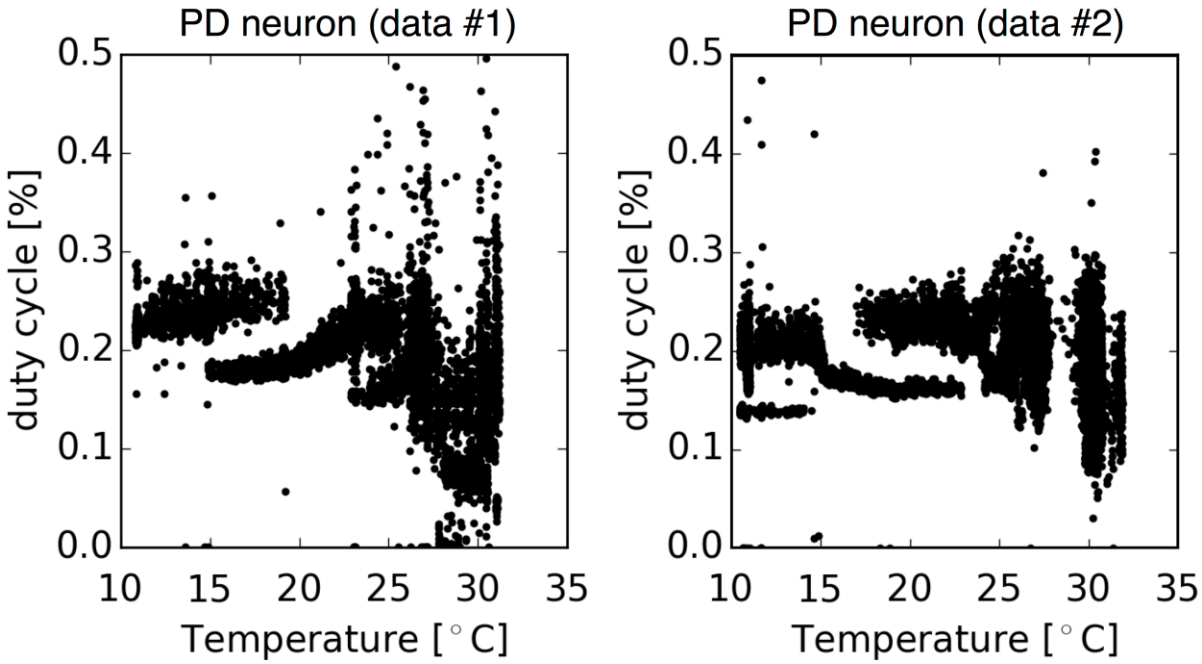
Support: NIH Grant R35 NS097343
NIH Grant T90 DA032435
The Swartz Foundation Grant 2017-6

Title: Mechanisms of temperature robustness and signatures of animal-to-animal variability in a rhythmic motor circuit

Authors: *H. D. RODGERS, L. M. ALONSO, E. MARDER
Volen Ctr. for Complex Systems and Dept. of Biol., Brandeis Univ., Waltham, MA

Abstract: Temperature affects the rate of biochemical processes including those that regulate neural activity. Previous work has shown that the phase relationships of oscillatory neurons in the crustacean pyloric circuit are maintained over a large temperature range (Tang et al, 2010, PLoS Biol). Strikingly, these networks produce similar activity despite a large variation in the number of ion channels across animals (Schulz et al, 2006, Nat Neurosci). Because individual ion channels possess different temperature sensitivities, the mechanism of temperature compensation is nontrivial. Here, we build on previous work in our lab (Tang et al, 2012, J Neurosci; Caplan et al, 2014, J Neurosci; O'Leary and Marder, 2016, Curr Biol) to further investigate these phenomena using the *C. borealis* stomatogastric ganglion (STG). We made

extracellular recordings of the STG during slow temperature ramps and found signatures of animal-to-animal variability in the duty cycle of pyloric units. The distribution of duty cycles of individual neurons changes with temperature in a structured way that differs across animals. Above a critical temperature, the rhythm deteriorates giving rise to aperiodic activity with long timescales. To gain further insight, we built temperature-sensitive models of the pyloric network that capture broad features of our data. In our models, the duty cycles remain approximately constant over the working range, and their precise distribution depends on temperature in a way that closely resembles our data. Near the critical temperatures, our models display complex dynamical states characterized by the emergence of timescales much longer than the period of the rhythm. In our models, the maximal conductances of all channels increase monotonically with temperature but the peak current for some ion species may decrease with temperature. Additionally, even though the temperature sensitivities of the channels are the same across cells, we find that the effect of temperature in a given current type can be different across cells.



Disclosures: H.D. Rodgers: None. **L.M. Alonso:** None. **E. Marder:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 313.02/QQ5

Topic: E.07. Rhythmic Motor Pattern Generation

Support: The Swartz Foundation, Grant: 2017-6

NIH Grant R35 NS097343

Title: The dynamics of ionic currents in conductance based models of neural activity during normal function and failure

Authors: *L. M. ALONSO[1], E. MARDER[2]
[1]Volen Ctr. for Complex Systems and Dept. of Biol., Brandeis Univ., Waltham, MA; [2]Volen Ctr. and Biol. Dept., Volen Ctr., Waltham, MA

Abstract: Recent computational studies have demonstrated that neurons and circuits with very similar behaviors can nonetheless have very different values of the conductances that control intrinsic excitability and synaptic strength [Prinz et al. Nat. Neuro. 2004]. While individual healthy animals may appear quite similar under control conditions, in response to extreme perturbations, they become dysfunctional, or "crash", and they appear to do so differently [Tang et al. J. Neuro 2012].
Inspired by this we studied a standard model of the pyloric network of crustaceans subject to temperature perturbations. We explored circuits with different sets of maximal conductances but the same temperature sensitivities, that respond similarly to temperature from 10-25 ˚C (as do crabs), but crash with entirely different dynamics at more extreme temperatures. We introduce a simple visualization of the dynamics of the ionic currents that allows us to represent in a syntactic manner the contribution of each current type to the neural activity. We find that even though the circuits behave similarly over a temperature range, the percent contribution of each current type depends on temperature in a non trivial manner. While the temperature sensitivities in the parameters is the same in all our circuits we find that failure occurs through diverse mechanisms.

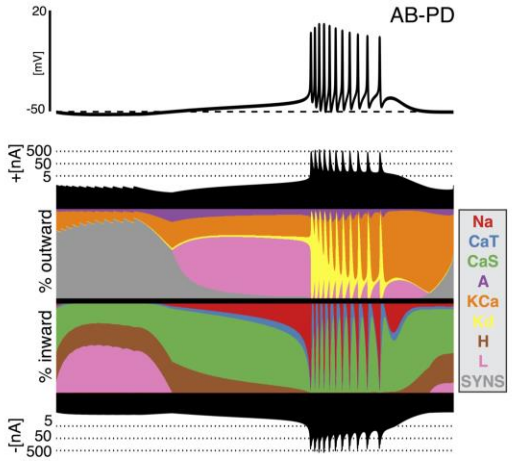


Fig 1: *A novel representation of the contribution of each current type to the neural activity. We compute the total inward and outward currents and represent the percent contribution of each current type in colors.*

Disclosures: L.M. Alonso: None. **E. Marder:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 313.03/QQ6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R90: Training in computational neuroscience. Grant Number: 1R90DA033463
The Swartz Foundation. Grant number: 2017-6
NIH Grant R35. Grant Number: NS097343

Title: Exploring robustness in small circuits of conductance based model neurons using landscape optimization

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Abstract: The numerical exploration of conductance-based models of neurons is a common approach to address fundamental questions in neuroscience. Because these models are high-dimensional and contain large numbers of parameters, exploring their solutions can become cumbersome. Here we describe a procedure to find parameters in small networks of model neurons so that the network will produce a specified target behavior. The procedure consists of optimizing a landscape function that scores the models' solutions according to a set of measures that encode the target or desired behaviors [Ben-Shalom et al. J. Neuro. Methods]. We show that this approach is an efficient tool to explore the solution space of these models.
We explored the solutions of a model of the crustacean's pyloric network which consists of three cells with eight ionic currents and seven inhibitory synapses [Prinz et al. 2004]. Previous work by our lab showed that these models are highly degenerate: there are many sets of parameters (e.g. maximal conductances) that result in similar activity. Theoretical studies by our group and others suggest that this degeneracy plays an important role in providing these circuits with robustness to perturbations [Caplan et al. 2014].
We employed landscape optimization to explore the solution space of the model. We generated 20000 circuits that produce pyloric rhythms between 1-4 Hz. Inspired by the effect of temperature in these circuits, we asked if it was possible to perturb all the kinetic variables and still obtain rhythms with similar properties. Mathematically, this amounts to finding paths in parameter space that interpolate regions where the models solutions correspond to the target pyloric rhythm. We found that there are multiple paths in parameter space where the models produce the pyloric rhythm. In many cases this is achieved by visiting attractors that satisfy the target behavior via distinct dynamical mechanisms. Thus in our models, the same perturbation at different temperatures may elicit qualitatively different responses.

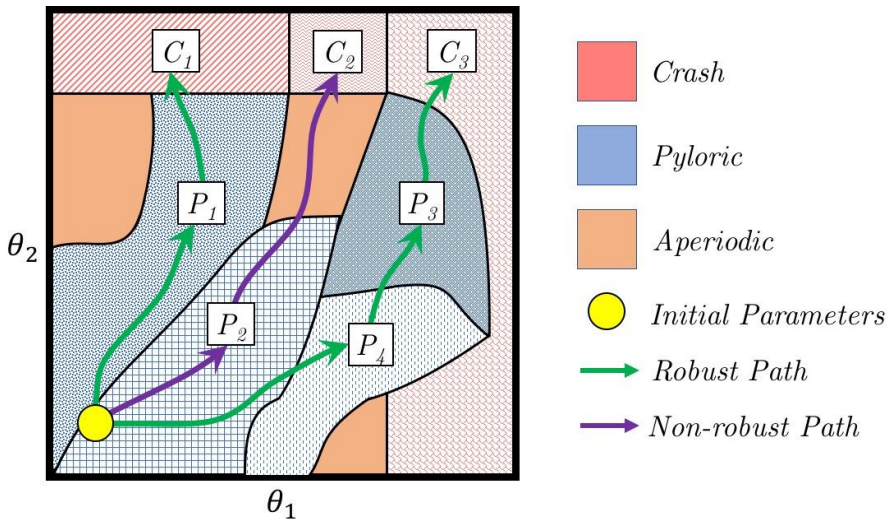

Fig. 1. A conceptual visualization of the parameter space. Bounded regions in the space represent unique attractor states with similar activity but different dynamical mechanisms. Robust paths through the space maintain pyloric rhythms until the point of crash by passing only through pyloric attractors, while non-robust paths pass through aperiodic states.

Disclosures: N. Guzman: None. **L.M. Alonso:** None. **E. Marder:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 313.04/QQ7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01 NS066587
NIH Grant R01 NS070583

Title: Network degeneracy and dynamics of task switching in the feeding circuit in *Aplysia*

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Abstract: Degeneracy is observed in neural networks in that particular patterns of motor activity are not necessarily encoded as a unique set of cellular and synaptic properties. Although this phenomenon is ubiquitous, its functional significance is poorly understood. We address this issue utilizing a multi-tasking network-the feeding circuit in *Aplysia*. The feeding circuit generates egestive and ingestive motor programs.

Previous data have shown that egestive activity can be triggered in the feeding circuit of *Aplysia* using two paradigms, egestive repetition priming and positive biasing. We hypothesized that circuit parameters (i.e., the properties of neurons and synapses) differ in the two situations. To generate egestive motor programs, there is an increase in the firing frequency of an identified protraction phase motor neuron, B8. In principle, this could happen either by a change in B8 excitability or by alterations in B8 synaptic input. Using voltage clamp techniques we demonstrate that there is a significant increase in phasic (presumably synaptic) input to B8 during both egestive priming and positive biasing. Previous work demonstrated that B65 is essential for positive biasing as measured approximately one minute after task switching. We now show that B20 is not essential at this time point. Previous data suggested that B20 plays an important role during egestive priming. We now demonstrate that egestive priming is not observed if B20 is hyperpolarized. In contrast, egestive priming is observed with B65 hyperpolarized. These results implicate one interneuron, B65, in positive biasing and a second interneuron, B20, in egestive repetition priming. We suggest that this degeneracy in circuit function will have implications for task switching. Consistent with this idea we demonstrate that an immediate return to ingestive activity is not possible after egestive priming but is possible after positive biasing. Taken together, these data suggest that degeneracy in network function is observed in the feeding network. In addition, our results support the idea that the dynamics of task switching can be determined by the nature of the mechanisms that are used to pattern activity.

Disclosures: Y. Wang: None. **K.R. Weiss:** None. **E.C. Cropper:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

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Program #/Poster #: 313.05/QQ8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R01 NS066587
NIH Grant R01 NS070583

Title: Dynamic changes in the character of a motor program may be determined by the complement of projection neurons activated

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Abstract: In many motor systems, multiple projection neurons are activated to initiate or maintain a behavior. In principle this may suggest there is redundancy, or alternatively that each

projection neuron has a unique function, contributing to specific parameters of the behavior. Although data are beginning to favor the latter view, little is known about these individual functions. We address this issue in the feeding system of *Aplysia*. *Aplysia*, motor programs can be ingestive, egestive or have intermediate characteristics. A population of about 13 cerebral-buccal interneurons (CBIs) project to the buccal ganglia (Wu et al. 2014). The most extensively characterized is CBI-2, which is activated by food and strongly and reliably drives motor programs. Previous work demonstrated that CBI-2 can trigger ingestive motor programs but that repetition priming is necessary to generate fully ingestive programs. Specifically, cycles of activity are initially intermediate but become ingestive over time (Proekt et al. 2004). We now report that in some preparations repetition priming is not observed, i.e., the conversion to ingestive activity does not occur. An issue we address is, can ingestive activity be triggered in these preparations if a second CBI is coactivated?

We study CBI-3 and CBI-12 (Jing and Weiss 2001, 2005; Hurwitz et al. 1999). Both are activated by food, additionally, CBI-3 is electrically coupled to CBI-2. We first sought to determine whether CBI-3 and CBI-12 are recruited when programs are triggered by CBI-2. We found that CBI-12 fires at a very low frequency and there is no correlation between its firing frequency and whether or not priming is observed. CBI-3 also fires at a low frequency but there is a significant increase in its firing frequency in preparations that undergo priming (i.e., the CBI-3 firing frequency reaches 3 Hz). However, it is unlikely that this change in CBI-3 activity accounts for priming. Intermediate programs triggered by CBI-2 do not become ingestive with bilateral co-activation of CBI-3 at 3 Hz.

Other experiments were conducted in preparations in which CBI-2 failed to induce repetition priming. We asked whether ingestive activity could be triggered by coactivating either CBI-12 or CBI-3. CBI-3 and CBI-12 were stimulated at physiologically relevant frequencies (15 Hz and 10 Hz respectively). Co-activation of CBI-12 failed to convert intermediate programs to ingestive. In contrast, with co-activation of CBI-3, programs were immediately ingestive, i.e., repetition priming was not necessary. Our data suggest that dynamic changes in the character of the motor program induced may be determined by the complement of activated CBIs.

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Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

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Program #/Poster #: 313.06/QQ9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant IIS160811

Title: Robustness of neuromechanical model with two layer CPGs and muscle synergies

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Abstract: This work demonstrates a neuromechanical model of rat hindlimb locomotion undergoing nominal walking with perturbations. A synthetic nervous system uses separate rhythm generator and pattern formation layers to activate antagonistic muscle pairs (extensor and flexor) about each joint in the sagittal plane. Two pattern formation groups are used to activate the six muscles in the leg, one activating hip muscles while the other activates knee and ankle muscles. In order to test the stability of the model, different perturbations were applied to the network. These include inhibitory tonic stimuluses to the synthetic nervous system and forces applied to the limb. Results show that the synthetic nervous system with two-layer central pattern generators exhibit more robustness than when individual half-center oscillators are used to control each joint. While any perturbation permanently altered the stepping rhythm of the half-center oscillators, the two-layer CPG often restored walking rhythms and coordination quickly. Some perturbations permanently resulted in an altered gait. For these perturbations, the two-layer CPG has improved stability over the individual half-center oscillators. We also observed another interesting result. For non-resetting deletions, unlike fictive motion which stepping phase immediately returned after perturbation ends. In our simulation, the stepping rhythm reset slowly over time. This difference between our simulation and fictive motion shows the importance of sensory feedback. This multi-layer model of locomotion demonstrates complex interdependencies of mechanics, sensory feedback, and rhythm generation during phase resetting and non-phase resetting deletions of locomotor rhythms. This model also demonstrates how the pattern formation network can activate muscle synergies in a coordinated way to produce stable walking.

Disclosures: A.J. Hunt: None. **K. Deng:** None. **R.D. Quinn:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

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Title: Circuit and computational analyses reveal specific contributions of synaptic strengths and noise to motor variability in a feedforward network

Authors: *G. ZHANG[1], K. YU[1], T. WANG[2], T.-T. CHEN[1], W.-D. YUAN[1], F. YANG[2], Z.-W. LE[1], S.-A. CHEN[1], F. LIU[2], E. C. CROPPER[3], K. R. WEISS[3], J. JING[1,3]
[2]Sch. of Physics, [1]Nanjing Univ., Jiangsu, China; [3]Mt Sinai Sch. Med., New York, NY

Abstract: When one repeats a motor act, the executions vary as a result of variable activity of the behavior mediating neurons. Variability must originate partly from mechanisms in the behavior-generating network. Whereas previous work showed that variable outputs are often produced by concurrent excitation and inhibition, we provide a first example where feedforward excitation in conjunction with synaptic noise generates variable motor output in the *Aplysia* feeding system. We identified a command neuron, cerebral-buccal interneuron-10 (CBI-10) that is active during feeding behavior. CBI-10 drives more variable motor programs than programs driven by a previously-identified command neuron, CBI-2. The difference in variability is partly attributable to differences in the strength of synaptic connections between the command-like neurons and B63 and B34 pattern-generating interneurons that excite motoneurons. In particular, B34 receives weaker excitation from CBI-10 than from CBI-2, and fires at lower frequency during CBI-10-elicited programs. B34 subthreshold depolarization decreases the variability of CBI-10 induced motor programs, suggesting an obligatory role of B34, and a role of the weaker synaptic connection between CBI-10 and B34 in generating variability. To determine whether this is the case, we constructed a simplified Aplysia-like feeding network model. Synapses between CBI-2 and CBI-10 and B34 and B63 were modeled using physiological data. We selected a set of parameters that result in network activity resembling the activity of the biological network. Variability is not seen if there is a weak synaptic connection between CBI-10 and B34 but no synaptic noise, suggesting necessity of synaptic noise in generating variable programs. With synaptic noise, activity of the model network is similar to activity of the biological network in several respects, e.g., CBI-10 evoked programs are more variable than CBI-2 induced. We also performed parameter analyses. First, we varied the synaptic conductance from CBI-10 to B34, as conductance increases, the network output shifts from no programs, to programs, to overactivated states. Interestingly, the variability in programs tends to be high near bifurcation points between the three states. Second, we varied the level of synaptic noise and found that moderate, not high, level of synaptic noise promotes more variability. Thus, our studies provide evidence for the joint roles of synaptic conductance and noise in variability generation within a feedforward network. Our findings may be broadly relevant because many neural circuits incorporate feedforward properties and show various degrees of variability.

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Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 313.08/QQ11

Topic: E.07. Rhythmic Motor Pattern Generation

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European Research Council under the Advanced ERC Grant Agreement Switchlet n.670645

Title: Cellular switches orchestrate rhythmic circuits

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Abstract: Small inhibitory neuronal circuits have long been identified as key neuronal motifs to generate and modulate the coexisting rhythms of various motor functions. Our paper highlights the role of a cellular switching mechanism to orchestrate such circuits. The cellular switch makes the circuits reconfigurable, robust, adaptable, and externally controllable. Without this cellular mechanism, the circuits rhythms entirely rely on specific tunings of the synaptic connectivity, which makes them rigid, fragile, and difficult to control externally. We illustrate those properties on the much studied architecture of a small network controlling both the pyloric and gastric rhythms of crabs. The cellular switch is provided by a slow negative conductance often neglected in mathematical modeling of central pattern generators. We propose that this conductance is simple to model and key to computational studies of rhythmic circuit neuromodulation.

Disclosures: A. Franci: None. **G. Drion:** None. **R. Sepulchre:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

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Program #/Poster #: 313.09/QQ12

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R35NS097343

T90 DA032435

Title: Adaptation of neurons in the crab stomatogastric ganglion to changes in extracellular potassium concentrations

Authors: *L. HE, E. MOROZOVA, M. RUE, D. J. POWELL, E. MARDER
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Abstract: Neural circuits must be robust to various environmental perturbations. This is especially true for central pattern generators (CPGs) that are active throughout an animal's lifetime and that produce essential motor patterns such as breathing, walking, and chewing. Stability over a range of perturbations requires multiple intrinsic and synaptic mechanisms that operate at various timescales in order for the neural network to maintain function. To achieve a better understanding of the regulatory mechanisms underlying the maintenance of robust output of pattern-generating neural circuits, we studied the responses of the pyloric neurons of the Cancer borealis stomatogastric ganglion (STG) to changes in extracellular potassium concentration. A 2.5-fold increase in [K+] in the extracellular bath solution led to membrane potential depolarization by ~15 mV for most pyloric cells. This depolarization coincided with the temporary loss of activity of the pyloric dilator (PD) neurons for up to an hour, followed by recovery of spiking and, in some cases, bursting activity, despite continued perfusion of 2.5x[K+] saline. To better understand whether the adaptation to elevated [K+] is largely due to circuit level, cell-intrinsic, or a combination of the two types of mechanisms, we isolated the pyloric pacemaker kernel (AB/PD) using the synaptic blocker, picrotoxin (PTX). The experiments in 2.5x[K+] with PTX saline revealed a two distinct phenomena. First, PD neurons demonstrated a shorter period of absence of activity than the preparations with intact circuitry, and soon switched to tonic spiking. Secondly, some neuronal firing properties of the pyloric cells changed, with their activity gradually becoming more burst-like over the timescale of hours. Together, these data support the involvement of more than one mechanism. Because the STG is modulated by neurons in the three presynaptic ganglia, we wanted to know if descending inputs play a role in the recovery in response to changes in [K+]. Therefore, we blocked all descending modulatory inputs. In these experiments, the pyloric neurons exhibited activity patterns very similar to the experiments with intact circuitry on a similar timescale. The results of these experiments support the presence of a cell-intrinsic adaptation mechanism. To determine what kinds of cell intrinsic mechanisms could be involved in the adaptation of pyloric neurons to elevated potassium, we measured gene expression changes in STGs exposed to 2.5x[K+] saline. We found that mRNA for the potassium channels IA and the IKD were upregulated. In addition, we found increases in stress-related heat shock proteins in STGs exposed to 2.5x[K+] saline.

Disclosures: L. He: None. **E. Morozova:** None. **M. Rue:** None. **D.J. Powell:** None. **E. Marder:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 313.10/QQ13

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Characterizing conductance variations in model crab cardiac ganglion networks

Authors: J. WANG[1], P. SAMARTH[2], T. BANKS[2], D. R. KICK[3], D. J. SCHULZ[3], *S. S. NAIR[2]
[1]Bioengineering, [2]Electrical & Computer Engin., [3]Biol. Sci., Univ. of Missouri Columbia, Columbia, MO

Abstract: The crustacean cardiac ganglion (CG) network coordinates the rhythmic contractions of the heart muscle to control the circulation of blood. The network consists of 9 cells, 5 large motor cells (LCs) and 4 small endogenous pacemaker cells (SCs). Variability in maximal conductances of intrinsic currents have been reported for the five LCs, even within the same animal. Despite this variability, the intact network maintains a synchronous output, but how it does so is unclear. Recent results using perturbations to the system using blockers showed that gap junction conductances provide compensation to restore network function. However, the role of synaptic conductances remain unexplored, although compensatory changes in synaptic conductances has been reported in the literature in other species.
To study the role of intrinsic and synaptic conductances in such compensatory mechanisms in a comprehensive manner, we first developed a new and morphologically realistic 3-compartment single cell model using first-hand recordings of intrinsic currents from LCs of the crab cancer borealis. The three compartments were the soma, neurite and a spike-initiation zone (SIZ). We then performed a modeling study in two steps. We first generated a large number of models, each with a different parameter set and then applied a 3-stage "rejection sampling" procedure to select: (i) isolated LCs that reproduce realistic passive properties and responses to a "stimulus protocol"; (ii) intact LCs that reproduce realistic responses to the same "stimulus protocol"; (iii) CG networks that reproduce realistic responses to a variety of realistic synaptic excitation.
At the next step, we studied the covariations among the currents that preserve model single cell and network outputs, and their relative roles in such compensation. Additionally, we investigated the interesting noise or "jitter" of synaptic input that improves the model performance.

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Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

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Program #/Poster #: 313.11/DP07/QQ14

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH NS82001
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Title: Similarities and distinctions among electroconvulsion- and proconvulsant-induced seizure discharges and native motor patterns during flight and grooming: Quantitative analysis of spike firing patterns in *Drosophila* flight muscles

Authors: *A. IYENGAR, J. LEE, C.-F. WU
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Abstract: In *Drosophila*, high frequency electroconvulsive stimulation across the brain triggers a highly stereotypic repertoire of spasms which are exaggerated in epilepsy gene mutants with a distinct spike discharge patterns known as electroconvulsive seizure (ECS). These seizure discharges manifest across the nervous system and can be conveniently and stably assessed throughout the seizure event in the large, isometric indirect flight muscles, the Dorsal Longitudinal Muscle (DLM). Despite the widespread use of DLM spiking activity to monitor ECS discharges [ref. 1, 2, 3], it is unknown how the ECS firing patterns relate to native motor programs, including courtship song, flight, and grooming which drive DLM activity. We employed quantitative spike pattern analyses to contrast ECS discharges against flight and grooming activity. We quantified: 1) overall spiking activity, 2) short-term alterations in firing regularity, 3) timing relationships among adjacent spikes, and 4) the bilateral coordination of motor patterns. Our results suggest ECS discharges share a number of similarities with spike patterns during sustained flight, including instantaneous firing rate (mean [95% interval]): 7.5 [3-14] vs. 6.7 [3-12] Hz respectively, but were distinct from grooming behavior whose spiking was highly variable (16.6 [0-60] Hz). Further, we constructed Poincare plots (return maps) of adjacent inter-spike intervals, which revealed that ECS discharges and flight generally displayed substantially greater short-term firing regularity compared to grooming-related activity. Finally, we utilized such approaches to examine the impacts of disrupting several critical neurotransmission systems. Picrotoxin (PTX) a known procovulsant that inhibits $GABA_A$ receptors, induced DLM seizure patterns which evolved over time with phases resembling flight but distinct from ECS discharges. A gain-of-function $GABA_A$ receptor mutant, *rdl* also modified flight patterns, without major alterations in ECS. Conversely, mutants affecting cholinergic

transmission, *Cha*, and electrical transmission, *ShakB* modified ECS repertoire more severely, while sparing flight patterning. Together, our results indicate that applications of quantitative techniques may be further explored to reveal further relationships between native and aberrant motor programs that drive the DLM.
[1] Pavlidis P, Tanouye MA (1995) *J. Neurosci. 15*(8) 5810-5819.
[2] Lee J, Wu C-F (2002) *J. Neurosci. 22*(24) 11065-11079.
[3] Iyengar, Wu C-F (2014) *J Neuogenet. 28*(3-4) 316-328.

Disclosures: A. Iyengar: None. **J. Lee:** None. **C. Wu:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

Location: SDCC Halls B-H

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Program #/Poster #: 313.12/QQ15

Topic: E.07. Rhythmic Motor Pattern Generation

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GSU Brains & Behavior seed grant to GC

Title: Balanced interaction of the Na/K pump and persistent sodium current as a robust mechanism of bursting activity

Authors: *G. S. CYMBALYUK[1], C. ERXLEBEN[2], A. WENNING[2], R. L. CALABRESE[2]
[1]The Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Biol. Dept., Emory Univ., Atlanta, GA

Abstract: Rhythmic motor functions like breathing and leech heartbeat require robust yet flexible operation of central pattern generator (CPG) circuits producing appropriate patterns of bursting activity. The interaction of multiple mechanisms supporting bursting at the neuronal level with network mechanisms could be responsible for the robustness and flexibility characteristic living CPGs. We investigate the role of Na^+/K^+ pump, a basic cellular engine maintaining the physiological gradients of Na^+ and K^+ ions across the membrane, for which growing evidence indicates that the Na^+/K^+ pump current plays important roles in the electrical activity of neurons, contributing to functional and dysfunctional dynamics. To understand how the pump dynamics contribute to neuronal activity, the kinetics of Na^+/K^+ pump function has to be quantitatively evaluated versus the dynamical properties of neurons.
The Na^+/K^+ pump contributes to the dynamics of neurons on the time scale of the period of their rhythmic bursting activity (6-10 s). In the leech heartbeat CPG, the basic building blocks are half-center oscillators (HCO), which are pairs of mutually inhibitory HN interneurons producing alternating bursting activity. A definitive role of the Na^+/K^+ pump current in HN bursting dynamics was revealed by using the H^+/Na^+ antiporter monensin, which stimulates the pump by diffusively increasing the intracellular Na^+ concentration. Application of monensin decreases the

period of the heartbeat HCO (Kueh et al. 2016).
To make quantitative analysis possible, we developed a dynamic-clamp implementation of a hybrid system with a living neuron and mathematical model in real time (corresponding to an HN HCO) in each of which we can manipulate pump parameters on the fly. We explored parameter space to fine-tune the real time model to support functional-like dynamics of a hybrid HCO under variation of the key parameters. We show that the interaction of the persistent Na^+ current (I_P) with I_{Pump} constitutes a mechanisms, which is sufficient to support endogenous bursting activity in HN interneurons and that this mechanism reinstates robust bursting activity in isolated living neurons rendered tonic by persistent leak associated with electrode penetration. This mechanism requires appropriate balance in the strength of I_P and pump activity. The functional alternating bursting of the HCO network requires the neurons to be in parametric vicinity of or in the state of the endogenous bursting. By focusing our analysis on a common network motif of an HCO, we generated insights that generalize to less accessible vertebrate nervous systems.

Reference

Kueh D, et al. *Elife* 5: 2016.

Disclosures: G.S. Cymbalyuk: None. **C. Erxleben:** None. **A. Wenning:** None. **R.L. Calabrese:** None.

Poster

313. Rhythmic Motor Pattern Generation: Stability and Variability

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Program #/Poster #: 313.13/QQ16

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant NS083319
NIH grant MH060605

Title: Neuromodulation of component variability and circuit output variability

Authors: *A. C. SCHNEIDER[1], D. M. BUCHER[2], F. NADIM[2]
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Abstract: Ionic currents and their corresponding channel gene mRNA levels can vary substantially in the same neuron type across animals. Yet, neural circuits produce outputs that are readily identifiable and have consistent characteristics. This disparity raises the question of how variable components can lead to consistent circuit outputs.
We address this question using the pyloric circuit of the crab stomatogastric nervous system (STNS), which has large variability in ionic currents of identified neurons, but produces a stable

triphasic rhythm with remarkably constant activity phases across animals. As in all neural circuits, pyloric activity is subject to actions of a variety of neuromodulators. When descending inputs are blocked in vitro to remove neuromodulator inputs (decentralization), the pyloric rhythm becomes less stable or stops altogether. Many of the individual STNS neuromodulators activate a stable identifiable pattern specific to that modulator. A number of these neuromodulators activate a persistent inward current, I_{MI}, albeit at different levels and in different subsets of pyloric neurons. It is therefore reasonable to assume that neuromodulation is necessary for producing the observed consistent output patterns by reducing component variability.
Hence, we compared the consistency of activity phases (circular variance with bootstrapped 95% confidence intervals) in the intact STNS with that of a decentralized STNS and then in the presence of the excitatory neuropeptide proctolin (1μM). Although some activity phases shifted significantly, their circular variance did not change. We also compared the variability (coefficient of variation, CV) of cycle period and ionic current levels in control (decentralized) and proctolin. CVs of all factors remained comparable and were not reduced. The variability of proctolin-induced I_{MI} was similar to that of other ionic currents.
These results show that a single neuromodulator, which rescues rhythmic activity of decentralized, silent STNSs, does not reduce variability at the component level or the circuit output level. We conclude that consistent circuit output does not require a reduction of variability at the component level. Alternatively, variability could be reduced only if more than one neuromodulator is present, which is the always the case in the intact system.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.01/QQ17

Topic: F.02. Behavioral Neuroendocrinology

Title: Monitoring fluctuations in brain extracellular estradiol levels in freely-moving female rats

Authors: *S. AJAYI, A. AMER, P. GOLD, D. KOROL
Biol., Syracuse Univ., Syracuse, NY

Abstract: Evidence for estradiol (E_2) synthesis in the brain suggests that the steroid may operate through a combination of neuromodulator and hormonal mechanisms to mediate improvements and impairments across different types of learning and memory tasks. In this study, we used *in vivo* microdialysis in awake, freely-behaving female rats to measure E_2 concentrations in dialysates of hippocampus extracellular fluid across the estrous cycle and in ovariectomized rats with and without hormone replacement. Dialysate samples were collected hourly for 4 hrs and an

additional 2 hrs when systemic E_2 was given during microdialysis. Cycling rats were staged for estrous cycle using 15 days of vaginal smears. On the day of microdialysis measures, rats in proestrus, the estrous cycle stage with the highest levels of circulating E_2, displayed levels of E_2 in the hippocampus samples of 18 ± 4 pg/ml. In contrast, rats at stages with lower levels of circulating E_2, i.e. estrus and diestrus, had significantly lower levels of E_2 in the hippocampus (estrus, 6.5 ± 2.5 pg/ml), diestrus (4.7 ± 1.2 pg/ml). Thus, as seen in blood, extracellular E_2 levels were significantly higher at proestrus than at estrus or diestrus ($ps<0.05$ vs proestrus). Twenty-one days following ovariectomy, rats that received s.c. injections of E_2 (45 µg/kg) 48 and 24 hrs before testing had higher hippocampal E_2 levels (13.9 ± 0.5 pg/ml) than did the oil-treated control (3.8 pg/ml). Thus, the brain levels persisted for 24 hr after the last injection, similar to results observed previously for blood levels. Interestingly, rapid increases in hippocampal E_2 levels after subcutaneous injections were observed in rats at low hormone states but not in those at high hormone states. We are currently evaluating whether the hippocampal increases in E_2 following rises in blood E_2 are the result of E_2 uptake from the blood into the brain, increased release of brain E_2 in response to a signal conveyed by high levels of blood E_2, or both. Finding increased hippocampus-derived E_2 in the absence of increased circulating levels would provide support for the view that E_2 functions as a neuromodulator and would point to brain targets for estrogen therapies that avoid the health risks of peripheral estrogenic stimulation.

Disclosures: S. Ajayi: None. **A. Amer:** None. **P. Gold:** None. **D. Korol:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.02/QQ18

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF IOS 13-18490
NIH P30 AG034464
NIDA DA038798

Title: Estradiol modulates extracellular hippocampal glucose and lactate during spatial working memory in female rats

Authors: *W. WANG, D. L. KOROL
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Abstract: Estrogens given to young adult ovariectomized rats enhance learning and memory on hippocampus-sensitive tasks, including tests of delayed spatial working memory. Using *in vivo* microdialysis with zero-net flux methods, we previously found that cognitively enhancing doses of estradiol, the predominant form of estrogen in young adults, also increased extracellular levels

of glucose and lactate in the hippocampus. The estradiol-induced increase in energy substrates was accompanied by higher glycogen concentrations in the hippocampus that were depleted after 20 minutes on a delayed spatial alternation task. Because glucose can be stored as astroctyic glycogen and astrocytic glycogenolysis produces lactate, estrogens may boost spatial working memory by increasing hippocampal provisions of glucose and lactate prior to or during cognitive activity. To test this hypothesis, we used wireless bioprobes to measure changes in extracellular glucose or lactate in the hippocampus during a four-arm spontaneous alternation task. Young adult ovariectomized rats were treated with estradiol benzoate (EB; 4.5 μg/kg) or oil 48 and 24 hours prior to testing. EB enhanced alternation scores above those of oil-treated controls. Baseline levels of glucose and lactate were elevated in EB-treated rats, supporting our prior findings with microdialysis. Memory testing produced a rapid reduction in glucose that recovered to and subsequently rose above baseline values throughout testing. EB potentiated the initial testing-induced depletion but not the recovery and elevation later in testing. Absolute values of glucose remained higher in EB-treated rats than in oil-treated rats at all times throughout testing. Testing-induced increases in lactate were significantly augmented by EB throughout the working memory task. Together, the results suggest that EB may enhance glucose storage into glycogen, potentiate glucose consumption early in the testing phase, and stimulate the production of astrocytic lactate to support continued memory processing. More generally, these results imply that estradiol effects on learning and memory may be mediated, at least in part, by the hormone's regulation of metabolic substrate availability and utilization in the brain.

Disclosures: W. Wang: None. **D.L. Korol:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.03/QQ19

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC

Title: The rapid effects of hippocampally-synthesized estrogens on recognition and spatial learning in ovariectomized mice

Authors: T. MARTIN, L. KING, M. KLEMENS, R. ROSE, E. CHOLERIS
Dept. of Psychology and Neurosci. Program, Univ. of Guelph, Guelph, ON, Canada

Abstract: Estrogen is known to play a role in modulating cognition. Specifically, estrogen has been found to facilitate recognition and spatial learning. The female hippocampus is known to synthesize its own estrogens, and to be highly sensitive to estrogenic action (Frick et al., 2015). Local hippocampal administration of 17-β estradiol was found to facilitate recognition and

spatial learning (Phan et al., 2015), whereas a significant decrease in estrogens impaired long-term recognition memory (Tuscher et al., 2016), with spatial memory still being left unexplored at this time. However, whether locally synthesized, physiological estrogens are also involved in the initial processes of learning of spatial and recognition tasks is unknown. Here, 2-3-month-old CD1 mice were ovariectomized, hippocampally cannulated and infused with the estrogenic synthesizing enzyme inhibitor, letrozole (at one of 3 doses: 0.01, 0.05 or 0.1µg/µL), or vehicle (2%-dimethyl-sulfoxide) 15 minutes before a social, object or spatial recognition task. These tasks included three 4-minute learning periods where the same two stimuli were repeatedly introduced, followed by a 4-minute test period where a novel stimulus was either replaced one of the repeated stimuli or moved to a novel location, each separated by 3-minute rest periods where the stimuli were removed. Our hypothesis was that hippocampally-synthesized estrogens are involved in the initial learning of spatial and recognition memories. It was therefore predicted that letrozole at all doses would impair recognition and spatial learning. In partial support of the predictions, groups treated with 0.01 or 0.05µg/µL of letrozole did not show social or object recognition, whereas groups treated with 0.1µg/µL were not impaired in either. In direct contrast, spatial recognition was unimpaired at the 0.01 and 0.05µg/µL doses, but impaired at 0.1µg/µL. These results contribute a greater understanding of the function of hippocampally-synthesized estrogens within the context of learning and memory. This further characterization of estrogenic action and its effects on cognition could aid in the development of safer hormone replacement therapies for women experiencing cognitive deficits as a symptom of menopause.

Disclosures: T. Martin: None. **L. King:** None. **M. Klemens:** None. **R. Rose:** None. **E. Choleris:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.04/QQ20

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant MH107886
University of Wisconsin-Milwaukee College of Letters and Science

Title: The role of androgen receptors and hippocampal estradiol synthesis in memory consolidation in male mice

Authors: *W. A. KOSS, R. L. ALF, J. J. TUSCHER, K. M. FRICK
Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: We have previously demonstrated that infusion of 17β-estradiol (E_2) into the dorsal hippocampus (DH) of ovariectomized female, gonadectomized (GDX) male, or sham-

gonadectomized (sham) male mice enhances memory consolidation as tested in object placement (OP) and object recognition (OR) tasks. We have also shown that DH infusion of the aromatase inhibitor letrozole disrupts OR and OP memory memory consolidation in ovariectomized female mice, which suggests that hippocampally-synthesized E_2 is essential for intact memory consolidation in ovariectomized females. In the current study, we examined effects of aromatase inhibition on memory in male mice. Sham and GDX mice were infused with vehicle or letrozole (1.0 μg/hemisphere) bilaterally into the DH immediately after training in OP and OR tasks. Mice were tested twenty-four hours later for OP, and forty-eight hours later for OR. Letrozole blocked OP and OR memory consolidation in GDX, but not sham, male mice, causing us to hypothesize that circulating androgens in sham males may have masked the memory-impairing effects of letrozole. To test this hypothesis, we designed a study to determine if blocking androgen actions with an androgen receptor antagonist could unmask the memory-impairing effects of letrozole in sham males. However, we first needed to determine how androgen receptor antagonism might affect memory consolidation independent of letrozole. Immediately after OP and OR training, sham males received bilateral DH infusion of vehicle or one of three doses of the androgen receptor antagonist, flutamide (0.25 μg/hemisphere, 0.5 μg/hemisphere, or 1.0 μg/hemisphere). In OP, the 0.25 μg and 1.0 μg doses, but not 0.5 μg dose, impaired memory consolidation. In OR, only 1.0 μg /hemisphere impaired memory consolidation. These data suggest that blocking androgen receptor activation can dose-dependently impair memory consolidation in sham male mice. However, to address our hypothesis about how androgen antagonism might influence effects of letrozole, we are currently co-infusing letrozole with 0.5 μg flutamide because this dose of flutamide had no effect on memory on its own. Together, these data will further define the role of hippocampus-synthesized E_2 and androgen signaling in the memory of male mice.

Disclosures: W.A. Koss: None. **R.L. Alf:** None. **J.J. Tuscher:** None. **K.M. Frick:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.05/QQ21

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH grant R15 GM118304

Title: Development of a novel estrogen receptor beta agonist for enhancing memory consolidation in female mice

Authors: *J. KIM[1], A. M. HANSON[2], I. S. PERERA[3], W. A. DONALDSON[3], D. S. SEM[2], K. M. FRICK[1]
[1]Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [2]Dept. of Pharmaceut. Sci.,

Concordia Univ. Wisconsin, Mequon, WI; [3]Dept. of Chem., Marquette Univ., MILWAUKEE, WI

Abstract: Estrogens promote hippocampal synaptic plasticity and memory, and low or fluctuating estrogen levels may contribute to cognitive symptoms in conditions like Alzheimer's disease, anxiety disorders, and depression. These effects are likely mediated by a combination of intracellular (ERα and ERβ) and/or membrane-bound estrogen receptors. Both ERα and ERβ are highly expressed in the hippocampus, and agonists of either receptor can enhance hippocampal-dependent memory consolidation in female mice. However, ERα agonists can be pro-carcinogenic, which has led to considerable interest in developing agonists that are highly selective for ERβ. Recently, we reported a novel ERβ agonist with higher selectivity for ERβ over ERα activation than previously reported drug candidates (McCullough, et al., Bioorg Med Chem. 2014;22(1):303-10). Here, we optimized a related class of molecules comprised of a 4-hydroxymethyl-cyclohexane ring tethered to a phenol ring, making an *A-C estrogen* that closely resembles the naturally occurring estrogen molecule, but lacks the B and D rings. In cell-based assays, our lead compound, ISP358-2, showed >750-fold selectivity for ERβ over ERα, and EC50s of 20-30 nM for ERβ in both cell-based and direct binding assays. Moreover, ISP358-2 showed no off-target activity with other nuclear hormone receptors including androgen and glucocorticoid receptors, nor did it stimulate breast cancer cell growth or affect peripheral pathology. To assess its effects on hippocampal memory consolidation, ISP358-2 was administered to ovariectomized mice immediately after training in object recognition and object placement tasks via 3 routes of administration: dorsal hippocampal infusion (10 pg, 100 pg, 1 ng), intraperitoneal injection, and oral gavage (0.5, 5 mg/kg). Post-training administration of ISP385-2 enhanced memory consolidation in both tasks via all three routes of administration. Overall, these findings suggest that ISP358-2, a highly selective ERβ agonist with no evidence of peripheral toxicity, can safely and effectively facilitate memory formation in ovariectomized females. This compound may be a promising drug candidate for enhancing memory in disorders characterized by memory dysfunction that occurs under low estrogen conditions, such as menopause.

Disclosures: J. Kim: None. **A.M. Hanson:** None. **I.S. Perera:** None. **W.A. Donaldson:** None. **D.S. Sem:** None. **K.M. Frick:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.06/QQ22

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC

Title: The interplay between gonadal sex hormones and dorsal hippocampus D2-type dopamine receptors in the mediation of social learning in mice

Authors: *N. BASS, J. ANTHONYPILLAI, R. MATTA, E. CHOLERIS
Univ. of Guelph, Guelph, ON, Canada

Abstract: Abstract: Social learning, learning that occurs following social interaction and observation, is evolutionally adaptive and allows a conspecific to avoid or mitigate the consequences of individual trial and error learning (Galef, 1988). Though important to survival, the mechanisms of social learning are poorly understood. Social learning may be investigated using a social transmission of food preference (STFP) paradigm, where a preference for a novel flavored food diet is transferred from a demonstrator (DEM) to an observer (OBS) animal during social interaction. Previous research has demonstrated that the dopamine (DA) system is directly involved in STFP (Choleris et al., 2011) and that there is a sex difference in the role of D2-type DA receptors (Matta et al., 2017). Intra-dorsal hippocampus (HPC) infusions of D2-type DA receptor antagonist raclopride blocked social learning only in female mice (Matta et al., 2017). Furthermore, estrogen treatment enhanced the STFP (Ervin et al., 2015) and regulates the DA system. Similarly, androgen treatments increase HPC DA release (Tucci et al., 2008). Together, these findings suggest an interplay between HPC D2-type DA receptors and male and female sex hormones in the mediation of social learning in mice. In this study, male and female, either gonadectomised or gonadally intact, experimentally naïve CD 1 mice (2-3 months old), are undergoing a STFP paradigm following dorsal HPC infusions (0.5 μL per hemisphere) of a D2-type DA receptor antagonist, raclopride (18 μg/μL, 20 μg/μL) or control physiological saline solution. Researchers are blind to the drug and dose. First, a DEM mouse consumes 1 of 2 novel flavored food diets for 1-hour while an OBS mouse receives dorsal HPC infusions of raclopride or saline. Following a 10-minute delay, a 30-minute social interaction between the DEM and OBS mouse occurs. Finally, an 8-hour OBS choice test is implemented where the OBS is free to consume the 2 novel flavored food diets. Food intakes are taken at 1, 2, 4, 6, and 8 hours. It is predicted that raclopride will block social learning in castrated males, ovariectomized females, and gonadally intact females, but not in gonadally intact male mice. Unlike previous research that has only explored the role of female sex hormones in social learning, this study considers the possibility that *both* male and female sex hormones are involved in the mediation of DA facilitated social learning.

Disclosures: N. Bass: None. **J. Anthonypillai:** None. **R. Matta:** None. **E. Choleris:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.07/QQ23

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Grant BGPIN 2016-06653

Title: Behavioral effects of 17B-estradiol and progesterone on the OVX female rat response to ketamine

Authors: *C. GAGNE, S. BENKETIRA, V. BOULOS, M. HERON, J. LACASSE, N. TITO, W. BRAKE
Psychology, Concordia Univ., Montreal, QC, Canada

Abstract: The NMDA-antagonist ketamine is a novel fast-acting anti-depressant shown to have therapeutic effects on individuals with treatment-resistant depression. Women are twice as likely to suffer from depression yet the majority of research on the effects of ketamine has focused on males. Moreover, little is known of the interaction between female sex hormones and ketamine. This research aimed to investigate the impact of 17β-estradiol (E2) and progesterone (P) on the ovariectomized (OVX) female rats' response to ketamine. Here 91 OVX female Wistar rats were split into three hormonal conditions (low E2, high E2, and high E2 + P) and five ketamine conditions (0, 2.5, 5, 10, & 20 mg/kg) resulting in 15 total groups. All rats were tested in the open field twice; before and 48 hours after ketamine and E2 administration. Between open-field tests rats were tested in the modified forced swim test (FST) 24 hours after ketamine. Early results show that high E2 + P replacement rats spent the most time immobile overall, compared to the other hormone conditions, and responded to ketamine by spending the least time immobile in the 20 mg/kg ketamine condition. The low E2 and high E2 replacement rats paradoxically spent more time immobile in the FST in all ketamine conditions compared to no ketamine. While there was an effect of hormones on the open field test, i.e. the low E2 group spent more time in the middle than the high E2 + P group, there was no effect of ketamine. Continuing this research should elucidate any interaction between female sex hormones and ketamine. Future work will investigate the neurobiological underpinnings of our findings.

Disclosures: C. Gagne: None. **S. Benketira:** None. **V. Boulos:** None. **M. Heron:** None. **J. Lacasse:** None. **N. Tito:** None. **W. Brake:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.08/QQ24

Topic: F.02. Behavioral Neuroendocrinology

Support: 2017 Sex and Gender in Alzheimer's (SAGA) Grant

Title: The role of APOE genotype, sex, and 17-beta estradiol in a mouse model of Alzheimer's disease

Authors: *L. TAXIER[1], S. M. PHILIPPI[1], J. M. YORK[3], M. LADU[4], K. M. FRICK[2]
[2]Dept. of Psychology, [1]Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [3]Dept. of Anat. and Cell Biol., Univ. of Illinois at Chicago Dept. of Anat. and Cell Biol., Chicago, IL; [4]Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL

Abstract: In women, the loss of circulating ovarian estrogens at the onset of menopause is correlated with increased risk for development of Alzheimer's disease (AD) relative to men. Additionally, women carriers of the APOE4 genotype, which is the leading genetic risk factor for late-onset AD, are more likely than women who carry other APOE genotypes and men of any APOE genotype to develop AD. APOE4 status, combined with estrogen loss after menopause, places women at greatest risk of developing AD. Our lab and others have previously shown that the potent estrogen 17β-estradiol (E_2) enhances memory in young and aging female mice. However, the interactions among APOE genotype, sex, and E_2 are not well characterized. The goal of this study was to examine the effects of sex and APOE genotype on memory, and to test the extent to which E_2 mediates memory consolidation in a mouse model of AD. First, to examine effects of sex and APOE genotype on memory, 6 month-old gonadally-intact male and female mice expressing 5 familial AD mutations (5xFAD-Tg) and human APOE3 (E3FAD) or APOE4 (E4FAD) were trained on object recognition (OR) and object placement (OP) tasks to test object recognition and spatial memory formation. Next, to test the extent to which E_2 mediates memory consolidation in E3FAD and E4FAD females, ovariectomized female E3FAD and E4FAD mice were trained in the OR and OP tasks. Mice received an immediate post-training infusion of E_2 into the dorsal hippocampus and then memory was tested 4 or 24 hours later. Male E3FAD mice exhibited intact OR and OP memory, whereas E3FAD females and E4FADs of either sex did not, suggesting preserved memory function in E3FAD males relative to females, and impaired memory in E4FAD mice of either sex. Additional data indicate that E_2 enhances OR and OP memory in E3FAD, but not E4FAD, females. These data suggest that APOE genotype and sex influence memory formation and/or the ability of E_2 to enhance memory consolidation in the EFAD mouse model. Future studies will characterize effects of APOE genotype, sex, and E_2 on hippocampal cell signaling and dendritic morphology.

Disclosures: L. Taxier: None. **S.M. Philippi:** None. **J.M. York:** None. **M. LaDu:** None. **K.M. Frick:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.09/QQ25

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Discovery Grant

Title: Time-dependent effects of bisphenol A and hop extracts exposure during adolescence on testosterone and corticosterone secretion in male Wistar rats

Authors: *A. MORIN[1], E. L. PERSON[1], L. VAN DE BEECK[1], H. PLAMONDON[2]
[1]Psychology, Univ. of Ottawa, Ottawa, ON, Canada; [2]Dept Psychol, Univ. Ottawa, Ottawa, ON, Canada

Abstract: Bisphenol A (BPA) is a widespread industrial compound found in many plastic containers, which is shown to act as an endocrine disruptor and promote anxiety. The current research aimed to investigate the effects of daily exposure to BPA (40mg/kg) during the juvenile/adolescent period on testosterone and corticosterone secretion measured at adulthood. In parallel, a second objective examined effects of dietary supplementation with hop extracts (HOP), shown to have antioxidant and anxiolytic effects, on hormonal output after a similar administration regimen. Also of interest were synergistic effects between the two compounds. Initially, the study included 41 male Wistar rats randomly separated into four groups: Control (Corn oil), BPA (Corn oil + BPA 40mg/kg), HOP (Corn oil + hop extracts 50mg/kg), and BPA-HOP (Corn oil + BPA 40mg/kg + hop extracts 50mg/kg). Rats were exposed by oral gavage for 20 consecutive days from PND28 to PND48. As part of this research, rats underwent behavioural testing to assess anxiety and depressive-like behaviour. Blood droplets were collected from the tail vein on PND28 (baseline), PND38, PND48, and PND71 (adulthood-endpoint of the study). Corticosterone and testosterone concentrations were measured using ELISA. Due to defects in the paper used to absorb the blood samples, the following groups were analyzed in the ELISA protocol: Control (n=10), BPA (n=9), HOP (n=10), and BPA+HOP (n=10). Although trends were present, our findings showed no significant differences in hormonal secretion between the groups, suggesting that juvenile exposure to BPA and hop extracts may not have enduring consequences on hormonal secretion during adolescence and adulthood in male rats.

Disclosures: E.L. Person: None. **L. Van de Beeck:** None. **H. Plamondon:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.10/QQ26

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Discovery Grant

Title: Effects of Bisphenol A and hop extract exposure during adolescence on anxiety- and depressive-like behaviors, memory, and social interaction in adult male rats

Authors: *E. L. PERSON[1], A. MORIN[1], L. VAN DE BEECK[1], H. PLAMONDON[2]
[1]Psychology, Univ. of Ottawa, Ottawa, ON, Canada; [2]Dept Psychol, Univ. Ottawa, Ottawa, ON, Canada

Abstract: In recent years, concerns have raised about the exposition to hormone disruptors compounds like Cisphenol A (BPA) because of their potential negative consequences on health. BPA acts as an endocrine disruptor by mimicking estrogens and have been involved in various health problems. On the other hand, hop extract, a constituent of beer, has long been used for its positive health effects, amongst which sedative and antioxidant actions. This study aims to examine the behavioral consequences of BPA and HOP exposition during the critical developmental period of adolescence on adult male rates. Wistar juvenile male rats (N = 41) were either orally administered a daily supplement of BPA (n = 10), HOP (n = 11), BPA and HOP (n = 10), or the vehicule only in the case of the control group (n = 10) each morning from post-natal day 28 (PND28) to post-natal day 48 (PND48). Animals were tested in the elevated plus maze (EPM), the social interaction and preference test (SIT and SP), the object recognition test, and the forced swim test (FST) and blood samples were collected through the experiment to measure the long-term effects of both supplements on testosterone and corticosterone circulatory levels. Adult rats exposed to hop extract spent significantly more time in the open arms of the EPM, less time in the closed arms of the EPM, and showed better long-term memory capabilities in the object recognition test than their peers in the BPA and BPA+HOP groups. These results support the anxiolytic properties of HOP while also suggesting the long-term negative effects of BPA exposure at a juvenile age.

Disclosures: E.L. Person: None. **A. Morin:** None. **L. Van de Beeck:** None. **H. Plamondon:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.11/RR1

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH R21 DA043072
State of Louisiana Board of Regents Graduate Fellowship LEQSF (2013-18)GF-17
Carol Lavin Bernick Faculty Grant

Title: Impact of gonadal hormone exposure on measures of sex differences in impulsivity in adult rats

Authors: *J. S. DARLING[1,2], L. DARTEZ[2], J. TAYLOR[2], A. MEHROTRA[2], W. SMITH[2], J. M. DANIEL[1,2,3]
[1]Neurosci. Program, Tulane Univ., New Orleans, LA; [2]Tulane Brain Inst., New Orleans, LA; [3]Tulane Psychology Dept., New Orleans, LA

Abstract: The goal of the current work was to examine the influence of gonadal hormones on adult sex differences on measures of impulsivity. Experiment One examined the influence of pubertal and adult gonadal hormones on sex differences in impulsive action and choice. Three sets of male and female rats were used in the study. The first set was gonadectomized prior to puberty (at 28 d of age), the second set was gonadectomized in adulthood (at 90 d of age), and the third set underwent sham surgeries and served as gonadally intact controls. Beginning at ~100 d of age, all rats were trained on the 5-choice serial-reaction time task (5-CSRTT), a test for impulsive action. The task requires rats to identify (via nose poke) the location of a brief light stimulus among five possible locations. When training was completed, impulsive action, as measured by premature responding, was assessed during sessions in which the onset of the stimulus was unpredictably lengthened. After testing on the 5-CSRTT was completed, rats were trained on a delayed-based reward task that measures impulsive choice, demonstrated as aversion to delayed reward. The task requires rats to choose between a delayed large food reward and an immediate small food reward. On the 5-CSRTT, adult males made significantly more impulsive (i.e. premature) responses across all hormone treatment conditions indicating that neither gonadal hormone actions during puberty nor during adulthood mediates the observed sex difference in impulsive action. On the delay-based reward task, no sex difference in impulsive choice was observed across all hormone treatment conditions. Experiment Two examined the influence of neonatal gonadal hormones on adult sex differences in impulsive action. Three groups of rats were used in the study. To serve as controls, one male group and one female group received subcutaneous injections of sesame oil vehicle on postnatal days 0 and 1. The third group, an experimental group of females, received 150 μg of testosterone propionate delivered subcutaneously in sesame oil vehicle on postnatal days 0 and 1. All three groups were gonadectomized prior to puberty (at 28 d of age). Under testing conditions, control males and females given neonatal testosterone, indistinguishable from one another, made significantly more impulsive action responses than did control females. Results indicate that 1) a sex difference in impulsive action observed in adult rats is due to organizing actions of testosterone during the neonatal period, and 2) no sex differences are apparent in adult rats in a delayed-based impulsive choice task.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.12/RR2

Topic: F.02. Behavioral Neuroendocrinology

Support: DA08259
HL098351

Title: Chronic immobilization stress primes the hippocampal opioid system for oxycodone associated learning in female but not male rats

Authors: B. REICH[1], Y. ZHOU[2], E. GOLDSTEIN[1], S. S. SRIVATS[1], N. H. CONTOREGGI[1], J. F. KOGAN[3], K. T. BEN[2], B. S. MCEWEN[3], M. J. KREEK[2], *T. A. MILNER[1], J. D. GRAY[3]
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Abstract: Our recent studies have shown that oxycodone conditioned place preference (CPP) induces sex-dependent changes in the redistribution of the hippocampal opioid receptors in a manner that promotes excitation and drug-related learning processes, particularly in females via increased disinhibition of inhibitory interneurons. We also found that chronic immobilization stress (CIS) "primes" the opioid system in adult female rats in a manner that would promote excitation and learning processes following subsequent exposure to either stress or an opioid ligand (McEwen and Milner, J. Neurosci. Res., 2017). The present study examined the effect of CIS on the opioid system in female and male Sprague Dawley rats following oxycodone CPP. Oxycodone-injected (Oxy) CIS females, but not Oxy-CIS males, acquire oxycodone CPP. By light microscopy, only Oxy-CIS females exhibited decreased Leu-enkephalin-immunoreactivity in the mossy fiber pathway in CA3 relative to saline-injected (Sal) CIS females. By electron microscopy, Sal-CIS females had fewer delta opioid receptor (DOR) silver-intensified gold (SIG) particles in the cytoplasm and in total in CA3b dendrites compared to Sal-CIS males, but there were no sex differences in DOR density following oxycodone CPP. Consistent with previous studies (Mazid et al., Neurobio. Stress, 2016), Sal-CIS females compared to Sal-CIS males had greater DOR-labeling within the dendritic spines of CA3b pyramidal cells, and this sex difference remained following oxycodone CPP. In the hilus of the dentate gyrus, Sal-CIS females compared to Sal-CIS males had greater total levels of DOR-SIG particles and mu opioid receptor (MOR)-SIG particles in GABAergic interneuron dendrites, and this sex difference is seen in Oxy-CIS females and males. Together, these results indicate that CIS primes the hippocampal opioid system in females for oxycodone-associated learning possibly by increasing DORs in mossy fiber-CA3 pyramidal cell synapses.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.13/RR3

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant R01AG041374

Title: The effects of continuous and previous estradiol exposure on nuclear and membrane estrogen receptor α in the hippocampus of aging ovariectomized rats

Authors: *N. E. BAUMGARTNER[1,2], M. E. SCHOENBERG[1,2], M. A. MODI[1,2], J. M. DANIEL[1,2,3]
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Abstract: Work from our lab has demonstrated that previous midlife estradiol treatment improves memory and results in lasting increases in levels of estrogen receptor (ER) α in the hippocampus of aging ovariectomized rats months after hormone exposure has ended. Traditionally, ERα acts as a nuclear transcription factor. However, membrane ERα can also result in non-genomic, rapid acting effects. In an initial experiment, we found that previous midlife estradiol exposure increases ERα specifically in the nuclear compartment of hippocampal cells. However, it is currently unknown how this increase in ERα following previous estradiol exposure compares to that of ongoing estradiol exposure. The goal of the current work is to compare the subcellular localization of ERα after previous and continuous estradiol exposure following ovariectomy. Middle-aged rats were ovariectomized and implanted with capsules containing either estradiol or vehicle. Forty days later, all capsules were replaced. Rats initially receiving vehicle capsules received another vehicle capsule (ovariectomized controls), and rats initially receiving estradiol capsules received either another estradiol capsule (continuous estradiol) or a vehicle capsule (previous estradiol). One month later, hippocampi were dissected and processed for subcellular fractionation. Hippocampal lysate was separated into cytosolic, membrane, and nuclear compartments using a commercially available kit. All compartments were processed for western blotting for ERα. Results indicate that both continuous and previous estradiol treatment significantly increase nuclear levels of classic 66 kDa ERα, but do not alter cytosolic or membrane levels. Additionally, we found that continuous, but not previous estradiol treatment, resulted in increased levels of a novel 52 kDa membrane-bound ERα. These data suggest that the increase in ERα following ongoing and previous estradiol may result in transcriptional changes that impact hippocampal function, and that continuous estradiol

treatment might also result in changes in the non-genomic actions of ERα through a novel membrane-bound receptor.

Disclosures: N.E. Baumgartner: None. **M.E. Schoenberg:** None. **M.A. Modi:** None. **J.M. Daniel:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.14/RR4

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC

Title: Determining which estrogen receptor rapidly interacts with oxytocin to mediate social recognition

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Abstract: Estrogens are gonadal hormones that have been found to have a variety of functions throughout the body, including effecting cognitive abilities like learning and memory. One cognitive function that estrogens have been found to affect is social recognition, the ability to distinguish between conspecifics. Previous studies have shown that knocking out the estrogen receptors impairs social recognition, while the administration of 17β-estradiol (E2) or estrogen receptor agonists were able to rapidly facilitate social recognition. Oxytocin is also necessary for social recognition, in the medial amygdala as shown by gene knockout and receptor antagonist studies. These studies as well as the high expression of estrogen receptors in the regions where oxytocin is produced, specifically the paraventricular nucleus (PVN) and supraoptic nucleus of the hypothalamus, led to the idea that estrogens and oxytocin may interact to rapidly mediate social recognition. We tested this by first infusing E2 into the PVN and using a rapid social recognition paradigm where two stimulus mice are presented to ovariectomized experimental mice in two habituation phases followed by a test phase where one of the stimulus mice is replaced with a novel stimulus mouse. We found that E2 in the PVN was able to facilitate social recognition within 40 minutes of administration. We then tested whether this effect occurs through an interaction with oxytocin by administering a subeffective dose of an oxytocin receptor antagonist into the medial amygdala while also administering E2 into the PVN. We found that the oxytocin receptor antagonist blocked the facilitative effect of E2 on social recognition. These results show support for the idea that the rapid effects of estrogens and oxytocin do interact to facilitate social recognition. However, it is not currently known which estrogen receptor is mediating this interaction with oxytocin. Both estrogen receptor β (ERβ) and

the G-protein coupled estrogen receptor (GPER) are highly expressed in the PVN and either one or both receptors could be involved. This is being tested by administering either the ERβ agonist DPN or the GPER agonist G1 into the PVN to determine if they can facilitate social recognition by using the social recognition paradigm that has been described above. This is the first demonstration of the estrogen-oxytocin interplay in regions of the social brain in the mediation of social recognition. Funded by NSERC.

Disclosures: P. Paletta: None. **A.C. Collins:** None. **E. Choleris:** None.

Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.15/RR5

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
NIH Diversity Supplement 3R01AG028084-09S1
ADHS and the Arizona Alzheimer's Disease Center
State of Arizona

Title: Progestogens impact cognition during the transition to menopause: Dissociation of progestogen- and memory- type

Authors: *V. L. PENA[1,2], S. V. KOEBELE[1,2], S. NORTHUP-SMITH[1,2], V. E. WONER[1,2], R. MELIKIAN[1,2], S. PATEL[1,2], H. L. BULEN[1,2], D. LADWIG[1,2], C. A. DYER[3], L. P. MAYER[3], H. A. BIMONTE-NELSON[1,2]
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Abstract: Progestogens, such as progesterone, medroxyprogesterone acetate (MPA), and micronized progesterone (mP4), are given to ovary-intact women during the transition to menopause to attenuate heavy uterine bleeding and other symptoms. Both progesterone and MPA administration have been shown to impair cognition in ovariectomized (Ovx) rats compared to vehicle-treated controls. mP4, however, has yet to be investigated for cognitive effects in a preclinical setting, despite widespread clinical use. Given that preclinical menopause-related progestogen investigations have been limited thus far to models of surgical menopause via Ovx, the goal of this experiment was to investigate the cognitive impact of the three clinically-used progestogens progesterone (P4), MPA, and mP4, in an ovary-intact transitional menopause model using 4-vinylcyclohexene diepoxide (VCD). One group of rats received vehicle injections, and the remainder of the groups received VCD to induce follicular depletion, modeling transitional menopause in women. Vehicle or hormone administration began during

perimenopause to model the time period when women often take progestogens alone. Rats then underwent testing to assess spatial working and reference memory in the water radial-arm maze (WRAM) and Morris water maze (MM). Results indicate that P4 and MPA improved learning for the working memory measure, but only MPA impaired delayed memory retention in the WRAM. mP4 showed no differences compared to vehicle controls for working memory. For the WRAM reference memory measure, rats that had undergone induced transitional menopause plus vehicle showed impaired learning and memory retention compared to vehicle controls with no induced transitional menopause; progestogens did not impact this impairment. No treatment differences were observed on the MM. Peripheral markers of hormone modulation and brain tissues are being analyzed. These findings indicate that while P4 and MPA have been previously shown to impair cognition in an Ovx model, giving these hormones early in an ovary-intact perimenopause model elicits divergent effects, such that these progestogens can improve cognition. Further investigation into progestogens is warranted to fully understand their impact on cognition and to detail parameters with variants of menopause type.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.16/RR6

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
State of Arizona
ADHS and the Arizona Alzheimer's Disease Core

Title: Behavior and brain: Uncovering relationships between 17-beta-estradiol dose, spatial memory performance, and protein expression in the brain of middle-aged ovariectomized rats

Authors: *A. V. PRAKAPENKA[1], R. NEELEY[1,3], C. BERNS-LEONE[1,3], S. NORTHUP-SMITH[1,3], V. L. PEÑA[1,3], A. A. GEORGE[4], R. MELIKIAN[1,3], S. PATEL[1,3], D. S. LADWIG[1,3], R. HIROI[1,3], A. L. MANN[2,3,5,1], M. J. VALENZUELA SANCHEZ[2,3,5,1], R. W. SIRIANNI[4,1], H. A. BIMONTE-NELSON[1,3]
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Abstract: The endogenous estrogen 17-beta-estradiol (E2) is involved in cognitive function, as evidenced in human work and in rodent studies. During the perimenopausal period and at menopause, there are alterations in E2 levels, with an eventual decrease in circulating E2 levels, along with other ovarian-derived hormones. E2-containing hormone therapy is commonly used to alleviate many physiological symptoms associated with menopause. Thus, it is critical to understand how E2 impacts not only cognitive performance, but also the putative underlying neuromechanisms involved in cognitive function. Studies indicate that E2 can increase the expression of insulin-like growth factor-1 receptor (IGF1-R) and activated extracellular regulated kinase (Erk) 2 in the dorsal hippocampus, and there is evidence that IGF1-R and activated Erk 2 are required for E2-induced cognitive effects. Here, we examined how two doses of E2 - 0.3 μg/rat for the low dose and 3.0 μg/rat for the high dose - impact IGF1-R expression and activated Erk 1/2 expression in the dorsal hippocampus, ventral CA1/2 hippocampus, perirhinal cortex, and entorhinal cortex in middle-aged, ovariectomized rats. All animals underwent testing on a behavioral battery evaluating spatial working and reference memory simultaneously (water radial-arm maze) and spatial reference memory alone (Morris water maze) prior to brain analyses, allowing us to evaluate how IGF1-R and activated Erk 1/2 expression relate to learning and memory performance. On the water radial arm maze, the low E2 dose improved spatial working memory performance compared to the vehicle and high E2 dose groups. Interestingly, a linear relationship was found between IGF1-R expression in the perirhinal cortex and E2 dose, whereby as E2 dose increased, IGF1-R expression increased linearly. Additional analyses are underway to determine how IGF1-R expression, and how activated Erk1 and Erk2 expression, in each of the brain regions analyzed relate to learning and memory performance. Determining how behavioral and brain outcomes change as a function of E2 dose, and how these measures relate to each other, is a crucial piece of the puzzle that will help elucidate the role E2 plays in cognitive function concurrent with other factors known to impact efficacy, such as variations in menopause status. A more complete understanding of how E2 impacts the brain, and how this relates to behavior, may lead to the design of hormone therapies that capitalize on E2-induced molecular changes in the brain to obtain optimized cognitive outcomes.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.17/RR7

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
State of Arizona
ADHS and the Arizona Alzheimer's Disease Core
NIH Grant 1F31AG056110-01A1

Title: Hysterectomy with ovarian conservation uniquely impacts cognition and serum hormone profiles in a rat model

Authors: *S. V. KOEBELE[1,3], J. M. PALMER[1,3], B. HADDER[1,3], R. MELIKIAN[1,3], C. FOX[1,3], I. M. STROUSE[1,3], D. DENARDO[2], C. GEORGE[4], E. DAUNIS[4], H. A. BIMONTE-NELSON[1]
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Abstract: Hysterectomy (surgical removal of the uterus) is the most common gynecological surgery following only cesarean section (CDC, 2010; Carlson et al., 1993). The majority of hysterectomies are performed in women prior to age 51 (Wright et al., 2013), which is the average age for natural menopause onset, and prior observations suggest that surgical removal of the ovaries before natural menopause onset may be detrimental to cognition. Thus, ovaries are preserved in about half of hysterectomy procedures. In the last decade, these findings have been extended, such that hysterectomy itself prior to natural menopause onset has also been implicated in an increased relative risk of developing dementia compared to women who did not undergo gynecological surgery (Rocca et al., 2007, 2012; Phung et al., 2010). The factors underlying cognitive and brain changes with variations in surgical menopause remain unclear and warrant further evaluation. Here, we examined spatial memory in a novel rat model of hysterectomy with ovarian conservation. Adult Fischer-344-CDF female rats underwent hysterectomy or sham surgery. Following surgery, subjects were tested on the water radial-arm maze, a spatial working and reference memory task. Results indicate that hysterectomy impaired spatial working memory performance when working memory load was taxed. Serum ovarian hormone profiles were altered in rats with hysterectomy compared to sham-operated rats, while histological analyses of the ovarian tissue suggested that surgical intervention did not alter ovarian morphology itself, at least at the time point assessed. This is the first systematic pre-clinical evaluation of the cognitive effects of hysterectomy. Relationships among cognition, hormonal changes, and ovarian morphology will be discussed. Overall, these data provide important insight into how hysterectomy may alter cognition during aging.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.18/RR8

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
State of Arizona
ADHS and the Arizona Alzheimer's Disease Center

Title: An evaluation of short-term and long-term ovarian hormone deprivation in the APP/PS1 mouse model of Alzheimer's disease

Authors: *V. E. WONER[1,3], J. M. PALMER[1,3], S. V. KOEBELE[1,3], I. M. STROUSE[1,3], M. N. WILLEMAN[1,3,4], V. L. PENA[1,3], W. WINSLOW[3,5], A. CACCAMO[3,5], S. ODDO[2,3,5], H. A. BIMONTE-NELSON[1,3]
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Abstract: With no known cure, Alzheimer’s disease (AD) is the most common form of dementia, affecting more than 5.7 million Americans. The aged population is not affected by AD equally; women are at a greater risk for developing AD than age-matched men. This disproportionate risk may be associated with changes in the female hormone profile that occur during reproductive senescence. Further, there is evidence that women who undergo surgical menopause (i.e. oophorectomy, or removal of the ovaries) before the onset of natural menopause are at a greater risk for dementia. We used a double transgenic AD mouse model (APP/PS1), with transgenic mice expressing APP and PS1 gene mutations resulting in beta-amyloid pathology development, to evaluate a short-term period (Study 1) and a long-term period (Study 2) of complete ovarian hormone deprivation. The long-term deprivation timepoint was based on prior work using a triple transgenic AD mouse model (Carroll et al., 2007).
At three months of age, wildtype (Wt) mice and APP/PS1 mice underwent either Sham surgery or Ovariectomy (Ovx) surgery, the surgical removal of the ovary in rodents. Study 1 consisted of a short-term cohort that was tested on a battery of behavioral tasks assessing spatial reference memory and spatial working memory one month following surgery and subsequent hormone deprivation. These tasks included the Morris water maze, the delayed match-to-sample (DMS) water maze, and the visible platform control task. Study 2 consisted of a long-term cohort tested three months following surgery and subsequent hormone deprivation on the same behavior battery. DMS results from Study 1 revealed that, in the learning phase of the task, genotype interacted with surgical menopause status, such that after a short-term deprivation, no genotype

effect was present after Sham surgery, while Ovx induced a genotype effect, with APP/PS1 mice showing poorer cognitive scores relative to their Wt counterparts. DMS results from Study 2 showed a similar pattern of effects, with a comparable interaction between genotype and surgical menopause status. However, this effect persisted across all testing days, suggesting a global, more persistent effect with a long-term ovarian hormone deprivation. These preliminary behavioral findings indicate that ovarian hormone deprivation exacerbates cognitive deficits in APP/PS1 mice. Additional behavioral and neuropathological analyses currently underway will allow us to determine relationships between temporal parameters of surgical menopause, cognitive status within varied domains, and AD-like pathology.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.19/RR9

Topic: F.02. Behavioral Neuroendocrinology

Title: Sex differences in olfaction and executive function among young adults

Authors: *A. A. WALF, D. Z. TAYLOR, A. KHAN, L. D. REID
Cognitive Sci. Dept, Rensselaer Polytechnic Inst., Troy, NY

Abstract: Emerging findings suggest the importance of olfactory function for mood/stress as well as cognitive functions among young adults as well as those from other clinical populations. For example, poor olfactory function may be an early symptom of cognitive disorders, such as Alzheimer's Disease (AD) or other diseases of neurodegeneration; brain injury is also a leading cause of loss of smell (Reid, Walf, & Avens, 2017). Considering the modern theory of AD, there are interacting setting conditions for accumulation of amyloid beta in the interstitial fluid of the brain, including poor fluid flow and immune/inflammatory responses. The brain-nasal cavity (B-NC) interface is a target here. Problems at the B-NC are usually manifest as hyposmia and anosmia. In this study, the hypotheses tested were that: 1) there would be associations between poor olfactory function (as measured by olfactory awareness scores) and executive function (including memory, problem and spatial processing), and mood/stress; 2) there would be sex differences in these tasks. Subjects were men and women, 18-24 years of age, with low and high scores on olfactory awareness/perception. Subjects were tested in a battery of tests to assess stress/mood, olfaction (e.g. discrimination, recent loss in), executive function (Mental Rotation Task, Trail-making Task, short-term and long-term verbal memory), and grip strength. There were no differences in olfactory awareness scores, or reported recent losses/difficulties with

olfaction, between men and women. Differences were noted in the Perceived Stress Score with the highest scores in the men with low olfactory awareness. In the Mental Rotation Task and Trail-making Task, men outperformed women, except those men with low olfactory awareness. In both the short-term and long-term verbal memory tests, women with low olfactory awareness had the lowest scores. As predicted, men had higher grip strength than women, especially when using their dominant hand. Together, this study confirms reported sex differences in executive function as well as expands on this literature to provide proof-of-concept about the relationship between olfactory function (measures of qualitative and quantitative sense of smell), mood, and cognitive function of human subjects. The olfactory system is both remarkably plastic and sensitive to damage. Our continued focus is how olfactory abilities may be related to mood, cognitive function, brain plasticity and the individual differences in these effects across the lifespan and how correcting deficits in these areas may restore brain health.

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Poster

314. Behavioral Neuroendocrinology: Hormones and Cognition I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 314.20/RR10

Topic: F.02. Behavioral Neuroendocrinology

Title: The effects of olfactory deficits on executive function among human subjects

Authors: *D. TAYLOR, A. KHAN, L. REID, A. A. WALF
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Abstract: Further elucidating a connection between olfaction and cognition has potential implications in maintaining neuronal health among both young and elderly individuals. The hypotheses tested were that olfaction and cognition are correlated and that resolving olfactory deficits may improve cognitive processing. Collaboration with a team of RPI computer scientists allowed for the construction of a testing platform and database to measure subjective and objective olfaction, working memory, attention processing, physical health, psychological profile, along with a number of demographic variables both in person and online. Human subjects have been tested, in the age demographic 18 to 24 to test these hypotheses and validate the novel approach to testing that has been designed. A connection between subjective olfaction and attention processing in the Trail-making Task and spatial processing in the Mental Rotation Task has been determined among young adult participants. Additionally, relationships have been found between subjective and objective olfactory measures in these study participants, validating the in person and online testing approach. Remaining questions being addressed are age differences for these effects and the role of long-term olfactory training. Physicians utilize lost olfaction as a predictor for Alzheimer's Disease; characteristic neural degeneration is initiated at

the olfactory portions of the brain, which may support the claim that amyloid beta (Aβ) contributes to an immune response against invading microbes entering the brain through the Brain-Nasal Cavity interface (B-NC). Aβ plaques may even be the product of aggregating invading pathogens. Investigations into the molecular targets for these effects are ongoing. Research has posited that Cerebrospinal Fluid (CSF), containing the destructive Aβ, clears out of the brain through the lymph vessels protruding from the cribriform plate in the B-NC. Correcting lost olfaction may restore health to this region, thereby, facilitating CSF flow and promoting neuronal health, which is the ultimate goal of this work.

Disclosures: D. Taylor: None. **A. Khan:** None. **L. Reid:** None. **A.A. Walf:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.01/RR11

Topic: F.04. Stress and the Brain

Support: CONACYT 238313
CONACyT 221092
PROMEP NPTC 236855

Title: Sex diferences in central activation of protooncogene c-fos after exposition to environmental noise

Authors: D. FERNANDEZ-QUEZADA[1], S. LUQUIN[2], A. GARCÍA-ZAMUDIO[1], J. GARCIA-ESTRADA[2], Y. RUVALCABA-DELGADILLO[2], *J. FERNANDO[2]
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Abstract: Noise is an inarticulate auditive stimulus that threats health in different ways. The Central Nervous System (CNS) is essential to respond and process auditive information. Processing of undesired sounds may involve a number of neural circuits outside the auditory system. Immediate early genes have been helpful to identify the central neural circuits that physiologically or behaviorally regulate the adaptation to environmental threats. Then, in this experiment, we analyzed the rat male and female brain to gain knowledge on how a noisy environment affects the expression of the immediate-early gene product c-Fos (marker of neural activation) in both sexes. Male and female wistar rats were exposed to a rats' audiogram-fitted adaptation of a noisy environment and sacrificed at 0, 2, 6 and12 hours for acute effect; and at 7, 14 and 21 days for chronic effect. Immunohistochemistry against c-Fos was performed on 70μm slices belonging to the male and female rat brains. We found differential patterns of c-Fos expression depending on sex, region, and time of exposure. Besides auditory cortex, we found

activity changes in regions that included the hypothalamus, prefrontal cortex, habenular complex, septum, cingulate cortex, nucleus accumbens, insular cortex, and hippocampus. We also found that female rats exhibited less intense c-Fos activation in most of the examined areas. Then, we demonstrated that environmental noise differentially activates brain structures outside the classic auditory circuits and that female rats are less sensible to the activity changes produced by environmental noise.

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Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

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Program #/Poster #: 315.02/RR12

Topic: F.04. Stress and the Brain

Support: Department of Atomic Energy, Government of India
Department of Biotechnology, Government of India
The Madan & Usha Sethi Fellowship

Title: Stress elicits contrasting effects on astrocytes not only in the hippocampus versus amygdala, but also between neurons and astrocytes within the amygdala

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Abstract: Stress causes divergent patterns of structural and physiological plasticity in the hippocampus versus amygdala (Chattarji et al., *Nature Neurosci.*, 2015). However, a majority of earlier studies focused primarily on neurons. Despite growing evidence for the importance of glia in health and disease, relatively little is known about how stress affects astrocytes. Hence, we examined the impact of chronic immobilization stress (2h/day, 10 days), on the number and structure of astrocytes in the rat hippocampus and amygdala. We observed a 14.5% reduction in the number of GFAP-positive astrocytes in the basal amygdala (BA) a day after the end of chronic stress (Control: 15997±594; Stress: 13669±465 cells/μm^3). Detailed morphometric analysis of individual dye-filled astrocytes also revealed a 21.9% decrease in the neuropil volume occupied by these astrocytes in the BA (Control: 41238±1715; Stress: 32175±1636 μm^3). By contrast, the same chronic stress had no effect on the number or morphology of astrocytes in hippocampal area CA3. Finally, we confirmed previous reports that chronic stress triggered dendritic growth in BA principal neurons. BA neurons exhibiting dendritic hypertrophy

(Total dendritic length: Control: 1871±97; Stress: 2286±101 µm) were located adjacent to astrocytes that had undergone atrophy, thereby providing striking examples of the opposite effects of the same stress on neurons versus astrocytes. Together, these findings offer new evidence that the morphological effects of stress not only vary with brain regions, but can also cause markedly different effects on neurons versus astrocytes within the same brain area.

Disclosures: S. Naskar: None. **S. Chattarji:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.03/RR13

Topic: F.04. Stress and the Brain

Title: Identification of molecular mechanisms of stress-induced changes in human emotion processing

Authors: M. MEIJER[1], A. KEO[1], J. M. C. VAN LEEUWEN[2], O. C. MEIJER[1], C. H. VINKERS[2], *A. MAHFOUZ[1]
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Abstract: Stress is a major risk factor for the development of almost all psychiatric disorders. One of the processes interfered by stress and often deregulated in psychiatric disorders is emotion processing. In this work, we aim to identify the molecular mechanisms underlying emotion processing during acute stress response. Previously, we reported that high-risk individuals (siblings of schizophrenia patients) did not show default mode network suppression when performing an emotion picture task following a stressful condition, in contrast to healthy individuals. We mapped these differentially regulated brain regions (region of interest) identified using fMRI to gene expression data from the Allen Human Brain Atlas (AHBA). We identified 63 genes with significantly different expression levels between the region of interest and the rest of the cerebrum (two-tailed t-test, FDR-corrected $p < 0.05$, $\log_2$(Fold-Change) > 1) in at least 5 out of the 6 donors in the AHBA. These genes are enriched for known schizophrenia risk-loci (Fisher's exact test, $p = 0.0059$), including *KCNV1*, *DOC2A*, *NGEF*, *NRGN* and *MEF2C*. Moreover, these genes included *CAMK2A*, *DLX1*, *CCK* and its cognate receptor *CCKRB*, *VIP* and *NEUROD6*, which are known to influence behavior and stress response. Previously, we found *NEUROD6* to have specificity for the mineralocorticoid receptor over the glucocorticoid receptor. Together, these results suggest that higher expression of schizophrenia-associated genes is associated with changes in the adaptive brain response to stress in siblings of schizophrenia patients.

Disclosures: M. Meijer: None. **A. Keo:** None. **J.M.C. van Leeuwen:** None. **O.C. Meijer:** None. **C.H. Vinkers:** None. **A. Mahfouz:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.04/RR14

Topic: F.04. Stress and the Brain

Support: Divisional and BCHP Network Institutional Research Grant

Title: Impaired epinephrine responses to acute insulin-induced hypoglycemia in germ free mice

Authors: *B. B. NANKOVA[1], P. GIRI[2], F. HU[3], E. F. LA GAMMA[4]
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Abstract: Prematurely born infants are at increased risk of developing neurodevelopmental impairments. The ability to survive postnatal stressors such as hypoglycemia, hypoxia, and hypothermia correlates with the ability to respond by releasing catecholamines. The maturation of the stress response system occurs in the early postnatal period, in parallel with initial gut colonization and microbiota-gut-brain axis development. Whether gut microbes and their metabolites influence the adrenal component of the sympathetic nervous system is not known. Here we tested the hypothesis that germ free (GF) mice (lacking microbiome) will have altered sympatho-adrenal responses to metabolic stress. We show that GF mice have significantly lower basal levels of urinary epinephrine compared to control (normally colonized) mice. Further, they displayed attenuated epinephrine response to acute insulin-induced hypoglycemia, while corticosterone (HPA axis) and glucagon (parasympathetic signaling) release was similar to the observed rise in counter-regulatory hormones of controls. 60' after insulin injection adrenal TH mRNA levels were increased only in the control group (qRT-PCR). Both control and GF groups displayed significant rise in TH mRNA levels with longer exposure to stress. The trans-synaptic regulation of NPY gene followed the pattern described for TH. In addition, a 2-fold increase in c-fos immunoreactivity (marker of neuronal activation) was observed in both, C and GF animals following insulin injection although baseline adrenal c-fos levels were significantly lower (immunofluorescense) in GF mice. Using a genome-wide transcriptome profiling approach we found that under both, basal and stress conditions GF mice display markedly altered adrenal gene expression profiles and process networks including neuropeptide, insulin and leptin signaling pathways. Thus, imbalances of the sympatho-adrenal system caused by the lack of a microbiome (or dysbiosis) during development could contribute to the adverse outcomes in preterm neonates.

Controlled manipulation of the intestinal microflora may provide a new therapeutic approach to improve their adaptation to common stressors, survival and overall health. In addition, our approach evaluating the gut-microbiota-brain-interface at a *single* synapse (the excitatory preganglionic-adrenal chromaffin cell synapse, the final step in the multi-neuronal signaling pathways that results in release of epinephrine) provides an easily accessible model of the more complex CNS dopaminergic pathways.

Disclosures: B.B. Nankova: None. **P. Giri:** None. **F. Hu:** None. **E.F. La Gamma:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.05/SS1

Topic: F.04. Stress and the Brain

Support: NIH Grant P50 MH096889
NIH Grant MH73136

Title: Aberrant CRH expression in the nucleus accumbens of adolescent mice after early-life adversity: A mechanism of anhedonia?

Authors: *Y. CHEN[1], C. A. ITOGA[2], A. K. SHORT[2], J. L. BOLTON[2], X. XU[2], T. Z. BARAM[3]
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Abstract: Premise: Anhedonia, the reduced ability to experience pleasure, is an important early sign of several mental illnesses including depression and schizophrenia. However, the processes provoking anhedonia are not fully understood. Early-life adversity is a known antecedent and risk factor for mental illness, and we have recently reported that early-life adversity, and specifically rearing in cages with fragmented unpredictable maternal care (FRAG) leads to anhedonia (Bolton et al., 2018). Here we probed the mechanisms by which FRAG leads to anhedonia, testing the hypothesis that they involve aberrant development of the pleasure-reward brain circuitry. We focused on corticotropin-releasing hormone (CRH)-expressing pathways to the nucleus accumbens (NAc), an established region in the reward circuitry underlying fundamental processes of pleasure, reward and happiness. CRH influences dopamine release in NAc, and is often upregulated by adversity (e.g., Lemos et al., 2012; Dubé et al. 2015). Thus, alteration of CRH-mediated neurotransmission within NAc by early-life adversity is a logical candidate mechanism for maladaptive plasticity of the reward circuitry resulting from this insult. **Methods**: CRH-expressing cells and fibers were assessed in the NAc using stereological principles, and their origin examined using both traditional and viral-tracing methods.

Results: CRH-expressing axon terminals were augmented in the middle and posterior regions of the NAc shell in mice exposed to early-life adversity compared with controls. Viral tracing methods identified a novel monosynaptic, CRH-expressing amygdala-NAc pathway originating in the basolateral amygdala (BLA). Studies are ongoing to test if this NAc-directed BLA-origin CRH expressing pathway is augmented after early-life adversity.
Conclusions: These data suggest that increased innervation and activation of NAc cells by CRH inputs may underlie early-life adversity-induced anhedonia, with major implications for the developmental origins of mental illness.

Disclosures: Y. Chen: None. **C.A. Itoga:** None. **A.K. Short:** None. **J.L. Bolton:** None. **X. Xu:** None. **T.Z. Baram:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.06/SS2

Topic: F.04. Stress and the Brain

Support: Defense Threat Reduction Agency

Title: Molecular alterations induced by yersinia pestis, dengue virus, and staphylococcus enterotoxin b under the background of battlefield-like stress

Authors: *S. MUHIE[1], R. CAMPBELL[2], A. GAUTAM[3], R. HAMMAMIEH[3], C. CUMMINGS[4], D. YANG[5], M. JETT[6]
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Abstract: Severe stress can have drastic and systemic effects with dire implications on the health and wellbeing of exposed individuals. Particularly, the effect of stress on the immune response to infection is of interest because of its implications for vaccine efficacy and treatment strategy during stressful scenarios. Battlefield-like stress has previously been shown to cause an anergic state in the immune system that persists following exposure to a potent mitogenic toxin. In this study, genome-wide alterations of gene expression were characterized using leukocytes collected from (15 consented, all male) U.S. Army Ranger cadets immediately before and after training followed by exposure to a representative group of pathogens (bacterial: *Yersinia pestis*; viral: dengue virus; toxin: *Staphylococcus* enterotoxin B). Here, we observed predicted inhibition of pathways significantly associated with lymphopoiesis, wound healing, inflammatory response, lymphocyte activation, anti-apoptosis, and predicted activation of cellular response to oxidative

stress. Using weighted correlation network analyses, we showed that these pathways were preserved across the different infection plus stress combinations. And yet, we have not found significant variation in the complete and differential counts of leukocyte-subpopulations between the pre- and post-stress cohorts. In addition, we identified regulatory (and modular) networks comprising a common set of upstream regulators (transcription factors: GATA2, YY1, FOXM1, CEBPB, EPAS1, HMGB1, NFATC1, RUNX3, MEN1, CIITA, NFKB1, RELA, IRF1, IRF7, STAT1; and micro RNAs: miR-124-3p, miR-183-5p, miR-153-3p, miR-135A-5p, miR-211-5p). Inhibition or activation of these upstream regulators may be leading to suppression of protective immunity (antigen presentation, T-cell activation and immune effector processes), accounting for the suboptimal responses of severely-stressed people to vaccines. Given that there were no significant difference in cell counts, inhibited lymphopoiesis may also be partly responsible for compromised immunity and for further cellular anergy towards mitogens requiring presence of naïve lymphocytes (T-cells).
Human subjects protection and disclaimer:
Research was conducted in compliance with IRB-approved human-subjects protocols. The views, opinions, and/or findings contained in this report are those of the author(s).

Disclosures: R. Campbell: None. **A. Gautam:** None. **R. Hammamieh:** None. **C. Cummings:** None. **D. Yang:** None. **M. Jett:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.07/SS3

Topic: F.04. Stress and the Brain

Support: NIH Grant R01DA020129
NIH Grant R01DA009082

Title: Sex differences in amyloid-beta monomer distribution and neuronal injury in the coeruleo-cortical circuit of mice conditionally overexpressing corticotropin releasing factor in the forebrain

Authors: *J. A. ROSS[1], B. A. S. REYES[1], V. B. RISBROUGH[2], E. J. VAN BOCKSTAELE[1]
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Abstract: Accumulating evidence from preclinical and clinical studies point to the Locus Coeruleus (LC)-Norepinephrine (NE) system as an understudied area of research in the context of Alzheimer's Disease (AD). Stress is a risk factor for developing AD. Amplification of the stress system disrupts cellular and molecular processes at the synapse, promoting the production

and accumulation of the amyloid beta (Aβ) peptide. Stress-induced activation of the LC is mediated by corticotropin releasing factor (CRF) and CRF receptors exhibit sex-biased stress signaling. In the present study, we examined the cellular substrates for interactions between Aβ and tyrosine hydroxylase (TH), a marker of noradrenergic somatodendritic processes in the LC, and dopamine-β-hydroxylase (DβH), a marker of noradrenergic axon terminals in the infralimbic medial prefrontal cortex (ILmPFC) of mice conditionally overexpressing CRF in the forebrain (CRF OE) under a Doxycycline (DOX) regulated tetO promoter. Using high resolution immunoelectron microscopy, semi-quantitative analysis revealed that 41.3% (214/518) of TH-immunoreactive (ir) somatodendritic processes also exhibited Aβ-immunogold silver particles in DOX treated males, compared to 27.62% (137/496) in male transgenic littermate untreated controls and 54.7% (267/488) TH-ir somatodendritic processes also exhibited Aβ-immunogold silver particles in DOX treated females compared to 36.67% (95/259) in female transgenic littermate vehicle-treated controls. Results showed significant increases ($p<0.05$) in Aβ in TH-ir somatodendritic processes of the LC in females, and a trend towards an increase in males. Interestingly, early signs of neuronal injury, including the presence of lipofuscin and abnormal morphology of Aβ-ir lysosomal compartments were observed in female DOX treated mice. While preliminary western blot analysis revealed no significant differences in the expression of APP-α, BACE-1, or TH expression in the LC, there is a trend towards significance in APP-β ($p=0.053$), indicating differences between male and female treated DOX groups. Additionally, female DOX treated mice exhibited enlarged microvessels that were Aβ-ir, and with lipid laden vacuoles. In DOX treated females, 14.19% (88/599) of the DβH-ir axon terminals exhibited Aβ-ir compared to 6.21% (39/628) in vehicle-treated female transgenic littermates, indicating a significant ($p<0.05$) increase in frequency of localization of Aβ to NE axon terminals. These data indicate potentially important sex differences in Aβ peptide accumulation and neuronal injury in the coeruleo-cortical circuit in a model of chronic stress signaling.

Disclosures: J.A. Ross: None. **B.A.S. Reyes:** None. **V.B. Risbrough:** None. **E.J. Van Bockstaele:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.08/SS4

Topic: F.04. Stress and the Brain

Title: Examining genetic differences in binge drinking at baseline and in response to stress

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Abstract: Binge drinking exerts a tremendous toll on American society through its numerous direct and indirect effects, including the promotion of increased risk-taking behaviors, aggression, sexual violence, poor academic performance, liver damage, and the development of psychological disorders, such as major depression. Two of the many factors that influence binge drinking are gender and stress. Although stress is typically considered to increase alcohol consumption, there is evidence to suggest that the relationship between stress and alcohol intake is complex and may be moderated by sex. For example, previous research has found that stress is positively associated with binge drinking in male college students but negatively associated with binge drinking in female college students. However, whether this clinically observed sex difference results from sexually dimorphic neurobiological responses to stress (or alcohol) in males vs. females or from societal or other factors has not been established. The current work sought to evaluate whether c57BL6/J mice exhibit sex differences in stress-induced alterations in binge drinking behavior. In addition to examining behavior, we also sought to provide new insight into the mechanisms through which stress might impact binge drinking in males and females. To do this, we used real-time PCR to examine stress and alcohol-induced alterations in gene expression in several brain regions that have been implicated in binge drinking. Given that the endorphin and glucocorticoid systems are both highly stress responsive and have been highly implicated in stress responses to alcohol, we compared the expression of several genes involved in endorphin and glucocorticoid signaling in male and female mice after chronic restraint stress and under control conditions. Although no significant sex differences in binge drinking were observed, stress was shown to significantly increase binge alcohol consumption and to lead to a significant upregulation of several genes in the amygdala, including corticotropin-releasing hormone and proopiomelanocortin. Overall, this study provides new insight into the effects of chronic stress on binge drinking and may help identify novel molecular targets to protect against or reverse stress-induced increases in alcohol consumption.

Disclosures: E. Dimitratos: None. **B. Sachs:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.09/SS5

Topic: F.04. Stress and the Brain

Support: Department of Atomic Energy, Government of India
Department of Biotechnology, Government of India
Madan and Usha Sethi fellowship

Title: Dendritic spine densities in hippocampus and amygdala reflect individual differences in aggressive and violent behavior in wild derived male rats

Authors: *S. ANILKUMAR[1,2,3], D. PATEL[4,1,3], B. BUWALDA[4], S. CHATTARJI[1,3,5]
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Abstract: Aggressive behaviors in many social organisms play a pivotal role in the defense of territory against intruders, as well as in acquiring social status and resources like food and mates. Further, individual differences in aggressive behaviors have been considered as important indicators of different coping strategies. Hence, the goal of the present study was to identify morphological correlates of aggressive and violent behaviors in the amygdala and hippocampus in Wildtype Groningen rats that exhibit a much richer repertoire of aggressive behaviors.
Four month old Wildtype Groningen rats were first characterized for their coping style measuring frequency and duration of offensive aggressive behavior in the resident-intruder paradigm wherein in one group, they were confronted on 4 subsequent days with male intruder rats and more than 20 times in another sub group, which exhibit extremely violent behavior and are unable to control their aggression and attacked even the anesthetized intruders. Next we carried out morphological analyses of dendritic spine-density on principal neurons of the basolateral amygdala (BLA) and hippocampal area CA1. This revealed no difference between aggressive and non-aggressive rats. However, stellate neurons in the medial nucleus of the amygdala (MeA) exhibited a significant decrease in spine-density in highly aggressive rats compared to non-aggressive rats. Notably, morphological analysis in the sub-group of pathologically violent rats revealed enhanced spine-density in the BLA, but the opposite effect in the CA1 area of hippocampus.
Together our results point to several distinct patterns of changes in spine-density that vary with brain regions, as well as the levels of aggressive behavior displayed by Wildtype Groningen rats. In rats that exhibited a normal range of aggression, we found no difference in spine-density between the BLA and area CA1, two brain areas that are known to undergo contrasting patterns of morphological plasticity in response to physical stressors. Strikingly, the same brain areas exhibited contrasting changes in spine-density only in those animals that displayed violently aggressive behaviors indicating the possibility that amygdalar and hippocampal neurons undergo structural plasticity which depends on the intensity of aggression of individual animals. Furthermore, ethologically natural behaviors in wild-derived rats, such as aggression towards intruders, elicit morphological plasticity in the amygdala and hippocampus that are distinct compared to those triggered by more traditional models of physical stress.

Disclosures: S. Anilkumar: None. **D. Patel:** None. **B. Buwalda:** None. **S. Chattarji:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.10/SS6

Topic: F.04. Stress and the Brain

Support: Department of Atomic Energy (DAE), Govt. Of India
Department of Biotechnology (DBT), Govt. Of India
Madan and Usha Sethi Fellowship
Central Imaging and Flow Facility, Bangalore Life Science Cluster

Title: Hippocampal and amygdalar cell-specific translation is similar soon after stress but diverge over time

Authors: *J. S. MADAN[1], K. GUPTA[1], S. CHATTARJI[1,2,3], A. BHATTACHARYA[2]
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Abstract: Stress is known to cause contrasting patterns of morphological and physiological plasticity in the hippocampus and amygdala. An obligatory cellular process underlying such neural changes is de novo translation and alterations in proteomic expression. Yet the nature of the translational response to stress in neurons remains largely unexplored. Even less is known about how glia are affected. Using a click-chemistry-based method to label the de novo proteome in live brain slices, we monitored translation in neurons and astrocytes of the basolateral amygdala (BLA) and dorsal hippocampal areas CA1(dCA1) and CA3 (dCA3) of male rats 1hour(1h), 24hours(1d) and 10 days(10d) after a single 2-hour exposure to immobilization stress. We observed large enhancements in neuronal translation in all the three brain regions BLA, dCA1 and dCA3 1h after stress. However, the neuronal translation profiles of the three brain regions follow different trajectories from this initial enhancement. The initial increase in neuronal translation persisted in the BLA 1d and even up to 10d afterwards. Surprisingly, the dCA1 neuronal translation was observed to be not different from control level 1d later but was again significantly higher 10d later. Further, even though the dCA3 neuronal translation stayed higher 1d later, it gradually decreased to below control levels 10d later. Similar to neuronal translation, astrocytic translation in the BLA and dCA3 only, but not in the dCA1, was also enhanced 1h after stress. However, the astrocytic translation in the dCA1 was enhanced 1d and 10d after stress. Further, the BLA astrocytic translation peaked 1d later and continued to remain higher even 10d later. Interestingly, translation profiles of dCA3 astrocytes followed timelines similar to that of the dCA3 neurons; the astrocytic translation continued to stay higher 1d later and decreased to below control levels 10d after stress.

Together our results demonstrate that a single episode of immobilization stress causes a general and immediate upregulation of protein synthesis in both amygdalar and hippocampal neurons and astrocytes. However, these profiles diverge and we observe cell specific and brain region specific temporal profiles of protein expression well after the end of stress. These findings identify new metrics of stress-induced plasticity at the level of cell-type specific proteomic landscape that may provide important insights into the molecular basis of the divergent temporal effects of stress across brain regions and biological scales.

Disclosures: J.S. Madan: None. **K. Gupta:** None. **S. Chattarji:** None. **A. Bhattacharya:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.11/SS7

Topic: F.04. Stress and the Brain

Support: KAKENHI Grant 15K18971

Title: Regulation of brain-specific splicing of Eef1d and activity control of its nuclear variant, eEF1BδL by stress-induced dephosphorylation

Authors: *T. KAITSUKA[1], M. MATSUSHITA[2]
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Abstract: Alternative splicing machinery enables a gene to generate more than one protein, which often have different molecular function. One of those, *Eef1d* gene produce canonical eukaryotic elongation factor 1Bδ (eEF1Bδ) and non-canonical long variant, named as eEF1BδL. Previously, we reported that the expression of this variant is restricted in brain and testis via alternative splicing and its protein functions as a transcription factor of heat-shock responsive genes. Tissue-specific splicing is regulated by some RNA-binding proteins, named as splicing factor, which bind to pre-mRNA and activate or repress the splicing of specific exon. In this study, to clarify the machinery of brain-specific expression of eEF1BδL, we investigated splicing factor to regulate splicing of *Eef1d* pre-mRNA. Furthermore, it was shown that the function of translated eEF1Bδ protein is regulated by phosphorylation. Therefore, we also examined whether its activity is affected by phosphorylation and dephosphorylation.
Neuro-2a and HEK293 cells were transfected with siRNA of several splicing factors, and then total RNA was extracted. The expression levels of short and long variants were measured by RT-PCR using primers, which were designed across specific exon to long variant. To measure the phosphorylation state of eEF1BδL, primary cortical neurons were treated with heat stress, and

then subjected to western blot analysis.
We found the consensus sequences around specific exon to long variant, which splicing factor Nova1/2 and Mbnl1/2 are expected to bind to. When each protein is inhibited by siRNA in Neuro-2a cells, the expression of eEF1BδL mRNA significantly decreased by Nova2 inhibition, while Mbnl1/2 inhibition did not affect on that expression. Consistently, overexpression of Nova2 significantly increased eEF1BδL mRNA in HEK293 cells. On the posttranslational regulation, we found that its protein was dephosphorylated under heat stress. Next, we constructed plasmids expressing eEF1BδL with mutation of putative phosphorylation site and examined their transcriptional activity. As a result, the expression of mutant that mimic dephosphorylated state significantly increased transcription of heat-shock responsive reporter compared to wild-type.
In conclusion, it is suggested that the splicing to produce eEF1BδL is regulated by Nova2. After translated, transcriptional activity of its protein is regulated by dephosphorylation under heat stress. It was reported that *EEF1D* gene is related to neurodevelopmental disorders, therefore, our study provides useful insight for understanding the role of eEF1BδL in neural development.

Disclosures: T. Kaitsuka: None. **M. Matsushita:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.12/SS8

Topic: F.04. Stress and the Brain

Support: Conacyt 243298
FAI 2017
CA-UASLP 254

Title: Sympathetic regulation of visceral adiposity and metabolism in a rat model of stress induced by sleep restriction

Authors: *L. E. AZUARA ALVAREZ, A. BÁEZ-RUIZ, O. RAMÍREZ-PLASCENCIA, S. CÁRDENAS-ROMERO, N. SADERI, R. SALGADO-DELGADO
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Abstract: The reduction of the hours dedicated to sleep is one of the most frequent causes of a stress response. Physiologically, stress is mediated by the Hypothalamus-Pituitary-Adrenal axis and the sympathetic nervous system. Prolonged stress, as it occurs of sleep insufficiency, increases plasma levels of corticosterone and catecholamine tone in the periphery. Metabolic homeostasis is particularly affected by stress and number of molecular and functional changes has been described in the adipose tissue (AT). In adipocytes, a mark of metabolic impairment

induced by stress is the increased activity of the 11β-Hydroxysteroid dehydrogenase type (11 β HSD1) enzyme, which catalyzes the local synthesis of glucocorticoids. In order to investigate the effect of sleep restriction-induced stress on both metabolic parameters and AT 11 β HSD1 levels/activity, we divided animal in 3 experimental groups: a group which was allowed to sleep for 6 hours (SR); a group that go through to sympathetic denervation of the AT (DX); a group that underwent to both sleep restriction and sympathetic denervation (SRDX), all of which were compared to control intact animals that slept *ad libitum* (CTL). The experimental protocol was carried out for 8 weeks, at the end of which animals were sacrificed. Body weight and food intake were monitored weekly. The glucose tolerance test (GTT) was performed on the eight week, before the sacrifice. Body temperature was registered by mean of a device placed intraperitoneally. During sacrifice, blood and AT samples were collected for the PCR analysis. Results showed that there were no changes in food intake among groups, but SR, DX and SRDX gained less weight; in particular, SRDX showed a significant decrease in AT mass. Denervation, but not sleep restriction, decreased the amplitude of body temperature daily fluctuations. Plasma adiponectin was augmented in SR, whereas leptin concentration was lower in SR and SRDX.These groups also showed glucose intolerance, although recovery was faster in denervated animals. Corticosterone levels were significantly higher in the SR group, whereas SRDX displayed intermediate levels between SR and CTL. In the AT, 11β HSD1 mRNA levels were upregulated in both DX and SRDX groups, while the enzymatic activity showed a significant increment only in DX animals. All these data demonstrate that indeed, sleep restriction induce a stress response and that affects metabolism. In addition we found that the sympathetic innervation has a protective role in the AT local glucocorticoids production

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Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.13/SS9

Topic: F.04. Stress and the Brain

Title: Multi-OMIC analyses of brain and serum from chronically stressed mice reveal network disruptions in purine metabolism, fatty acid beta-oxidation, and antioxidant function that can be ameliorated upon antidepressant treatment

Authors: P. J. HAMILTON[1], E. Y. CHEN[2], V. TOLSTIKOV[2], C. J. PENA[1], A. N. STRAT[1], P. SHAH[2], K. PANAGOPOULOS[2], D. M. WALKER[1], Z. S. LORSCH[1], S. GESTA[2], N. MERVOSH[1], D. KIRALY[1], R. SARANGARAJAN[2], N. R. NARAIN[2], M. A. KIEBISH[2], *E. J. NESTLER[3]

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Abstract: Major depressive disorder (MDD) is a multifaceted, heterogeneous disorder and a leading cause of disability worldwide. The molecular changes that occur in the brain and body of depressed individuals and the extent to which common antidepressants influence these mechanisms to improve symptomatology remain poorly understood. To explore this, we utilized an ethologically validated mouse model of MDD where mice underwent chronic social defeat stress (CSDS) to induce MDD-like symptoms. A portion of the stressed mice display MDD-like behaviors, termed 'susceptible', whereas the remainder do not display MDD-like behaviors, termed 'resilient'. To capture the spectrum of molecular changes that occur within the brain and periphery, we performed metabolomic, lipidomic, and proteomic profiling on serum and on prefrontal cortex (PFC), nucleus accumbens (NAc), and ventral hippocampus (vHipp) of susceptible, resilient, and undefeated control mice. In serum, proteomic analysis identified 17 proteins affected in stress-exposed mice and three proteins uniquely affected in susceptible animals; lipidomic analysis identified >1170 lipid species and detected changes in resilient versus susceptible animals; and metabolomic analysis identified >50 significantly affected metabolites, and implicated dysfunctions in purine metabolism, fatty acid beta oxidation, and antioxidant function in stressed animals. In brain metabolomic analysis, we observed these same molecular pathways being differentially affected in susceptible versus resilient animals by brain region. Interestingly, we observed the same metabolites regulated in both the vHipp and NAc. However, changes observed in vHipp occurred within susceptible animals whereas changes observed in NAc occurred in resilient animals, suggesting that metabolic function of these regions may differentially contribute to stress susceptibility. Considering these findings, we investigated how an antidepressant affects these mechanisms to alleviate MDD-related symptoms. We performed injections of saline or 10 mg/kg imipramine and observed that imipramine treatment reversed MDD-like behavioral deficits, and specifically altered the levels of metabolites in the purine metabolism and fatty acid beta oxidation pathway to undefeated control levels. This work elucidates how brain region- and tissue-specific alterations in proteins, lipids, and metabolites are altered in a mouse depression model and how the behavioral effects of antidepressants are associated with regulation of key metabolic pathways. This approach reveals promising molecules and pathways as targets for potential therapies for MDD.

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Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

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Program #/Poster #: 315.14/SS10

Topic: F.04. Stress and the Brain

Title: The dimorphic role of apontic in olfaction and ethanol sedation in *Drosophila*

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Abstract: Alcohol is a widely used drug that greatly affects the nervous system and animal behavior. In small quantities alcohol can cause hyperactivity while large quantities can have sedating effects. Numerous genes have been identified in *Drosophila melanogaster* that function in the sedating effect of ethanol including *apontic* (*apt*), a Myb/SANT-containing transcription factor. There is evidence suggesting that an animal's alcohol tolerance can alter its olfactory preference, although how this is accomplished molecularly is poorly understood. In order to better understand how *apt* functions within the nervous system to modulate an animal's response to ethanol a combination of olfactory and ethanol response assays were performed. Assays were performed on both males and females in order to identify potential sexual dimorphism in*apt* function. Both male and female *apt* mutants showed an increased resistance to ethanol vapor. Interestingly, even though *apt* mutants are more resistant to the sedating effects of ethanol it takes longer to recover from the sedated state, suggesting that these animals have a "hangover" like phenotype. In order to determine whether ethanol resistance because of *apt* can impart a change in olfactory preference, animals were presented with traps containing apple juice and apple juice supplemented with ethanol. At low concentrations ethanol enhances the attractiveness of the apple juice for wildtype flies, but at high concentrations ethanol becomes aversive, and flies will preferentially choose non-supplemented apple juice. *apt* mutants demonstrated a continued preference for apple juice supplemented with ethanol. Surprisingly, *apt* animals showed a decrease in response rate in olfactory assays with *apt* females (WT=86.0±0.0%, n=2, *apt*=4.9±2.2%, n=2) responding significantly less frequently than *apt* males (WT=88.7±4.7%, n=3; *apt*=42.0±9.0%, n=2). This suggests a novel role for *apt* in the development or function of the olfactory system. These results suggest that *apt*may function broadly within the nervous system during development as well as adulthood in order to generate wild-type ethanol behavior.

Disclosures: F.J. Vonhoff: None. **N. Reger:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

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Program #/Poster #: 315.15/SS11

Topic: F.04. Stress and the Brain

Support: Hope for Depression Research Foundation

Title: Sex-specific behavioral endocrinology of BDNF Val66Met mice maintained on chronic oral corticosterone

Authors: *J. MARROCCO[1], N. R. EINHORN[1], G. H. PETTY[1], C. LE FLOCH[1], I. N. KARATSOREOS[2], F. S. LEE[3], B. S. MCEWEN[1]
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Abstract: Sex and gender influence a variety of behaviors beyond reproduction, including the response to stress. Overexposure to stress induces chronically elevated cortisol/corticosterone (CORT) levels, leading to allostatic overload and sex-specific susceptibility to psychiatric disorders and metabolic dysfunctions. Little is known about the factors that may aggravate the effects of CORT overexposure, such as genetic variants and biological sex. Exogenous, chronic low-doses of CORT have been shown to blunt the endocrine response to stress, without disrupting the rhythmic levels of plasma CORT. Using a model of non-invasive chronic CORT treatment in mice, we investigated the metabolic and behavioral effects of oral CORT in heterozygous BDNF Val66Met (Het-Met) male and female mice, a model of genetic sensitivity to stress. Het-Met and wild type (WT) mice were treated with CORT (25mg/L) or vehicle in drinking water for 8 weeks. During treatment, a battery of behavioral tests was performed, body weights were recorded weekly, and blood was collected to measure glycaemia. We found that oral CORT did not affect body weight in either sex, but Het-Met females exhibited higher body weight than WT females independently of treatment. Fasting glycaemia was lower in CORT-treated males regardless of genotype, whereas Het-Met females showed reduced fasting glycaemia levels compared to WT females regardless of treatment. CORT-treated mice of either sex, but not Het-Met females, displayed lower adrenal gland mass than vehicle-treated mice. Consonant with that, CORT-treated mice of either sex, except Het-Met females, exhibited lower levels of glucocorticoid receptor (*Nr3c1*) in the ventral hippocampus. This suggested a lack of plasticity in females carrying the BDNF Met allele. Anxiety- and depressive-like behaviors, referred to as emotional behavior, were tested with the light-dark box and the splash test, respectively. When a z-normalization was applied across complementary measures of emotional behavior, we demonstrated that CORT significantly decreased z-score in Het-Met females but had an opposite effect in WT and Het-Met males. These findings indicate that the chronic oral

CORT model highlights sex-specific sensitivity to CORT overexposure that intersects the Met genotype.

Disclosures: J. Marrocco: None. **N.R. Einhorn:** None. **G.H. Petty:** None. **C. Le Floch:** None. **I.N. Karatsoreos:** None. **F.S. Lee:** None. **B.S. McEwen:** None.

Poster

315. Stress and the Brain: Cellular Actions

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 315.16/SS12

Topic: F.04. Stress and the Brain

Support: NIMH Grant MH002865
NIAAA Grant AA000301
Hope For Depression Research Foundation

Title: Cross-species epigenetic signature of stress-related psychiatric disorders

Authors: *N. R. EINHORN[1], H. LI[2], K. F. BERMAN[3], D. GOLDMAN[4], F. S. LEE[5], P. J. SCHMIDT[6], B. S. MCEWEN[1], J. MARROCCO[1]
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Abstract: Behavioral neuroscience has used animal models of environmental and genetic sensitivity to stress to investigate targets for the treatment of mental health disorders. This research identifies genes conserved across species that may also serve a greater biological purpose, such as adaptation to environmental challenges. Here, we emphasized genes that regulate gene expression independently of cell type using comparative whole-genome RNA-seq analysis, encompassing mouse models and human studies. To this end, we used mice subjected to acute stress and ovariectomized mice treated with estradiol that were wild type (WT) or heterozygous for the BDNF Val66Met single-nucleotide polymorphism (Het-Met), which alters the sensitivity to stress. Human data consisted of subjects diagnosed with a spectrum of psychiatric disorders. RNA-seq data of a homogenous population of CA3 pyramidal neurons or ventral hippocampus (vHPC) isolated from mice were compared to data of central or peripheral tissues obtained from humans. When comparing mouse brains and lymphoblastoid cell lines isolated from women with premenstrual dysphoric disorder or healthy controls, we found genotype (mouse)- and diagnosis (human)-specific overlaps of several epigenetic modifiers. These genes included the Extra Sex Comb/Enhancer of Zeste (ESC/E(Z)) complex, an effector of

response to ovarian steroids. In the CA3 pyramidal neurons of another subset of mice, acute stress affected the expression levels of signaling- and transcription-related genes that were also shared across major psychiatric disorders (i.e. bipolar disorder, major depressive disorder, alcoholism, autism spectrum disorder, and schizophrenia). Interestingly, a number of regulatory genes that overlapped across species and cell types showed a pre-stressed and a pre-estrogen effect in Het-Met mice, i.e. the same genes that were activated without stress or estradiol were also induced in WT mice by stress or estradiol treatment. These findings suggest that the BDNF Met allele induces an epigenetic signature that recapitulates that of subjects who are vulnerable for major psychiatric disorders. Animal models of stress-related disorders can help shed light on epigenetic markers conserved across species relevant for novel diagnostic and therapeutic interventions.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Topic: F.04. Stress and the Brain

Support: NIH Grant R21 MH106817 (MVB)
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Title: Control over stress engages a corticostriatal projection for the production of long-term stress resilience

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Abstract: Behavioral control over stress not only blunts the impact of the adverse event being controlled, but also blunts the impact of future adverse events, even those that are uncontrollable (termed “behavioral immunization”). The stress-buffering effects of behavioral control are enduring, trans-situational, and require the prelimbic region (PL) of the medial prefrontal cortex. It has been argued that the PL is critical to this process, in part, because it participates in a corticostriatal system that is sensitive to action-outcome contingencies that lead to what can be called an “expectation”. Here we investigated the role of the corticostriatal system in producing behavioral immunization. In EXP1, infusion of the NMDA antagonist, D-AP5 (30 mM), into

bilateral dorsal medial striatum (DMS) during the initial experience with control blocked the typical long-term protective effects of controllable stress. EXP2 and EXP3 addressed if the critical glutamatergic input to the DMS originates from the PL. DMS-projecting PL neurons were retrogradely labeled following deposit of fluorescent retrobeads in the DMS. Relative to yoked uncontrollable stress and home cage controls, controllable stress selectively increased Fos expression in retrobead-positive PL-to-DMS layer V neurons. Next we used a Cre-dependent, intersectional viral vector approach to express $G_{i/o}$-DREADDs selectively in PL afferents to DMS. Chemogenetic inhibition of this pathway also prevented the production of behavioral immunization. Lastly, EXP4 sought to determine if PL-to-DMS neurons, hypothesized to "DETECT" behavioral control, represents the same or separate population of PL cells hypothesized to "USE" control information to inhibit stress-responsive brainstem structures (PL-to-Dorsal Raphe Nucleus). Retrobeads tagged with different fluorescent markers labeled completely different but intermingled populations of PL layer V neurons following injection into DMS and DRN. In sum, the action-outcome corticostriatal circuit is critical for the production of behavioral immunization, but how control-related information transfers from the DETECT to USE systems remains unknown.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Program #/Poster #: 316.02/SS14

Topic: F.04. Stress and the Brain

Support: MH053851
MH072672

Title: Role of Akt in JAK2-mediated regulation of Arc expression in the orbitofrontal cortex-effects on reversal learning

Authors: *M. GIROTTI, J. D. SILVA, D. A. MORIALK
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Abstract: Cognitive flexibility is the ability to modify established behaviors or previous learning in response to a change in the environment. Reversal learning is a specific form of cognitive flexibility predominantly mediated by the orbitofrontal cortex (OFC). Our laboratory has shown that rats exposed to chronic intermittent cold stress (CIC, 6h per day at 4°C for 2 weeks), exhibit a selective and replicable cognitive deficit in reversal learning that resembles cognitive

components of stress-related psychiatric illnesses.
Using this model, we have found that basal activity of JAK2/STAT3 signaling in the OFC is required for optimal performance in reversal learning and that CIC stress reduces JAK2 activation in the OFC. Importantly, an acute injection of ciliary neurotrophic factor (CNTF), an endogenous activator of JAK/STAT, into the OFC increases JAK2 phosphorylation and corrects reversal-learning deficits produced by CIC stress. This phenomenon is observed also when CNTF is administered 24 h before testing, implying that activation of JAK2 results in long-term plastic changes in the OFC. Supporting this hypothesis, we have observed that silencing JAK2 reduces the expression of the synaptic plasticity protein Arc in primary neurons. In the present study, we set out to test the mechanism by which JAK2 regulates Arc, and its impact on reversal learning.
Interestingly, silencing STAT3, a major effector of JAK2 activation, in primary neurons did not impact Arc expression, suggesting the involvement of an alternate pathway. Indeed, within the OFC, we observed that low doses of CNTF did not increase activated STAT3 (pSTAT3) but did increase levels of pJAK2, pT-Akt and Arc, pointing to Akt as a potential intermediary. In support of this, we find that injecting a PI3 kinase inhibitor (LY294002, 4.3ng/0.5ul/side) into the OFC, 5 min before CNTF blocks Akt activation and prevents the increase in Arc levels produced by the neurotrophin.
In ongoing experiments we are testing the impact of LY294002 on reversal learning, predicting that inhibition of Akt will prevent the beneficial effects of CNTF on reversal learning in stress-compromised rats. In future experiments we will continue to test potential downstream effectors of Akt signaling involved in regulation of Arc expression. These studies will test the potential utility of targeting endogenous JAK2 signaling as a novel approach to treating cognitive impairment in stress-related psychiatric disorders.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

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Topic: F.04. Stress and the Brain

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CORFO INNOVA 14IDL2-30195

Title: The role of the insula in anxiety

Authors: *J. STEHBERG[1], S. LINSAMBARTH[2], F. PEÑA[2], P. MUÑOZ[3], T. BAHAMONDE[2], D. QUINTANA[2]

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Abstract: Abstract
The Insula has been associated to anxiety and anxiety-related disorders in humans, but a systemic study of its role on anxiety in rodents has not been performed to date. Here we present a series of studies using *in vivo* pharmacology and the elevated plus maze (EPM) in rats to determine the role of the insula in anxiety, to identify the regions within the insula that are relevant for anxiety and the cellular pathways by which stress hormones act on the insula to modulate stress responses and anxiety. We have found using AMPA antagonist CNQX intra-insular microinjections that different regions within the insula show differential involvement in anxiety. Pharmacological manipulation of the insula before EPM showed that anxiety is modulated by actions of noradrenaline and glucocorticoids at the insula, mediated by adrenergic, mineralocorticoid and membrane glucocorticoid receptors, and that noradrenaline inhibits slow spiking interneurons at the insula.

Disclosures: J. Stehberg: None. **S. Linsambarth:** None. **F. Peña:** None. **P. Muñoz:** None. **T. Bahamonde:** None. **D. Quintana:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

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Program #/Poster #: 316.04/TT2

Topic: F.04. Stress and the Brain

Title: Chronic stress causes circuit specific loss of inputs to the posterior parietal cortex

Authors: *G. LUR[1], Y. LIBOVNER[1], D. TABBA[1], M. HOLLEARN[2]
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Abstract: Severe loss of excitatory synapses in key brain regions is thought to be one of the major mechanisms behind stress induced cognitive impairment. To date however, the identity of the affected circuits is elusive. Here we examined the effect of chronic, multi-modal stress on the connectivity of the posterior parietal cortex (PPC). We found that stress lead to layer specific elimination of excitatory synapses with the most pronounced loss observed in layer 1 and 5. Fluorescent labeling of input pathways highlighted that these layers are targeted by sensory feed-forward and frontal top-down axons. Quantitative analysis of these projections revealed a significant loss of sensory and frontal inputs to the PPC while contralateral projections were unaffected. The PPC is considered to be a cortical hub for multisensory integration, working memory and perceptual decision making. Our data suggests that sensory and top-down

information streams targeting the PPC are severely impacted by chronic stress, likely contributing to stress induced cognitive impairment.

Disclosures: G. Lur: None. **Y. Libovner:** None. **D. Tabba:** None. **M. Hollearn:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Topic: F.04. Stress and the Brain

Support: UIUC start-up fund from the Department of Psychology to NCL

Title: Exercise-induced neuronal activation differs following acute and chronic exposure to wheel running

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Abstract: Acute exercise is a stressor that has immediate effects on energy metabolism whereas chronic exercise can become rewarding and produce multiple beneficial effects, including the maintenance of a healthy body weight and improvement of emotional and cognitive function. Human studies have found increased functional connectivity in the cortical network, which includes the insular (IC) and medial prefrontal cortex (mPFC), following chronic exercise. However, changes in neuronal activation following acute versus chronic exercise in this network have not been explored. We hypothesized that adaptation to exercise will alter patterns of neural activation in the IC and mPFC. To test this hypothesis, male Sprague-Dawley rats were exposed to acute (1 day) or chronic (18 days) wheel running (WR) after habituating to the running wheel cages with the wheel locked. The control rats remained sedentary (Sed) in standard cages throughout these periods. On the day of sacrifice, running activity was closely monitored starting 2 h before dark onset. WR rats were perfused ~1.5 h after a running burst (189 ± 41 revolutions). Brain sections of WR and Sed rats were processed for c-Fos immunohistochemical staining. c-Fos positive cells, which are indicative of neural activation, were quantified and analyzed in the mPFC and IC. Results showed that acute WR rats had significantly higher c-Fos immunoreactivity in both the mPFC and IC than their Sed controls whereas this was only true for the IC in chronic WR rats. Although the amount of running during the running burst did not differ, running induced greater neural activation in both the mPFC and IC in acute compared with chronic WR rats. Additionally, the amount of WR during the running burst was positively correlated with the number of c-Fos positive cells in the mPFC, but not IC, in chronic running rats. The result that neural activation in the mPFC and IC was lower after chronic relative to acute exercise implies that the chronic WR rats may have adapted to the stress of exercise.

Furthermore, the positive correlation between running activity and mPFC neuronal activation suggests that the mPFC, but not IC, may be responsible for mediating effects that are associated with the amount of exercise.

Disclosures: T.Y. Yang: None. **J.C. Gardner:** None. **N. Liang:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

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Program #/Poster #: 316.06/TT4

Topic: F.04. Stress and the Brain

Title: Dynamic change of resting-state functional connectivity associated with acute stress

Authors: *M. KITAWAKI[1], M. R. DELGADO[2], M. HARUNO[3]
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Abstract: The experience of acute stress can have significant consequences on human behavior and well-being. While the effects of stress are often discussed in the context of particular processes, such as decision making (e.g., Porcelli & Delgado, 2017), less is known about the influence of stress on neural circuits when an individual is at rest and not performing a task. A previous study proposed that the abnormal activity of resting state brain networks (RSNs) under stress may work as a neurobiological marker for stress-induced increases in emotionality (Soares et al., 2013). However, systematic understanding of the whole-brain RSN dynamics in association with acute stress experience is still lacking. Here, we investigated whole-brain RSNs dynamics before and after the Cold pressor test (Silverthorn et al., 2013) using high temporal and spatial resolution 3T fMRI (TR=1s, 2x2x2 mm voxel, 10 minutes). Region of interest (ROI)-to-ROI resting-state functional connectivity analysis was conducted using the Functional Connectivity toolbox on MATLAB (CONN). Participants (n=25) were required to undergo a baseline resting-state fMRI scan. They were then exposed to the Cold pressor test, involving immersion of one hand in ice water (3~4 degrees Celsius) for 2 minutes. Next, they were scanned for a second resting-state fMRI session. Salivatory cortisol was acquired from participants to assess stress levels at different times: before and after the baseline scan; after the Cold pressor test, after the second scan and 20 minutes post experimental session. We found that general functional connectivity during baseline (first) scan was diminished post stress as observed in second scan. We hypothesized that functional connectivity changed dynamically during the second scan. Therefore, we analyzed the first and second half of the second scan separately. Most importantly, the caudate nucleus was found to constitute a network hub in the first 5 minutes of the post-stress scan ($p < 0.05$, FDR correction). In contrast, functional connectivity in the second half was highlighted by enhanced connections between regions such

as the premotor cortex, primary somatosensory cortex and temporopolar area ($p < 0.05$, FDR correction). These results highlight the dynamic change of RSNs and caudate centered network structures under acute stress.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Title: Effects of adverse maternal care on prefrontal cortex, hippocampal, and amygdalar development in rhesus monkeys: Relationship with brain serotonin function

Authors: *A. RATLIFF[1,2], K. KUITCHOUA[2], B. KOCHOIAN[2], E. L. MORIN[1,2], B. R. HOWELL[1,2,3], Z. KOVACS-BALINT[2], M. STYNER[4], M. SANCHEZ[1,2]
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Abstract: Early life stress (ELS) is a major risk factor for numerous psychopathologies and social deficits. Adverse maternal care, including childhood maltreatment (abuse and neglect), is a devastating form of ELS and co-occurs with rapid brain development, leading to long-term effects on brain and behavioral development. How maternal maltreatment (MALT) affects neurobehavioral development is still not well understood. Additionally, it is difficult to isolate the effects of maltreatment from heritable factors in human studies. To circumvent these difficulties, we utilized a well-established cross-fostering design in a highly translational rhesus monkey model. Maternal care in rhesus macaques is similar to humans, and spontaneous maternal MALT occurs at rates comparable to human populations. Here we studied potential neurodevelopmental alterations underlying increased stress and emotional reactivity reported in MALT animals, focusing on the development of brain serotonin (5HT) and structural development of the amygdala, hippocampus and prefrontal cortex, all during the infant and

juvenile periods. We collected (1) structural MRI in 42 infant rhesus monkeys (20 Control (11 F, 9 M), 22 maltreated (MALT; 8 F, 14 M)) during infancy (2 wks, 3, 6 mo) and the juvenile period (12, 18 mo), and (2) cerebral spinal fluid (CSF) samples to measure central levels of 5HIAA, the main 5HT metabolite. Replicating previous reports in this model, MALT animals had lower CSF levels of 5HIAA than controls at 12 months of age ($t(29) = 1.71$, $p = 0.048$). In a subset of animals, (8 Control (5 F, 3 M), 7 MALT (3 F, 4 M)), we found group by age interactions in total brain volume ($F_{2,13} = 3.76$, $p = 0.04$, $\eta^2 = 0.22$), grey matter volume in the prefrontal cortex ($F_{2,13} = 5.45$, $p = 0.01$, $\eta^2 = 0.30$), and hippocampal volume ($F_{2,13} = 4.07$, $p = 0.03$, $\eta^2 = 0.24$), so that MALT animals showed blunted volumetric growth of total brain size, as well as region-specific volumes, emerging at the later ages. There was a negative correlation between maternal rejection rates during infancy and rate of growth in right hippocampus such that animals that experienced higher rates of rejection were at greatest risk for reduced hippocampal growth ($r=-0.638$, $p=0.035$). Studies in rodents suggest that early tactile stimulation is important for the development of 5HT in hippocampus, supporting that reduced levels could in turn play a role in its growth. We are currently exploring the possibility that reduced serotonin in the CSF is related to reduction in hippocampal volume. We plan to extend these studies to include the remaining subjects, additional regions of interest, and analysis of all time points collected.

Disclosures: A. Ratliff: None. **K. Kuitchoua:** None. **B. Kochoian:** None. **E.L. Morin:** None. **B.R. Howell:** None. **Z. Kovacs-Balint:** None. **M. Styner:** None. **M. Sanchez:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 316.08/TT6

Topic: F.04. Stress and the Brain

Support: NIH 1R21MH098203-01

Title: DTI-identified cerebral microstructural changes in mice overexpressing CRF in the forebrain

Authors: *J. DESLAURIERS[1,4], M. TOTH[1,4], M. SCADENG[2], R. RISSMAN[3], V. RISBROUGH[1,4], G. BROWN[1]
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Abstract: Background/hypothesis: Corticotropin releasing factor (CRF) regulates endocrine and behavioral responses to stress. Excess CRF signaling has been linked to alterations in cortical and hippocampal functions, spine formation and related cognitive functions. In humans, CRF levels are increased in the cerebrospinal fluid of individuals with childhood trauma history and

some mood and anxiety disorders. By using diffusion tensor imaging (DTI), a methodology translatable across species, we tested the hypothesis that forebrain-specific CRF overexpression induces changes in brain microstructure, specifically in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHP).
Methods: Male and female mice with inducible forebrain-specific CRF overexpression were generated by crossing two genetically modified mouse lines carrying a CaMKIIα promoter-driven rtTA2 transgene and a doxycycline-regulated tetO promoter fused to the CRF gene to produce double mutant mice. CRF overexpression was induced with doxycycline (DOX) administration in mouse chow at a dose of 3.5 mg/g body weight/day from postnatal day ~90 - 120, after which DOX was removed. DTI was performed at three time points in each animal: baseline (before DOX treatment), ~3 weeks of DOX treatment, and again ~3 months after DOX treatment was ended. Histology showed significant increases in CRF protein levels in the cortex and hippocampus 3 weeks after start of treatment, which returned to normal 3 months after treatment had ended. DTI parameters fractional anisotropy (FA) and mean diffusivity (MD) were assessed in the mPFC and dHP.
Results: In the mPFC, CRF-overexpression induced a decrease in FA in male and female mice only 3 weeks after start of DOX treatment. No effect of time, CRF-overexpression or sex was found on MD. In the dHP, no significant effect of CRF-overexpression or time was found on FA in both males and females. In male mice, MD increased with time in the dHP of control mice, with significant higher MD 3 months after the first scan, whereas no change in MD was found across time in mice overexpressing CRF. These effects were not observed in females.
Discussion: CRF-overexpression was associated with cortical microstructural changes in the mPFC and appeared, surprisingly, to block aging-related elevations in MD, suggesting some potential modulatory effects of CRF on hippocampal microstructure. Previous studies implicate CRF both as a potential protective factor and a driver of tau-pathology in aging-related neurodegeneration. Future studies are required to delineate the mechanisms underlying the region-specific effects of CRF-overexpression, as well as the aging-induced effects on MD.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 316.09/TT7

Topic: F.04. Stress and the Brain

Support: NIH Grant MH110907

Title: Inhibition of prefrontal monoacylglycerol lipase promotes stress resilience

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Abstract: Neural activity within the ventromedial prefrontal cortex (vmPFC) is a critical determinant of stressor-induced anxiety. Pharmacological activation of the vmPFC during stress protects against stress-induced social anxiety suggesting that altering the excitatory/inhibitory (E/I) tone in the vmPFC may promote stress resilience. E/I balance is maintained, in part, by endogenous cannabinoid (eCB) signaling with the calcium dependent retrograde release of 2-arachidonoylglycerol (2AG) suppressing presynaptic GABA release. We hypothesized that raising 2AG levels, via inhibition of its degradation enzyme monoacylglycerol lipase (MAGL) with KML29, would shift vmPFC E/I balance and promote resilience. In acute slice experiments, bath application of KML29 (100nM) augmented evoked excitatory neurotransmission as evinced by a left-shift in fEPSP I/O curve, reduced paired-pulse facilitation, and decreased sEPSC amplitude and frequency. In vmPFC whole-cell recordings, KML29 increased resting membrane potential but reduced the after depolarization, bursting rate, membrane time constant and slow after hyperpolarization. Systemic administration of KML29 (40mg/kg, i.p.) 2h prior to inescapable stress (IS) exposure (25, 5s tail shocks) exacerbated the reduction in juvenile social exploration observed after IS in male rats that received vehicle injections. Conversely, intra-vmPFC (200ng/0.5μL/hemisphere) administration blocked the reduction in juvenile social exploration typically observed after IS. Raising 2AG in the vmPFC may promote resilience by augmenting the output of neurons that project to the proximal neural mediators of the stress response. The results support the continued investigation of the eCB system in stress resilience and susceptibility.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 316.10/TT8

Topic: F.04. Stress and the Brain

Support: MH095972

Title: A prefrontal-bed nucleus circuit limits both HPA output and passive coping behaviors

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Abstract: The prelimbic subfield (PL) of the medial prefrontal cortex has received considerable attention for its role in directing behavioral, endocrine, and autonomic stress responses, yet the efferent pathways underlying these vital systems have yet to be elucidated. Our previous work has implicated the anteroventral subdivision of the bed nuclei of the stria terminalis (avBST) as a neural hub for the coordination of hypothalamo-pituitary-adrenal (HPA) and behavioral responses via divergent pathways to the paraventricular nucleus of the hypothalamus and ventrolateral periaqueductal gray area (vlPAG), respectively. These observations and those of tract tracing studies raise the prospect that avBST acts as a substrate for the prefrontal cortex to coordinate neuroendocrine and behavioral output and thus bias the organism toward certain response strategies. To assess this putative role, we employed an optogenetic approach to bidirectionally manipulate PL-avBST pathway activity while measuring HPA and behavioral responses during acute challenges. Photoinhibition of halorhodopsin(Halo)-expressing PL neuron axons in avBST during 10 min tail suspension augmented both immobility ($p<0.05$) and HPA output (adrenocorticotropin hormone 10 min, and corticosterone 30 min after stress onset; $p<0.05$), as compared with YFP controls. Photoexcitation of the pathway diminished passive immobility behavior ($p<0.05$) while HPA output was unaffected ($p>0.05$). Next, we examined the role of this circuit in the shock-probe defensive burying (SPDB) test which allows animals to engage in a broader range of behaviors, including both active (burying) and passive (immobility) coping responses. Animals receiving photoinhibition of the PL-avBST pathway spent more time immobile ($p<0.05$) and buried less than YFP controls ($p<0.05$). Photoexcitation of the pathway diminished freezing ($p<0.05$) but was insufficient to enhance burying behavior relative to YFP counterparts ($p>0.05$). Given recent evidence from our group implicating the avBST-vlPAG pathway in passive behavioral output, we next examined whether this pathway might act downstream of the PL-avBST pathway to modulate coping behavior. Here, animals receiving photoinhibition of the avBST-vlPAG pathway spent more time immobile ($p<0.05$) and buried less than YFP controls ($p<0.05$), recapitulating the effects of PL-avBST photoinhibition. Together, these studies point to a novel multisynaptic pathway mediating stress coping responses. Moreover, this work may point to a circuit mechanism linking withdrawal of top-down control with aberrant behavioral and endocrine responses in stress-related disorders.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 316.11/TT9

Topic: F.04. Stress and the Brain

Support: NIH Grant MH107007

Title: Enhanced activity of a vmPFC-DRN neural circuit in resistance to acute social defeat stress

Authors: *A. GRIZZELL[1], T. CLARITY[2], B. N. DULKA[2], M. A. COOPER[1]
[1]Dept. of Psychology, [2]Univ. of Tennessee, Knoxville, TN

Abstract: The ventromedial prefrontal cortex (vmPFC) plays a critical role in stress resilience through top-down inhibition of key limbic and hindbrain structures, including the dorsal raphe nucleus (DRN). Our laboratory developed a model of experience-dependent stress resistance in Syrian hamsters wherein following 14 days of dyadic encounters, dominant animals display less submissive/defensive behavior following an acute social defeat compared to their subordinate counterparts or social status controls. Subregions of the vmPFC are more active in dominant hamsters and pharmacological inhibition of the vmPFC prevents resistance to the effects of social defeat in dominants. While the DRN is a critical neural substrate regulating the effects of social defeat stress, it is unknown whether status-dependent differences in defeat-induced anxiety are associated with activity in a vmPFC-DRN circuit. In this project, we stereotaxically injected the retrograde tracer, Cholera Toxin B (CTB), into the DRN of dominant and subordinate hamsters as well as social status and non-stressed controls. After the formation of dominance relationships, animals were then exposed to an acute social defeat stress and euthanized 60 minutes afterward for a determination of defeat-induced neuronal activity via cFos protein expression. Preliminary immunohistochemical data demonstrate that dominant hamsters display more cFos and cFos + CTB labeled cells in both the infralimbic (IL) and prelimbic (PL) subregions of the vmPFC compared to subordinates and controls. These findings suggest that the reduced behavioral consequences of acute social defeat are associated with increased activity in a vmPFC-DRN pathway. Overall, social dominance may activate vmPFC neurons that are capable of inhibiting stress-induced DRN activity and thereby promote stress resistance.

Disclosures: A. Grizzell: None. **T. Clarity:** None. **B.N. Dulka:** None. **M.A. Cooper:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Program #/Poster #: 316.12/TT10

Topic: F.04. Stress and the Brain

Support: NIH Grant MH107007

Title: Neuroendocrine correlates of dominance relationships in female Syrian hamsters

Authors: A. L. LOEWEN, B. N. DULKA, J. A. GRIZZELL, A. V. CAMPBELL, *M. A. COOPER
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Abstract: Understanding the neuroendocrine mechanisms that support stress resilience is an early step toward developing more effective treatment options for patients who suffer from stress-related psychopathologies. Although social defeat models in male rodents are frequently used to investigate the cellular mechanisms of stress susceptibility and resilience, much less research has included female subjects. We have previously shown that male Syrian hamsters exhibit elevated social avoidance following acute social defeat stress. Interestingly, male hamsters with dominant social status exhibit elevated plasma testosterone, increased androgen receptor expression in the medial amygdala (MeA) and less defeat-induced social avoidance compared to subordinates and controls. The objective of this study was to investigate whether female hamsters show status-dependent differences in defeat-induced social avoidance and androgen and estrogen receptor expression in the MeA. Adult female hamsters were matched according to their estrous cycle and paired in 12 daily social encounters to establish dominance relationships. To avoid dyadic encounters when females were in estrous, we skipped encounters every four days. Immediately before the first dyadic encounter, 15 min after the first dyadic encounters, and 15 min after the 12^{th} dyadic encounter, blood was collected via retro-orbital eye bleed. After the final dominance encounter, animals experienced acute social defeat stress and 24 hours later received a social interaction test with a same-sex, unfamiliar, confined hamster. While acute social defeat stress produced social avoidance in the female hamsters, dominance status did not alter social avoidance, plasma testosterone, or androgen receptor expression in the MeA. We are currently testing whether dominance status alters the expression of estrogen-alpha and estrogen-beta receptors in the MeA. These findings suggest a sex-difference in the neuroendocrine mechanisms controlling the effects of social status on defeat-induced changes in behavior. This line of research improves our understanding of the neuroendocrine mechanisms regulating sex-differences in vulnerability to stress-related mental illness.

Disclosures: A.L. Loewen: None. **B.N. Dulka:** None. **J.A. Grizzell:** None. **A.V. Campbell:** None. **M.A. Cooper:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Program #/Poster #: 316.13/TT11

Topic: F.04. Stress and the Brain

Support: NIH Grant MH107007

Title: The link between dominance status and passive and active coping strategies

Authors: *M. CANNON, E. L. GRAHAM, M. D. BURZINSKI, M. A. COOPER
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Abstract: There are a great deal of individual differences in how humans and other animals cope with stress. Differences in coping abilities are linked to several environmental factors, including social dominance. The present study investigated whether coping strategies predict dominance status in male and female Syrian hamsters and whether the maintenance of dominance relationships alters subsequent coping strategies. We hypothesized that hamsters showing an active coping strategy would be more likely to achieve dominant social status compared to hamsters with a passive coping strategy. Also, we hypothesized that the maintenance of dominance relationships would increase active coping strategies in dominants and passive coping strategies in subordinates. Finally, we investigated whether changing dominance status would similarly change coping strategies. Male and female hamsters were weight-matched and paired with a same-sex partner in daily aggressive encounters for two weeks. Dyads quickly formed a dominance relationship that remained stable throughout the study. To assay coping strategies before and after the formation of dominance relationships, we tested animals in a series of behavioral tests, including open field, novel object exploration, elevated zero maze, light/dark transition, Porsolt forced swim, and social defeat tests. We found that dominance status has a greater effect on stress-induced anxiety-like and depression-like behavior in male hamsters compared to female hamsters. Because most preclinical neuroscience research is conducted exclusively in male animals, these data will extend our understanding of sex-differences in the expression of passive and active coping strategies. In addition, these data indicate that dominance status plays a role in the development of coping strategies and stress vulnerability.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Program #/Poster #: 316.14/TT12

Topic: F.04. Stress and the Brain

Support: NIH Grant MH107007

Title: Chemogenetic activation of an infralimbic cortex to basolateral amygdala neural projection and resistance to conditioned defeat

Authors: *B. N. DULKA, E. D. BAGETALAS, K. S. BRESS, M. A. COOPER
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Abstract: Stress is a contributing factor in the development of several mood and anxiety disorders, although there are significant individual differences in vulnerability. Animal models of social defeat are used to investigate the biological basis of stress susceptibility and resilience. Male Syrian hamsters are highly aggressive and territorial, but after an acute defeat experience they exhibit a conditioned defeat (CD) response which is characterized by increased submissive behavior and a failure to defend their home territory in a social interaction test with a smaller, non-aggressive intruder. Hamsters that achieve dominant social status show increased c-Fos expression in the infralimbic (IL) cortex following social defeat and display a reduced CD response at testing compared to subordinates and controls. Moreover, dominant hamsters show increased defeat-induced neural activity in IL neurons that send efferent projections to the basolateral amygdala (BLA) compared to subordinates and controls. In the current study, we aimed to determine if selective activation of these IL-to-BLA projections using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) is sufficient to induce CD resistance in subordinates. To answer this question, we used a dual virus approach and injected a Cre-dependent Gq DREADD virus into the IL and a retrograde Cre virus into the BLA. This dual virus approach was first validated through c-Fos analysis. Next, we performed a control experiment to ensure that clozapine-N-oxide (CNO), the drug that activates the DREADD vector, in itself has no effect on CD behavior. Finally, we tested whether CNO-treated subordinate hamsters show a reduced CD response compared to vehicle-treated subordinates. This project extends our understanding of the neural circuits underlying resistance to social stress, which is an important step towards delineating a circuit-based approach for the prevention and treatment of stress-related psychopathology.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Topic: F.04. Stress and the Brain

Support: NIH Grant R01MH111751
Postdoctoral Fellowship for Academic Diversity at Children's Hospital of Philadelphia

Title: Exploring the effects of locus coeruleus corticotropin-releasing factor on cortical network activity

Authors: *S. BATES[1], J. ARNER[2], A. L. CURTIS[3], S. BHATNAGAR[4]
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Abstract: The LC is part of a stress responsive system that is involved in arousal and cognitive function. This is accomplished through extensive projections to many regions, including the prefrontal cortex (PFC). The reciprocal connection between the LC and the PFC has been shown to underlie the role of arousal on cognition. Additionally, this circuit is disrupted following chronic stress, which is thought to underlie impairment in executive function that arises during stress. Evidence suggests that stress-induced alterations of LC activity are mediated through the release of corticotropin-releasing factor (CRF) in the LC. A previous study from our lab in male animals showed that intracoerulear infusion of 20ng of CRF impacted performance in the attentional set shifting task, which engages the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC). However, it is unknown how CRF release in the LC affects network activity of neurons in the OFC and in the mPFC to influence behavior. This study examined the effects of CRF administered into the LC of male and female rats on mPFC and OFC network activity, measured as local field potentials (LFPs). In awake, behaving animals, network activity was recorded in the mPFC and OFC for 30 minutes before and after intracoerulear infusion of aCSF or 20ng of CRF in male and female adult rats through a cannula. Following this, power spectral density (PSD) was calculated. Preliminary data (n=3/group) suggest that, following CRF infusion, there is increased activity in the beta frequency band in the OFC in both sexes, increased theta activity in the mPFC in females, and increased beta activity in mPFC in males as compared to their respective aCSF (control) groups. This is the first analysis of the effect of LC activation with CRF on network activity in these cortical areas and the preliminary results suggest a greater impact on cortical network activity following CRF actions in the LC of females compared to males. These data are consistent with sex differences in CRF receptor internalization. In ongoing studies, we are examining additional doses of CRF in both sexes and

determining if activating LC with CRF affects performance in the attentional set-shifting task in female rats, a paradigm that is dependent on cortical activity.

Disclosures: S. Bates: None. **J. Arner:** None. **A.L. Curtis:** None. **S. Bhatnagar:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Program #/Poster #: 316.16/TT14

Topic: F.04. Stress and the Brain

Support: NIH R01MH111751
Postdoctoral Fellowship for Academic Diversity at the Children's Hospital of Philadelphia

Title: Examining coherence between locus coeruleus and cortical network activity

Authors: *J. ARNER[1], S. BATES[2], A. L. CURTIS[3], S. BHATNAGAR[4]
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Abstract: The locus coeruleus (LC) is a major stress response system that is involved in arousal, vigilance and cognitive function. This is accomplished through extensive projections to several regions, including the prefrontal cortex (PFC). The reciprocal connection between the LC and the PFC underlies the role of arousal on cognition. Additionally, this circuit is disrupted following chronic stress, and this disruption is thought to underlie impairments in executive function that arise during stress. Interestingly, different activation levels of LC are associated with various cognitive states. More specifically, “phasic” LC activation underlies focused attention and task-oriented processes, while “tonic” LC activation underlies scanning attention and cognitive flexibility. While it is known that the LC-PFC circuit underlies these cognitive states, little is known about whether different levels of LC activity might drive distinct cortical regions to produce these cognitive states. We designed a study to examine functional connectivity between LC and PFC using network activity by assessing coherence in local field potentials (LFPs). Initial results with adult males (n=8) are reported here. Specifically, we recorded LFPs from medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) because of our previous data revealing their roles in facilitating extradimensional shifting and reversal learning, respectively. Coherence is the result of complementary oscillations in different regions and represents functional connectivity between those regions. Network activity in adult, male rats was recorded before and after exposure to a novel cage for five consecutive days in LC, mPFC, and OFC. Coherence and power spectral density (PSD) were calculated. Coherence

between the two cortical regions was higher than coherence between LC and OFC or between LC and mPFC in all frequency bands. This coherence was unchanged by repeated novel cage exposure. This finding confirms that repeated exposure to a novel cage, typically a control for social defeat occurring in the cage of a resident rat, does not have significant effects on its own. This is the first analysis of the relationship between LC and OFC network activity. In ongoing studies, we are assessing the impact of repeated social defeat on coherence between LC, mPFC, and OFC and determining if differences in LC activity might lead to changes in LC drive to distinct PFC regions that might underlie different cognitive states. Additionally, we are assessing whether sex differences exist in LC activation following repeated stress and how these differences might alter PFC network activity and cognitive function.

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Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Program #/Poster #: 316.17/TT15

Topic: F.04. Stress and the Brain

Support: NIH Grant K08 MH109735
Hope for Depression Research Foundation

Title: Acute restraint stress alters reward-related VTA and NAc activity

Authors: *D. C. LOWES[1], E. S. HOLT[3], J. A. GORDON[4], A. HARRIS[2]
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Abstract: Acute stress can impair the sensitivity to rewards in humans, and preclinical studies suggest that while mice are restrained, passively received rewards induce blunted activity of ventral tegmental area (VTA) dopamine neurons. However, it is unclear how acute stress contribute to lasting changes in VTA and nucleus accumbens (NAc) activity as individuals actively engage in rewarding behavior. We hypothesized that after acute restraint stress, reward would elicit reduced VTA and NAc neural activity. To test this hypothesis, we simultaneously recorded single unit and local field potential (LFP) activity in the VTA and LFP activity in the NAc of mice during a cued-reward task before and after they experienced acute restraint. We found that acute restraint stress decreases the rate at which mice lick in anticipation of a reward and increases the latency to reward retrieval (both $p<0.05$). In addition, we observed that restraint stress alters cue-evoked firing in the VTA, as well as a cue-evoked potential in the NAc (all $p<0.05$). Together, these data suggest that acute stress produces lasting changes in reward-seeking behavior and VTA and NAc neural activity.

Disclosures: D.C. Lowes: None. **E.S. Holt:** None. **J.A. Gordon:** None. **A. Harris:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

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Program #/Poster #: 316.18/TT16

Topic: F.04. Stress and the Brain

Support: PAPIIT IN 306918

Title: Effect of WAY 100,635 on the behavioral indicators of anxiety and anhedonia after exposure to chronic stress

Authors: *I. GONZALEZ RIVERA[1], O. GALICIA-CASTILLO[2], H. SANCHEZ-CASTILLO[3]
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Abstract: Actually, the serotonergic system it seems to play a major role in the regulation of the stress response, in fact, one of the main treatments for stress-related disorders is the use of serotonergic antidepressants. However, the specific mechanism by which they exert their therapeutic effects in such disorders remains unknown. 5-HT1A receptors could play an important role in the mechanism of regulation of the stress response. The aim of the present study was to evaluate the effect of a 5-HT1A receptor-specific antagonist (WAY 100,635) on behavioral indicators of stress. We used 40 male Wistar rats of 250-350 grams housed in standard laboratory conditions and treated in accordance with the ethical standards of use and care of laboratory animals. Rats were subjected to an unpredictable chronic stress protocol for ten days; then they were divided into four groups to be administered with WAY 100,635 at doses 0.0, 0.05, 0.1 and 0.2 mg/kg respectively. The administration was intraperitoneal with saline as a vehicle for seven days. Finally, they were measured in tests of anxiety, anhedonia, and cognition. Statistically significant differences were found in all tests between groups, showing an anxiolytic effect of WAY 100,635 on the stress model, this results are related to the effect of the drug on the 5-HT1A autoreceptors and it suggests that these particular receptors are importantly involved in the mechanisms of regulation of stress response.

Disclosures: I. Gonzalez Rivera: None. **O. Galicia-Castillo:** None. **H. Sanchez-Castillo:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 316.19/TT17

Topic: F.04. Stress and the Brain

Support: NIH MH103322
MH10332S1

Title: Social defeat stress induces similar transcriptional profile changes in California mice as compared to patients with depression in reward-related brain regions

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Abstract: Social defeat stress (SDS) is a widely used model of chronic psychosocial stress for inducing anxiety-like and depression-like behavioral abnormalities in rodents. It has been difficult to use SDS in female rodents due to a lack of aggressive behavior. However, female California mice show similar levels of territorial aggression as males, allowing us to study the effects of SDS in both sexes. Using this model, we exposed both male and female California mice to SDS. In order to assess the long-term effects of SDS, brains were extracted two weeks following the end of SDS and immediately flash frozen. Using RNAseq, we assessed SDS-induced transcriptional profile changes in the nucleus accumbens (NAc) of both stressed and unstressed male (unstressed = 7, stressed = 6) and female (unstressed = 8, stressed = 7) California mice. Additional analyses were also performed in the prefrontal cortex (PFC) in stressed and unstressed female (unstressed = 8, stressed = 7) California mice. These data sets were compared to transcriptional profiles observed in either the NAc or PFC from human tissue of both men (MDD = 13, control = 13) and women (MDD = 13, control = 9) patients with or without major depressive disorder (MDD). Using rank-rank hypergeometric overlap (RRHO) analyses, we found more overlap in genes that were decreased by stress in female California mice and decreased in women diagnosed with depression. Based on patterns observed using RRHO, we used gene ontology (GO) and KEGG analyses to look for highly enriched GO terms and pathways that were altered by stress and depression. In the NAc, one of the more highly enriched terms affected is G-protein coupled receptor (GPCR) signaling and regulation of GPCR, where both GPCR signaling and regulation of GPCR signaling are down-regulated by stress or in human depression. In the PFC, major terms arising using KEGG analyses are associated with ribosomal translation. In addition, many immediate early genes are

downregulated by stress and in patients with depression, suggesting less activity in the PFC in general. Follow-up qPCR analyses are in progress to confirm these findings in separate biological replicates. Together these results suggest that the California mouse model of social defeat may be particularly effective at modeling aspects of depression that involve transcriptional repression as opposed to transcriptional activation.

Disclosures: A.V. Williams: None. **C.J. Pena:** None. **B. Labonté:** None. **S. Ramos-Maciel:** None. **E.J. Nestler:** None. **B.C. Trainor:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 316.20/TT18

Topic: F.04. Stress and the Brain

Support: NARSAD Young Investigator Award (DD)
R01MH111918 (DD)

Title: Propranolol-mediated inhibition of the priming effect of acute social defeat stress to increased susceptibility to subsequent social defeat stress

Authors: *J. Y. ZHANG, C. FILLINGER, Y. S. GROSSMAN, D. DUMITRIU
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Abstract: Social defeat stress is an accepted animal model of human depressive-like symptoms with demonstrated predictive power and ethological validity. Chronic social defeat stress (CSDS, 10-day) induces pervasive depressive-like symptoms in mouse. When tested in a social interaction (SI) test following CSDS, defeated mice show lower SI ratio, indicative of social avoidance. The majority of animals that undergo CSDS develop this avoidant phenotype and are classified as “susceptible”. However, approximately one third of mice do not become socially avoidant and are classified as “resilient”. Because our lab is primarily interested in the pre-existing neural connectivity that mediates this divergent stress response, we developed an acute social defeat stress model (ASDS) that differentiates resilience and susceptibility one hour post-defeat, the time-point of maximal immediate early gene expression.This allows us to interrogate differences in the initial stress-activated neural ensemble. ASDS does not lead to pervasive depressive-like symptoms, but interestingly does prime animals to increased susceptibility to subsequent social stress, including subthreshold social defeat stress (StSDS). Here, we seek to determine whether the beta-adrenergic antagonist propranolol is capable of inhibiting ASDS-induced priming to future social stress. Propranolol has been shown to impair fear memory consolidation in the rat and reduce recall for negatively-valenced emotional content in both healthy and PTSD-afflicted adult humans. Our preliminary data suggests that propranolol has a

mediating effect on ASDS-induced stress priming. Further investigation of this mediating effect could offer insight into the mechanisms underlying selective resilience and susceptibility.

Disclosures: J.Y. Zhang: None. **C. Fillinger:** None. **Y.S. Grossman:** None. **D. Dumitriu:** None.

Poster

316. Stress-Modulated Pathways: Cortex and Striatum

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 316.21/TT19

Topic: F.04. Stress and the Brain

Support: Dow Scholars Fund

Title: Understanding the role of CRF receptor in the development of anxiety-like behaviors and obesity using diet manipulations in selectively-bred rat populations

Authors: *J. HAAN[1], P. J. VOLLBRECHT[2]
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Abstract: Epidemiological data shows that obesity continues to develop as a serious public health concern in the United States. Interestingly, anxiety disorders have been shown to be associated with obesity. However, cause and effect is not well established due to poor mechanistic understanding of the relationship between these conditions. Several brain regions have been shown to be affected by obesity and related to anxiety disorders such as the nucleus accumbens (NAc), prefrontal cortex (PFC), and hypothalamus. Here we tested the effects of diet and obesity development in both outbred and selectively bred obesity prone and obesity resistant rat populations.
Outbred and selectively bred animals were subject to three diets, standard chow, junk food diet (19.6% fat) used to mimic a western diet, or high fat diet (60% kcal from fat). Selectively bred obesity prone rats did not show increases in anxiety-like behavior when tested before obesity development. Both groups were tested for anxiety-like behaviors using open field and elevated plus maze behavioral paradigms following a 4-week diet manipulation. Outbred animals fed a high fat diet did not show significant differences in anxiety-like behaviors compared to chow-fed animals despite enhanced weight gain. However, post obesity development testing in obesity prone rats showed drastic increase in anxiety-like behavior compared to their obesity resistant counterparts, regardless of diet manipulation. These data suggest that a combination of both predisposition and obesity development are necessary to cause anxiety-like behaviors, while diet and obesity are not independently sufficient to cause changes in anxiety-like behaviors in our studies.
Following behavioral testing, NAc, PFC, and hypothalamus were dissected out and blood

samples were collected. Plasma corticosterone levels were quantified in outbred rats using ELISA analysis. No significant differences in corticosterone concentration were found between the diet groups showing a lack of direct effect of diet on HPA-axis activation. Furthermore, corticotropin-releasing factor receptor 1 (CRFR1) was analyzed in a variety of brain regions by western blot due to its role as a primary initiator of the HPA-axis. Increased CRFR1 has been observed independently in studies of both anxiety and obesity making it a possible link between the two conditions.
These studies indicate that anxiety development is dependent on both susceptibility and obesity development. Biochemical analysis of corticosterone levels and CRFR expression may help to better understand the relationship between obesity development and the development of anxiety-like behaviors.

Disclosures: J. Haan: None. **P.J. Vollbrecht:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.01/TT20

Topic: F.04. Stress and the Brain

Support: JSPS KAKENHI Grant Number JP17J02160
JSPS KAKENHI Grant Number JP18K06011

Title: A potential screening paradigm for antidepressants using the nest building evaluation after acute social defeat stress (ASDS)

Authors: *H. OTABI[1,2], T. OKAYAMA[1,2], D. KOHARI[1,2], A. TOYODA[1,2]
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Abstract: [Introduction] Appropriate models of depression and their behavioral evaluation are essential to identify potential antidepressant candidates. In our previous researches, we clarified that nest building behavior was significantly delayed in the subchronic mild social defeated mice (Otabi et al., Bahave Processes., 2016). Nest building is an instinctive and goal-directed behavior involved in hippocampus and prefrontal cortex. Furthermore, we confirmed that nest building behavior was also delayed in the acute social defeated stress (ASDS) mice. In this study, we tried to establish the paradigm for drug screening combining ASDS with nest building behavior. [Materials and methods] The animal experiments were described by the previous report (Otabi et al., Behav Processes., 2017). After injecting (i.p) of drugs such as SR-46349B, fluoxetine, methylphenidate, and duloxetine, C57BL/6J male mice were exposed to ASDS with ICR male mice. We assessed the nest score using the method as previously described (Deacon, Nat Protoc., 2006). [Results and discussion] The nest building delay in ASDS mice was partially rescued by

administering a specific 5-HT2a receptor antagonist (SR-46349B). However, a popular SSRI (fluoxetine), methylphenidate, and duloxetine could not rescue this nest building deficit. Possibly, nest building deficit in ASDS mice is based on the unknown mechanism in CNS, so the drug screening using the proposed paradigm will produce fruitful outcome in the drug discovery for depressive disorders. [Conclusion] Nest building evaluation after ASDS may be a potential method to discover novel antidepressants.

Disclosures: H. Otabi: None. **T. Okayama:** None. **D. Kohari:** None. **A. Toyoda:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.02/TT21

Topic: F.04. Stress and the Brain

Support: NIMH R01 MH053851
NIH T32 NS082145

Title: Stress effects on neuronal connectivity in the orbitofrontal cortex

Authors: *S. M. ADLER, S. E. BULIN, M. GIROTTI, D. A. MORILAK
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Abstract: Depressed patients often experience impairments in cognitive flexibility, a symptom dimension that may underlie illness maintenance and is poorly treated by classic antidepressants. One major risk factor for depression is chronic stress, which has frequently been utilized in rodent models to cause a depression-like phenotype. Using chronic intermittent cold stress (CIC), we can induce a deficit in the reversal learning phase of the attention set-shifting test (AST) in Sprague-Dawley rats ($p<.01$), and this deficit can be corrected by antidepressants like citalopram, vortioxetine, and ketamine ($p<.05$). We hypothesize that an increase in dendritic complexity and synaptic spine density induced in the orbitofrontal cortex (OFC) by cold stress causes an aberrant potentiation of afferent-driven response in the OFC, leading to dysregulated reversal learning.
Field potentials evoked acutely in the OFC by mediodorsothalamus (MDT) afferent stimulation in rats were potentiated after 2 weeks of CIC stress compared to baseline ($p<.01$). Additionally, CIC rats had an increase in distal apical spine density ($p<.05$) and distal apical dendritic complexity ($p<.05$) after stress, and this effect is specific to the medial region of the OFC. Finally, since functional changes in excitatory transmission correlate with altered AMPA receptor surface expression, we performed a surface labeling experiment and discovered that CIC rats have significantly more surface GluR1 in the medial OFC relative to non-stressed controls ($p<.05$).

To determine if increased activity in the OFC is sufficient to cause deficits in reversal learning, we plan to use optogenetics with the ChETA variant of channelrhodopsin, delivered by an AAV viral vector, to induce long-term potentiation (LTP) in the MDT to OFC pathway in non-stressed rats. In preliminary studies to first validate this approach, we successfully induced opto-LTP in this pathway. Further, to determine if the increase in spine density is necessary for the deficit in reversal learning after CIC, we will use a construct, AS-PA-Rac1, that expresses photoactivatable Rac1 to shrink recently potentiated spines upon laser stimulation. In preliminary studies to first validate this approach, we have demonstrated that the construct works as expected in neurons in culture.
This work was supported by NIMH grant R01 MH053851 and by a NIH Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences training grant T32 NS082145.

Disclosures: S.M. Adler: None. **S.E. Bulin:** None. **M. Girotti:** None. **D.A. Morilak:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.03/TT22

Topic: F.04. Stress and the Brain

Title: Effects of repeated and acute stress on expression of Arc/Arg3.1 in the rat hippocampus and prefrontal cortex

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Abstract: Stress has been shown to alter the structure and function of the hippocampal formation (HF) and prefrontal cortex (PFC), however the mechanisms by which these changes occur is not well defined. Of note, differential effects on mRNA and protein expression in these regions have been observed depending on the type of stress experienced. The activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) is associated with dendritic spine morphology, long-term potentiation, and more broadly, learning and memory, which are all impacted by stress. Collectively, these data suggest that Arc protein expression may provide an entry point into understanding the connections between stress, cognition and learning-related protein expression. The purpose of the present study was to determine the effects of different types of stress on the expression of Arc in brain regions associated with cognition. We exposed male rats to either acute or repeated stress with the hypothesis that Arc expression in the acute group, but not the repeated stress group, would increase. To evaluate the stress paradigms, we measured body weight, behavior and hormone production. The data reveal that rats in the repeated stress group

gained less weight compared to acute and control groups and, as expected, both acute and repeated groups displayed anxious behavior on the open field test. Furthermore, rats in the repeated stress group showed reduced corticosterone levels, a common symptom of post-traumatic stress disorder. Together these data suggest that the stress paradigms successfully induced behavioral and physiological changes in stressed rats. Moreover, following these stress paradigms, in the HF, Arc expression was increased after acute stress and reduced after repeated stress, consistent with the view that high corticosterone levels elevate Arc expression, perhaps through glutamate-mediated mechanisms. Conversely, in the PFC, acute stress decreased Arc expression but repeated stress did not, highlighting a differential effect of both acute and repeated stress on the HF and PFC. Overall these data provide insight into Arc protein regulation that may underlie stress-induced structural and functional changes in neurons.

Disclosures: A. Mogul: None. **E. Taylor-Yeremeeva:** None. **A. Khan:** None. **H. Wang:** None. **S. Robinson:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.04/TT23

Topic: F.04. Stress and the Brain

Support: NIH K08 MH109735
Hope for Depression Research Foundation
NIH R01 MH096274

Title: Chronic social defeat stress increases ventral hippocampal - prefrontal synchrony

Authors: *A. HARRIS[1,2], L. A. CHAMBERLIN[1], L. KRETSGE[1], D. C. LOWES[1], M. A. TOPIWALA[1,2], A. I. ABBAS[1], A. J. PARK[1], P. ATSAK[1,2], E. D. LEONARDO[1], R. HEN[1], J. A. GORDON[3]
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Abstract: Anatomical evidence implicates the hippocampus and prefrontal cortex in patients with depression, and preclinical studies have revealed that chronic stress impacts the anatomy and functioning of these structures. Although we have previously demonstrated that ventral hippocampal (vHPC) medial prefrontal cortex (mPFC) communication plays a crucial role in mediating anxiety-related behavior, it remains unknown how chronic stress impacts this communication. Since vHPC-mPFC theta range (4-12 Hz) synchrony is enhanced in negative valence (anxiogenic) environments, we hypothesized that chronic social defeat stress (CSDS) - which leads to social avoidance in susceptible mice - would increase vHPC-mPFC synchrony.

To test this hypothesis, we recorded simultaneous vHPC and mPFC neural activity in mice and compared their synchrony before and after they underwent CSDS. We found that CSDS increases multiple measures of vHPC-mPFC theta range synchrony relative to baseline values (coherence $p<0.05$; power-power correlations $p<0.05$, paired sign rank test; n=13). Moreover, a sub-analysis revealed that these results held true for susceptible (n=9), but not resilient mice (n=4). These synchrony changes were pathway specific as they did not occur in the vHPC to nucleus accumbens pathway (n=7). Finally, we found that the degree of increase in vHPC-mPFC synchrony significantly correlates with social interaction scores of individual mice. Collectively, these data suggest that vHPC-mPFC communication plays a role in the manifestation of susceptible behavior seen after chronic social defeat stress.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.05/TT24

Topic: F.04. Stress and the Brain

Support: NARSAD Young Investigator Award, U. Albany Brain and Behavior Research Foundation

Title: Chronic variable stress and nursing demand interact to alter depression-like behavior and hippocampal neurogenesis in postpartum rats

Authors: *J. MEDINA[1], R. M. DEGUZMAN[1], A. I. SAULSBERY[2], K. W. UNGER[1], E. CEBALLOS[1], J. L. WORKMAN[1,3]
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Abstract: The postpartum period is characterized by dramatic peptide and steroid hormone fluctuations and represents a time of increased risk for developing depression. However, the underlying mechanisms of postpartum depression (PPD) are incompletely understood. Stress is a major risk factor for depression and lactational experience suppresses hypothalamic-pituitary-adrenal axis stress responsivity. Women who do not breastfeed or discontinue breastfeeding early have a higher risk of developing PPD compared with women who breastfeed exclusively. Further, prospective studies indicate that cessation of breastfeeding precedes PPD in some women. Thus, we sought to determine whether different lactational experience would alter susceptibility to stress-induced changes in depression-like behavior and hippocampal

neurogenesis during the postpartum period. Adult female Sprague-Dawley rats underwent thelectomy (thel; surgical removal of teats), sham surgery, or no surgery (control). Litters were rotated between yoked thel and sham dams every 12 h from postpartum days (PD) 0 – 26. Thus, thel dams had offspring contact throughout the postpartum period and sham rats bore a higher nursing demand. Control litters were rotated between paired control rats. From PD 2 – 25, dams and their litters were either left undisturbed or exposed to chronic variable stress. Stressors were presented once per day in a semi-random order and included wet bedding, empty water bottle, overnight illumination, tail pinch, dirty bedding, stroboscopic lighting, white noise, low bedding, and cage tilt. Maternal behavior observations revealed stressed rats spent more time with offspring compared with non-stressed rats, regardless of nursing condition. Sham and thel rats spent more time with offspring compared with control rats regardless of stress. Nursing and stress interacted to alter immobility in the forced swim test: among non-stressed rats, thel rats spent more time immobile compared with sham rats. Stress increased immobility in control and sham rats, but unexpectedly, reduced immobility in thel rats. Preliminary data also suggest that lactational experience interacts with stress to alter hippocampal neurogenesis. These data suggest that nursing does not necessarily yield resistance to stress-induced changes in depression-like behavior or neurogenesis. Thus, the relationship between absence of breastfeeding and PPD could be unrelated to stress susceptibility in non-breastfeeding women. These data will also be discussed in the context of allostatic load.

Disclosures: J. Medina: None. **R.M. DeGuzman:** None. **A.I. Saulsbery:** None. **K.W. Unger:** None. **E. Ceballos:** None. **J.L. Workman:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

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Topic: F.04. Stress and the Brain

Support: National Natural Science Foundation of China #81501171
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Programme of Introducing Talents of Discipline to Universities #B14036
National Natural Science Foundation of China #81601066

Title: Physical exercise-elicited adiponectin increase affects hippocampal neuronal plasticity and attenuates behavioral despairs in stressed mice

Authors: *A. LI, P. WANG, K.-F. SO, P. YU
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Abstract: Major depressive disorder causes profound personal suffering and economic burden. We have previously demonstrated that adiponectin, a neuroprotective cytokine secreted by mature adipocytes, may mediate physical exercise-elicited adult hippocampal neurogenesis, subsequently mitigating behavioral despairs. However, whether such antidepressive effect involves adiponectin's regulation of hippocampal plasticity in neurons other than neural precursor cells remains unexplored. By means of repeated corticosterone (COR) injections to mimic stress insult, we here showed that voluntary wheel running was sufficient to ameliorate depression-like behaviors in stressed wild-type (WT), but not adiponectin-knockout (KO) mice. Likewise, impaired neuronal morphology in hippocampal dentate gyrus following COR treatment could only be significantly restored by running in WT rather than KO mice, suggesting that adiponectin also directly affects hippocampal neuronal plasticity. Meanwhile, running increased serum and hippocampal levels of adiponectin in WT rather than KO mice receiving either COR or vehicle injections, whereas other well-known cytokines including brain-derived neurotrophic factor, insulin-like growth factor, vascular epithelial growth factor and nerve growth factor remain comparable between these two mouse strains, regardless of running or not. Overexpression of glucocorticoid receptors and the adaptor protein APPL2 have been reported to incur depressive phenotypes in mice. Interestingly, in WT but not KO mice, running downregulated the expression of these two targets, and yet left that of mineralocorticoid receptors, the adaptor protein APPL1 and adiponectin receptors unchanged. Taken together, our data suggest that adiponectin potentially mediates physical exercise-exerted antidepressive effect by restoring stress-triggered impairment on dendritic plasticity of hippocampal neurons through selectively reducing the expression of glucocorticoid receptors and APPL2.

Disclosures: A. Li: None. **P. Wang:** None. **K. So:** None. **P. Yu:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.07/UU2

Topic: F.04. Stress and the Brain

Support: NIH R01 DA019921

Title: Membrane and cytosolic corticosterone receptors in the ventral hippocampus contribute to stress-induced alterations of accumbal dopamine output in control and amphetamine withdrawn rats

Authors: *B. BRAY[1,2,3], K. A. CLEMENT[1,2,3], M. A. WEBER[1,2,3], G. L. FORSTER[1,2,3,4]
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Abstract: Corticosterone (CORT) is a stress hormone that can act centrally to mediate stress- and reward responses. The ventral hippocampus (vHipp) mediates stress responses and has a high expression of glucocorticoid (GR) and mineralocorticoid (MR) receptors, making it sensitive to CORT and stress. We previously found that a stress-relevant concentration of CORT infused into the vHipp of adult male Sprague-Dawley rats enhances dopamine (DA) output in the nucleus accumbens shell (NAcS) (n = 11). This effect is rapid, peaking 40 - 60 min post-infusion, and may provide a mechanism by which stress can enhance incentive salience to promote goal-oriented behavior. Interestingly, the same stress-relevant vHipp CORT infusion *reduces* NAcS DA output in amphetamine withdrawal (n = 11), when vHipp GR protein expression is reduced. This effect is rapid and bi-phasic, peaking at 30- and 75 min post-infusion, and suggests that reduced vHipp GR expression may contribute to reduced NAcS DA output and dysphoric states in amphetamine withdrawal. GRs and MRs can be cytosolic or membrane-bound, genomic or non-genomic, and differ in their affinity for CORT, and in their downstream signaling mechanisms and effects. For example, findings suggest GRs may be excitatory or inhibitory, and MRs may be excitatory or disinhibitory, depending on their location. To explore the receptor mechanisms that mediate the ability of vHipp CORT to alter NAcS DA release, we selectively blocked either GRs or MRs in the vHipp by infusing mifepristone or spironolactone (respectively) into the vHipp prior to a stress-relevant infusion of vHipp CORT in control- and amphetamine-withdrawn rats (n = 7 - 8 / group). *In vivo* chronoamperometry was used to assess accumbal DA output. Interestingly, all conditions resulted in vHipp CORT reducing NAcS DA levels, suggesting that vHipp MRs and vHipp GRs both reduce NAcS DA release in control- and withdrawal states. We then infused a stress-relevant concentration of membrane-impermeable CORT (CORT-BSA) into the vHipp of drug-naïve adult male rats (n = 8). This infusion rapidly increased NAcS DA output, peaking 20 min post-infusion, then returning to baseline 60 min post-infusion. This suggests that concomitantly activating MRs and GRs in the vHipp membrane has an excitatory effect on NAcS DA output, and may contribute to the rapid ability of stress to enhance NAcS DA levels and incentive salience in control conditions. These findings provide important information on vHipp CORT receptors, and implicate vHipp CORT in mediating stress-induced reward responses in healthy conditions and in diseased- and dysphoric states.

Disclosures: B. Bray: None. **K.A. Clement:** None. **M.A. Weber:** None. **G.L. Forster:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.08/UU3

Topic: F.04. Stress and the Brain

Support: UNAM-DGAPA PAPIIT 204718
NIH/VA BX-003040

CONACYT Scholarship: 574065

Title: Role of reproductive status on tau phosphorylation induced by chronic stress in the hippocampus of the female rat

Authors: *D. MUNOZ-MAYORGA[1], R. A. RISSMAN[2], T. MORALES[1]
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Abstract: Sex and the exposure to chronic stress have been identified as risk factors to develop Alzheimer's disease as documented by epidemiological studies. Although the majority of patients with this disease are women, the sex of the individual has been overlooked in most studies. Previous work in rodents showed that the exposure to physical and psychological stressors induces hyperphosphorylation of tau (tau-P), which has been shown to be tempered by reproductive status in female subjects. To test the hypothesis that the reproductive status can modulate stress-induced tau-P in the hippocampus of females, cohorts of virgin, lactating (4-5 days pp), and 1-month postweaned rats were subjected to a daily episode of 30 minutes of restraint stress or handling (control) for 14 days, and were sacrificed either 20 min or 24 h after their last stress/handling episode. Two well characterized AD-relevant tau-P epitopes (AT8 and PHF-1) and possible phosphorylation mechanisms such as GSK3 and ERK1/2 were analyzed by Western blot. This analysis showed no differences at 20 min in hippocampal tau-P among the reproductive conditions, although a trend to increase in tau-P levels was observed in stressed virgin rats sacrificed at 24 h after their last stress episode. No changes were detected in GSK3 or ERK1/2 levels in rats sacrificed 20 min after the last stress episode. Immunodetection of s422 epitope revealed increased tau-P in CA3 and CA4 subfields of the hippocampus of virgin rats exposed to chronic stress. Whereas stress did not modify labeling of s422 in the lactating and 1-month postweaned stressed groups. These results suggest a slightly higher sensitivity of the virgin rats to increase tau-P in the hippocampus after chronic stress compared to that in lactating and postweaned rats. Since no differences were detected between lactating and postweaned rats, current results support the idea of reproductive experience having an impact on tau processing in the brain of the female.

Disclosures: D. Munoz-Mayorga: None. **R.A. Rissman:** Other; VA San Diego Healthcare System. **T. Morales:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

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Program #/Poster #: 317.09/UU4

Topic: F.04. Stress and the Brain

Support: Chicago Biomedical Consortium Award

Title: Hippocampal RNA editing mediates the long-term effects of prenatal stress

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Abstract: A post-transcriptional process known as RNA editing, which is catalyzed by ADAR enzymes, regulates brain development. Although ADAR enzymes alter the sequences of thousands of mRNA and miRNA targets, one of the most important targets is the mRNA encoding the GluA2 subunit of the AMPA glutamate receptor (AMPAR). RNA editing reduces the trafficking of GluA2-AMPARs to the synaptic surface, a process that is critical for synaptic maturation, synaptic plasticity, learning and memory. These processes are impaired in psychiatric disorders that are exacerbated by stress, including schizophrenia. In this study, we investigated a developmental model of schizophrenia, where we exposed mice to environmental stress during gestation i.e. prenatal stress (PRS). PRS mice have abnormal brain development and abnormal behavior in adulthood. We treated adult PRS mice and controls with haloperidol (1mg/kg), clozapine (5mg/kg) or saline twice daily for 5 days. 16hrs after the final injection, we assessed mice for social interaction behavior and locomotor activity. We analyzed the frontal cortex and hippocampus of each mouse for the expression of the RNA editing enzymes (ADARs 1-3) in addition to performing tagged next-generation sequencing analysis of the RNA editing levels of 24 genes, including the AMPAR subunits. PRS mice exhibited reduced social interaction behavior, which was inversely correlated with hippocampal RNA editing of the AMPAR subunits GluA2-4, the potassium channel Kv1.1, and the serotonin2C receptor (5-HT2CR), in addition to other mRNA targets of the ADAR enzymes. Treatment with clozapine, but not haloperidol, eliminated deficits of social interaction in the PRS mice, and reduced abnormal GluA2 RNA editing in the hippocampus. We also observed increased ADAR3 expression in the clozapine-treated PRS mice, indicating that PRS and clozapine both alter transcriptional pathways associated with RNA editing in the hippocampus. Our data indicate that PRS produces long-term changes in behavior that may be due to abnormal development of the hippocampus, which are mediated by RNA editing. These data indicate that RNA editing may contribute to the pathophysiology of schizophrenia, and may contribute to the antipsychotic efficacy of clozapine.

Disclosures: G. Bristow: None. **A. Segismundo:** None. **M.S. Sodhi:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.10/UU5

Topic: F.04. Stress and the Brain

Title: PKA phosphorylation of the L-type, voltage-gated calcium channel $Ca_V1.2$ positively regulates learning and anxiety behaviors

Authors: *K. E. IRETON, A. GROVER, J. HELL
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Abstract: The L-type, voltage-gated calcium channel (VGCC) $Ca_V1.2$ is a primary mediator of neuronal post-synaptic Ca^{2+} influx in the brain, and consequently influences cellular excitability, gene expression, and synaptic plasticity. Its activity is known to be modulated by stress, mediated by norepinephrine (NE), which effectively increases Ca^{2+} influx through $Ca_V1.2$ by increasing probability of channel opening. $Ca_V1.2$ modulates learning, stress, and reward related behaviors in rodents, and mutations in its gene CACNA1C are implicated in human autism spectrum disorder, bipolar disease, schizophrenia, and major depressive disorder pathologies. However, it has not been known how NE regulation of $Ca_V1.2$ specifically impacts behavior, if at all. NE regulates CaV1.2 activity by downstream activation of PKA via the β_2-Adrenergic receptor, which then causes phosphorylation of the channel C-terminal tail at Ser^{1928}, its most prominent site of PKA phosphorylation. Our lab has demonstrated previously that phosphorylation of $Ca_V1.2$ at Ser^{1928} is necessary for the induction of prolong-theta-tetanus long term potentiation (PTT-LTP) in rodent hippocampal brain slices, and thus hypothesized that spatial learning behaviors would be impaired in mice carrying a knock-in mutation at Ser^{1928} to prevent PKA phosphorylation (S1928A). We now present evidence that S1928A spatial learning is impaired relative to wildtype in the Morris Water Maze during acquisition of the platform location during training, although not after further training. Impairments in short-term memory and anxiety related behaviors also appeared in S1928A mice. These behavioral data show that PKA phosphorylation of $Ca_V1.2$ is not only relevant to learning and stress-related behaviors, but that it positively regulates them, indicating the potential importance of NE regulation of this VGCC in the brain to animals *in vivo*.

Disclosures: K.E. Ireton: None. **A. Grover:** None. **J. Hell:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.11/UU6

Topic: F.04. Stress and the Brain

Support: Grass Foundation

Title: Understanding neural mechanisms of resilience to stress: Role of hippocampal brain-derived neurotrophic factor

Authors: *K. ALVINA, M. JODEIRI-FARSHBAF, H. BLAKLEY, J. BLAKLEY, D. CHERKOWSKY, E. X. LEE, D. J. SMITH
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Abstract: Stress is a powerful stimulus that can modify neural processes and ultimately precipitate the onset and/or exacerbation of neuropsychiatric disorders. Extensive research has shown that glutamatergic synaptic transmission is an important target of stress. In the CA3 area of the hippocampus for instance, one of the most stress-sensitive brain regions, chronic stress causes severe dendritic retraction in CA3 pyramidal cells. These changes depend on NMDA-type glutamate receptors (NMDARs), however the actual mechanisms of action are not entirely clear. Therefore, we focused on NMDAR-mediated synaptic transmission in the CA3 area of the hippocampus and intracellular pathways altered by stress. One such molecule is the brain-derived neurotrophic factor (BDNF), which is highly expressed in the hippocampus and contributes to cell growth and proliferation, synaptic transmission and plasticity. Thus, using a mouse model of chronic stress we studied changes occurring in the hippocampus of stressed female and male mice, combining virally-mediated gene manipulation, behavioral analysis and in vitro electrophysiology. Behavioral analysis showed that mice subjected to a chronic stress paradigm spent significant more time in the periphery of an open field test and in the closed arms of the elevated plus maze, indicating a heightened level of anxiety. Similarly, both female and male chronically stressed mice showed increased immobility in the forced swimming test, indicating depression-like behavior. Furthermore, excitatory post-synaptic potentials in hippocampal slices showed decreased responses in the CA3 region of stressed mice compared to controls. However, when pharmacologically isolated, NMDAR-mediated responses showed increased amplitude in stressed mice, suggesting that stress differentially modulates the function of glutamate receptors. Lastly, using a virus-mediated strategy we probed the role of hippocampal BDNF in mediating stress-induced changes in behavior. Our results show that reducing BDNF via shRNA expression in the CA3 region reduces circulating levels of corticosterone and recapitulates the anxiety-like behaviors observed in stressed mice. In summary, our results link stress-induced alterations in excitatory synaptic transmission in the CA3 area of the hippocampus with specific behavioral deficits and reduced BDNF levels. Understanding the physiological mechanisms affected by stress could provide important clues to understand resilience and to explore possible therapeutic avenues.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.12/UU7

Topic: F.04. Stress and the Brain

Support: NIH Grant P30 EY13079
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Fulbright Graduate study Grant
T32 MH109524
NYU's Research Challenge Fund

Title: Experience of wheel-running and food restriction in adolescent female rats results in increased GABA response and mIPSC frequency in hippocampal pyramidal neurons despite fewer GABAergic axo-somatic synapses

Authors: T. G. CHOWDHURY[1], Y.-W. CHEN[1], G. S. WABLE[1], K. TATEYAMA[1], I. YU[1], J.-Y. WANG[1], A. D. REYES[1], *C. J. AOKI[2]
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Abstract: Adolescence is marked by increased vulnerability to mental disorders, due, in part, to increased stressors that evoke maladaptive behaviors even in healthy individuals. Food-restriction (FR) stress evokes an innate behavior of foraging, which translates to increased wheel running exercise (EX) for caged rodents with wheel access. EX within a cage is maladaptive, since it does not improve food access and exacerbates weight loss. While almost all adolescents increase EX following FR, many also exhibit resilience by the 3rd or 4th day by suppressing EX: this helps survival by minimizing weight loss. We asked whether plasticity of the GABAergic system in dorsal hippocampus (dHPC) may underlie this resilience to FR. In vitro slice physiology by whole-cell recording revealed that response of pyramidal neurons in the dHPC of food-restricted animals with wheel access (FR+EX) to bath-applied GABA is more than doubled, compared to CON without FR or EX ($p=0.01$), even though mIPSC amplitudes trended towards a decrease (-15%, $p=0.09$). This suggests the emergence of extrasynaptic $GABA_AR$s, which would not contribute to mIPSC amplitude measurements but would contribute to bath-applied GABA response. mIPSC frequency of FR+EX neurons is greater by 46%, compared to CON ($p=0.02$), but electron microscopic immunocytochemical labeling of GAD-terminals revealed a trend towards decrease in the number of axo-somatic GABAergic axon terminals on pyramidal cells (-25%, $p=0.07$) and only a modest difference (+26%, $p=0.02$) of GABAergic synapse lengths. This suggests un-silencing of GABAergic synapses through addition of $GABA_AR$s at previously receptor-less axo-somatic synapses or increased probability of vesicular release. Moreover, an individual's mean length of GABAergic synapses correlated strongly with the extent of wheel running suppression ($R=0.9$, $p=0.01$). GABAergic changes evoked by FR+EX were distinct from the changes following EX or FR, alone, indicating that EX can have dual roles - exacerbate weight loss during FR but also promote resilience by dampening excitability of the dHPC. Anorexia nervosa (AN) is a mental illness with high mortality rate, surpassing that of depression and is still without accepted pharmacological treatments. The rodent paradigm of FR+EX captures maladaptive behavioral hallmarks of AN - excessive EX plus voluntary FR. Using adolescent female rats in this model, we uncovered plasticity in the

GABAergic system of the dHPC only of rats exhibiting behavioral signatures of resilience - suppressed wheel running and suppressed weight loss, providing clues regarding individual differences in vulnerability to AN and therapeutic interventions.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.13/UU8

Topic: F.04. Stress and the Brain

Support: NIH Award Number R25GM076321

Title: Epigenetic regulation of retrotransposons by corticosterone mediates NLRP3 inflammasome complex activation in the rat hippocampus

Authors: *M. J. CLARK[1], A. A. BARTLETT[2], R. G. HUNTER[2]
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Abstract: Stress and immune signaling converge in the hippocampus to alter synaptic function. Glucocorticoids are capable of regulating expression of pro-inflammatory cytokines but the precise mechanisms remain unknown. The acute stress induced repressive histone modification histone H3 lysine 9 trimethyl (H3K9me3) regulates retrotransposon (RT) expression. RT expression in neurodegenerative diseases such as macular degeneration has been associated with the immune response (i.e NLRP3 complex assembly) however, these mechanisms have yet to be understood within the brain (Tarallo et al., 2012). The NLRP3 inflammasome, a multiprotein complex made up of NLRP3, caspase-1 and ASC proteins, facilitates the production of mature pro-inflammatory cytokines. Glucocorticoids (e.g. corticosterone in the rat) are released from the adrenal glands, and circulate throughout the body and brain binding to glucocorticoid receptors (GRs). In the rat, acute restraint stress increases H3K9me3 within the hippocampus, accumulating at RTs thereby decreasing RT expression. RT abundance has been linked to the NLRP3 inflammasome activation. Data from acute corticosterone (CORT) treated-adrenalectomized animals supports the idea that CORT is sufficient for increased hippocampal H3K9me3 within the CA1 and DG (n=6, CA1: $p<.05$, DG: $p<.01$). CORT-induced hippocampal H3K9me3 is effectively blocked through pretreatment of chaetocin, a H3K9me3-specific methyltransferase inhibitor (n=6, CA1: $p<.05$, DG: $p<.01$). *In vitro*, CORT dynamically regulates RT expression -increasing expression acutely and repressing expression via H3K9me3 upon depletion (Bartlett and Hunter, 2017). Our data shows that in the acute CORT treated rat, blocking CORT-induced H3K9me3 via chaetocin co-treatment is permissive for NLRP3-

inflammasome assembly in the CA1 and DG regions of the hippocampus observed via immunofluorescent co-localization of NLRP3 and caspase-1 (n=6 per group, CA1: $p<.05$, DG: $p<.001$). We further investigated the relationship between H3K9me3 and NLRP3 complex activation with a new cohort of animals (n=6 per group, control, CORT alone and CORT/chaetocin co-treatment). We examined cleaved caspase-1, a required subunit of the NLRP3 inflammasome, within the CORT alone and chaetocin co-treatment group. We also examined RT expression within these groups to determine if chaetocin co-treatment correlated with increased RT expression. These results may suggest a novel molecular epigenetic link between stress and immune axes with significant implications for hippocampal function.

Disclosures: M.J. Clark: None. **A.A. Bartlett:** None. **R.G. Hunter:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.14/UU9

Topic: F.04. Stress and the Brain

Support: Merit Award BX002468

Title: 7,8-Dihydroxyflavone reduces anxiety and ameliorates GABAergic abnormalities in a mouse model of Gulf War Illness

Authors: *I. CARRERAS[1,2], T. J. MELLOTT[3], N. AYTAN[2], J.-K. CHOI[4], A. LIU[3], C. M. TOGNONI[1,3], J. K. BLUSZTAJN[3], B. G. JENKINS[4], A. DEDEOGLU[1,2]
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Abstract: In an effort to find early markers of Gulf War Illness (GWI) to efficiently screen therapies in preclinical trials, we have used a validated mouse model of GWI that is based on exposure to relevant doses of pyridostigmine bromide (PB; a cholinesterase inhibitor), permethrin (PER), and DEET combined with behavioral stress. We found latent post-exposure markers of the illness: anxiety, brain neuroinflammation, cholinergic, GABAergic, and neurotrophic factor abnormalities. In the current study, we have used this mouse model of GWI to test the effects of 7,8-dihydroxyflavone (7,8-DHF), a TrkB agonist that mimics BDNF signaling. Adult male and female mice (70 days old) were exposed daily to PB, PER, DEET, and 5 min of restraint stress for 28 days or exposed to vehicle only (unexposed control). Two months later, mice were orally treated with 7,8-DHF for 1 month. At the end of treatment, anxiety-like behavior was assessed using the elevated plus maze, after which mice were euthanized and brains collected for analysis by Western blot and *in vitro* magnetic resonance spectroscopy

(MRS). Western blot analysis of hippocampal extracts showed that treatment with 7,8-DHF resulted in a significant increase in phosphorylated TrkB (p-TrkB) levels with no effect on the levels of full length TrkB or the truncated form of the receptor, indicating successful activation of the BDNF-TrkB signaling pathway. In addition, we found that treatment with 7,8-DHF neutralized the increased levels of anxiety that were detected in mice following exposure to GW-associated chemicals and stress. We also detected decreased levels of GAD67 protein, the rate limiting enzyme in the synthesis of GABA, in the hippocampus in response to chemical exposure and stress, which were restored by treatment with 7,8-DHF. However, by *in vitro* MRS we detected a decrease (−19.7±2%; $p < 0.01$) in NAA (a marker of neuronal health), and GABA (−17.3±4%; $p < 0.05$) neither of which were affected by 7,8-DHF. Our results show that 7,8-DHF treatment can alleviate some of the anxiety-related changes observed in this mouse model of GWI and suggest that additional research is needed to determine if 7,8-DHF treatment alone or in combination with other treatments can be an effective strategy for treating GWI.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.15/UU10

Topic: F.04. Stress and the Brain

Support: NSERC Discovery Grant 2015-04537

Title: MircoRNA regulation by stress and estradiol in the hippocampus of the mouse

Authors: *K. C. NICHOLSON[1], C. E. CREIGHTON[1], E. R. MARTIN[2], J. LAMARRE[1], N. J. MACLUSKY[1]
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Abstract: Stress and gonadal hormones exert sexually-differentiated effects on the structure and function of the hippocampus. While several different receptors and cell signaling pathways have been implicated in these interactions, the underlying mechanisms have yet to be clearly delineated. MicroRNAs (miRNAs), small 19-23 nucleotide non-coding RNAs that are involved in post-transcriptionally regulating gene expression, are known to regulate synaptic plasticity and other important neuronal functions. Furthermore, miRNAs have been proposed to exert effects on estrogen receptor expression, while estradiol has been shown to alter the expression of specific miRNAs in non-neural tissues. Acute and chronic stress exposure has been shown to exert effects on miRNA regulation within stress-sensitive regions of the brain, such as the hippocampus. However, the relationship between the effects of estradiol and stress on miRNA

expression in the brain has yet to be determined.
To explore the potential role of miRNAs as mediators of estradiol and stress hormone interactions, two month old male and female CD1 mice were gonadectomized and randomly allocated to four treatment groups 7-10 days later: (1) control untreated, (2) handed but non-injected, (3) subcutaneously injected with 3 μg/kg estradiol, or (4) subcutaneously injected with the sesame oil injection vehicle (n=9-11 mice per group). Six hours following treatment, mice were sacrificed for brain extraction, removal of the hippocampus, and subsequent isolation and quantification of RNA. Using next-generation sequencing for small RNAs followed by RT-qPCR, differences in miRNA expression levels were analyzed and compared relative to untreated ovariectomized controls. Estradiol treatment significantly reduced expression of miR-204-5p when compared to control and vehicle treated females. In addition, significant sex differences were noted in expression of miR-34c-5p and miR-148a-3p, with both targets being higher in males than females. Sex differences were also noted between miR-216b and miR-217-5p in vehicle-treated and handled groups, respectively (n=5-12 mice per group), with females showing significantly higher expression than males. These differences were eliminated in groups that had received estradiol injection. These results suggest that interactions between estradiol and stress hormones in the regulation of specific miRNA expression may contribute to sex differences in hippocampal function.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.16/UU11

Topic: F.04. Stress and the Brain

Support: Hope for Depression Research Foundation
American Foundation for Suicide Prevention

Title: Role for mGlu2 receptors in a circuit signaling mechanism underlying rapid behavioral responses to LAC

Authors: *B. BIGIO[1], J. DOBBIN[1], P. DE ANGELIS[1], H. M. CATES[2], O. ISSLER[3], E. J. NESTLER[4], B. S. MCEWEN[1], C. NASCA[1]
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Abstract: Regulation of the glutamatergic signaling is increasingly recognized as a promising mechanism for fast-acting medications to treat major depressive disorder (MDD). Our group and others have shown that supplementation of acetyl-L-carnitine (LAC) leads to rapid behavioral responses that have been observed after few hours to days of administration. The mechanism of action of LAC has been suggested to involve increased transcription and translation of the metabotropic glutamate receptors-2 (mGlu2Rs), a regulator of spontaneous glutamate release, in the ventral Hip (vHip). Supplementation with LAC also increases expression of the neurotrophin BDNF in the medial prefrontal cortex (mPFC). Here we studied whether targeting mGlu2Rs in the vHip with the use of LAC regulates gene expression in the mPFC. Our findings confirmed previous work from our group and others by showing that short-term treatment with LAC reduced immobility at the forced swim test (FST) as well as increased time in the social zone at the three-chamber sociability test (ST) in wild-type (WT) male mice. As previously showed, the behavioral responses to treatment with LAC are associated with up-regulation of mGlu2Rs transcripts and proteins in the vHip. Preliminary RNAseq data and bioinformatics analyses show transcriptome-wide alterations in the mPFC of WT male mice in response to short-term treatment with LAC (adjusted-$p < 0.15$, fold change >1.3) or vehicle. Among these genes, WT mice receiving treatment with LAC showed increased transcripts of synaptic plasticity markers, including the neurotrophin BDNF in the mPFC as compared to age- and sex-matched WT mice that received vehicle. Using gene ontology (GO) analyses, we found that both WT mice receiving treatment with LAC showed altered transcription of several signaling pathways with meaningful gene categories that include for example synaptic transmission, metabolic processes and immune responses. Expressional and functional validation of the most significant genes is underway in the circuit between the vHip and mPFC. This data shows that the action of LAC involves key synaptic plasticity markers that are known targets for the rapid antidepressant action of ketamine. Therefore, this data suggests that regulation a yet-to-be-determined common pathway in a circuit between the vHip and mPFC may be required for rapid antidepressant action.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.17/UU12

Topic: F.04. Stress and the Brain

Support: Hope for Depression
Robertson Foundation
Pritzker Neuropsychiatric Disorders Research Consortium

Title: Acetyl-L-carnitine deficiency in patients with major depressive disorder: Implications for treatment resistant depression

Authors: *C. NASCA[1], B. BIGIO[1], F. LEE[2], S. YOUNG[3], M. KAUTZ[4], A. COCHRAN[2], J. BEASLEY[3], A. A. MATHE[5], J. KOCSIS[2], J. MURROUGH[4], B. S. MCEWEN[1], N. L. RASGON[6]
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Abstract: The lack of biomarkers to identify target populations greatly limits the promise of precision medicine for major depressive disorder (MDD), a primary cause of ill health and disability. The endogenously produced molecule acetyl-L-carnitine (LAC) is critical for hippocampal function and several behavioral domains. Converging evidence has demonstrated that supplementation with LAC has rapid antidepressant responses via epigenetic regulation of hippocampal glutamatergic function in rodents with a deficiency in the levels of the endogenously-produced LAC in plasma and mood regulatory brain regions. Responses to standard antidepressant medications required repeated weeks of administration in the experimental models. This mechanistic model led us to evaluate LAC levels in humans with major depressive disorder (MDD). Our data show that LAC levels, and not the levels of free-carnitine, were decreased in patients with MDD as compared to age- and sex-matched healthy controls in two independent study centers. Furthermore, the degree of LAC deficiency reflected both the severity and age of onset of MDD. In a subgroup of patients defined for history of treatment resistant depression (TRD), we find that decrease in LAC was larger and was associated with history of childhood trauma, and specifically emotional neglect. Supported by an initial validation in two independent cohorts, these findings suggest that the LAC deficiency may aid with the diagnosis of a clinical phenotype of depression. Further studies of LAC as a therapeutic target may help to define individualized treatments in biologically-based depression subtype consistent with the spirit of precision medicine.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.18/UU13

Topic: F.04. Stress and the Brain

Support: Hope for Depression Research Foundation
Rockefeller Family Grant

Title: Rapid behavioral responses to treatment with ketamine or acetyl-L-carnitine in males and females

Authors: *J. DOBBIN, B. BIGIO, P. DE ANGELIS, D. ZELLI, T. LAU, B. S. MCEWEN, C. NASCA
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Abstract: Currently available antidepressants that mainly act through the monoamine system have several limitations, including a long therapeutic lag. Pioneering research has demonstrated that ketamine, a noncompetitive NMDA antagonist, has fast-acting antidepressant efficacy. However, ketamine faces known roadblocks that limit its use, highlighting that there remains a need for safe, fast-acting treatments for major depressive disorder (MDD). Recently, our group and others have shown that administration with acetylcarnitine (LAC) has rapid and enduring antidepressant efficacy in rodent with a deficiency in the endogenously-produced levels of LAC. LAC is an essential molecule for mitochondrial functioning and a biomarker of insulin resistance. The mechanism of action of LAC has been suggested to involve increased transcription and translation of the mGlu2 receptors, a glutamate inhibitor in the ventral hippocampus (vHip). Here, we compared the antidepressant efficacy of LAC to that of ketamine in ameliorating the prolonged effects of chronic stress in male and female mice. We quantified the effects of LAC and ketamine on two core behavioral domains of MDD, that is sociability and psychomotor behavior, in either the chronic restraint stress (CRS) paradigm in both males and females or the chronic social defeat stress (SDS) in males. Mice that underwent CRS paradigms showed decreased time spent in the social interaction zone of sociability tests and increased immobility in the forced swim test (FST) as compared to unstressed age and sex matched controls. These behavioral phenotypes were brought closer to those of control animals either by treatment with ketamine (10 mg/kg, IP injection) or with LAC (3% in water, oral intake; 100 mg/kg, IP injection), suggesting rescue from the depressive-like phenotype. Similarly, in male mice subjected to SDS, sociability was improved by either ketamine or LAC administration when compared to that of stressed vehicle-treated controls, with animals treated with LAC showing a more dramatic improvement. Our work suggests that LAC is superior to ketamine in ameliorating depressive-like symptoms in experimental rodent models. Further research should focus on elucidating the mechanisms of LAC action, including the suggested role of mGlu2 receptors in the vHip. Future research should also continue to investigate the molecular targets of ketamine, including any effect it may have on mGlu2. Improved understanding of fast-acting antidepressants will allow for the development of more effective rapid and target-directed treatments.

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Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.19/UU14

Topic: F.04. Stress and the Brain

Support: NIMH R01 086828

Title: The fast antidepressant actions of MRK-016 on anhedonia and synaptic function are mediated by binding at the benzodiazepine site of the $GABA_AR$

Authors: *T. TROPPOLI[1], P. ZANOS[2], T. GOULD[3], S. THOMPSON[1]
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Abstract: Major depression is a common debilitating psychological disorder. Current clinical treatment options are primarily reuptake inhibition of monoamine neurotransmitters, but these drugs are only effective in half of patients and have a delayed onset of therapeutic action. Negative allosteric modulators of $GABA_A$ receptors containing α5 subunits (GABA-NAMs), such as MRK-016, exhibit rapid antidepressant properties in preclinical models of stress-induced anhedonia and restore stress-weakened glutamatergic excitation at hippocampal temporoammonic-CA1 synapses (TA-CA1). Here we test the prediction that the anti-anhedonic and synaptic responses to these compounds require binding to the benzodiazepine binding site of $GABA_ARs$. Six-week old, male C57BL/6 mice were subjected to a 10 day chronic stress paradigm, sufficient to induce anhedonia, as assayed with sucrose preference and female urine sniff tests. IP injections of MRK-016 (3mg/kg) significantly reversed deficits in these reward behaviors, whereas vehicle (DMSO) or the benzodiazepine antagonist flumazenil (20mg/kg) alone did not. The strength of TA-CA1 synaptic transmission was increased in stressed animals treated with MRK-016 compared to those given vehicle or flumazenil alone, as quantified via fEPSP AMPA:NMDA ratios. In contrast, MRK-016 failed to restore reward-seeking behavior or TA-CA1 synaptic strength in stressed animals pretreated with flumazenil. Unstressed animals showed no change in reward-seeking behavior or AMPA:NMDA ratios following treatment with MRK-16. We have suggested previously that transient GABA-NAM - induced increases in EEG gamma-power in mood-relevant brain structures is responsible for its persistent antidepressant activity. Preliminary results indicate that that the MRK-016-induced increase gamma-power was also inhibited by pretreatment with flumazenil. We conclude that GABA-NAMs act via the benzodiazepine binding site of the $GABA_AR$ to produce a transient increase in correlated neuronal discharge at gamma frequencies and that this correlated discharge induces intrinsic activity-dependent synaptic strengthening in critical reward circuits that account for its anti-anhedonic actions. Together, these data provide additional support that alpha5 selective GABA-

NAMs have promise as novel, fast-acting antidepressants and provide new clarification for their mechanism and site of action.

Disclosures: T. Troppoli: None. **P. Zanos:** None. **T. Gould:** None. **S. Thompson:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.20/UU15

Topic: F.04. Stress and the Brain

Support: NIH R01MH086828

Title: The antidepressant effects of the alpha5 subunit-selective negative allosteric modulators of GABA-A receptors in rodent models of depression

Authors: *A. M. BAILEY[1], K. BELL[1], J. LYNN[1], M. MADDEN[1], M. STEYERT[1], S. ZHANG[1], S. M. THOMPSON[2]
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Abstract: Negative allosteric modulators of GABA-A receptors (GABA-NAMs) with an alpha5 subunit (such as L-655,708) have been reported to produce rapid antidepressant effects in rodent models of anhedonia. We examined multiple aspects of L-655, 708 including sex specific behavioral differences, long-lasting effects of L-655, 708 and important neuroanatomical areas. As expected, in male rodents chronic exposure to stress significantly reduced sucrose intake compared to control animals. However, sucrose intake in female rodents significantly increased with stress exposure. One injection of L-655, 708 (0.7mg/kg) reversed sucrose intake patterns in both male and female chronically stressed animals within 24 hours normalizing the intake to that of control animals. In the forced swim test one injection of L-655, 708 significantly reduced immobility time in CUS exposed females compared to vehicle injected animals 24-hours following injection, an effect previously reported in male rodents. Additionally, we found the antidepressant behavioral effects of L-655, 708 to persist in measures of social interaction and sucrose intake for up to one week despite continued exposure to chronic stress.

Disclosures: A.M. Bailey: None. **K. Bell:** None. **J. Lynn:** None. **M. Madden:** None. **M. Steyert:** None. **S. Zhang:** None. **S.M. Thompson:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

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Program #/Poster #: 317.21/UU16

Topic: F.04. Stress and the Brain

Support: K99 MH108719
K01 AG054765
R37 MH068542,
R01 MH083862;
R01 AG043688
R01 295 NS081203
T32 MH01574

Title: Inhibiting ventral dentate gyrus activity reduces anxiety-like behavior

Authors: *C. ANACKER[1], V. M. LUNA, 10032[1], G. STEVENS[1], A. MILETTE, 10032[1], R. SHORES, 10032[1], B. CHEN, 10032[1], R. HEN[2]
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Abstract: The hippocampus is crucially involved in stress responses and emotional behavior. Within the dentate gyrus of the hippocampus new neurons are being generated during adulthood, but how these new cells contribute to dentate gyrus function remains elusive. Here, we exposed transgenic iBax mice with increased adult neurogenesis (1.8±0.2 fold) to chronic social defeat stress (10 days) and tested anxiety-like behavior in a social interaction test. We then virally-expressed the Ca^{2+} indicator, GCamp6f, in mature granule cells of the ventral dentate gyrus and we used *in vivo* Ca^{2+}-imaging with head-mounted miniature microscopes (Inscopix, CA) to investigate dentate gyrus activity in response to stress. Wild-type mice spent less time interacting with a novel mouse following chronic stress than undefeated control mice (***p=0.001, n=12-14 mice), while iBax mice with increased neurogenesis spent as much time interacting with a novel mouse as controls. Social defeat increased the number of dentate gyrus granule cells that selectively respond to stressful attacks in both wild type mice (by 34%) and in iBax mice (by 29%). However, the Ca^{2+} activity of these "attack"-selective cells was decreased in iBax mice with increased neurogenesis (U=12725, ***p<0.0001; n=169-211 cells). The number of cells that were selectively active during periods at which no attacks occurred were unaffected by stress and their Ca^{2+} activity was not different in iBax mice with increased neurogenesis. Direct inhibition of the ventral dentate gyrus by activating a virally-expressed inhibitory DREADD receptor (hM4Di) during stress reduced anxiety-like behavior in the social interaction test, mimicking the effect of neurogenesis (*p=0.01, n=9-10). We then activated the 5-HT1A receptor with the agonist 8-OH-DPAT in transgenic mice expressing 5-HT1A only in the dentate gyrus.

Activation of 5-HT1AR during chronic stress also silenced dentate gyrus activity and reduced social avoidance in the social interaction test (**p=0.009, n=18). Our findings suggest that adult-born neurons in the hippocampus inhibit a specific subpopulation of "stress-responsive" cells in the ventral dentate gyrus to reduce anxiety-like behavior, and that direct inhibition of the dentate gyrus, potentially by pharmacologically activating 5-HT1A receptors, could represent a new strategy to treat stress-induced psychopathology.

Disclosures: C. Anacker: None. **V.M. Luna:** None. **G. Stevens:** None. **A. Milette:** None. **R. Shores:** None. **B. Chen:** None. **R. Hen:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.22/UU17

Topic: F.04. Stress and the Brain

Support: Brain and Behavior Foundation
Quinnipiac University

Title: Maternal separation induces inflammation, microglia activation and changes in actin-binding proteins in the hippocampus of rats Maternal separation induces inflammation, microglia activation and changes in actin-binding proteins in the hippocampus of rats

Authors: *A. J. BETZ[1], M. MIRRIONE[2], K. JONES[2], L. TELISKA[1], M. SZAHAJ[1], D. MATINHO[1], T. ZARIN[1], J. SCHURICK[3]
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Abstract: Early life experiences have pronounced effects on brain function and behavior. Maternal separation in rodents is a widely used animal model used to induce early-life stress. This model has reliably demonstrated an increased risk of depressive-like behavior later in life. Clinically, adversity in early life increases the risk for the development of psychiatric disorders, such as Major Depressive Disorder (MDD), in adulthood. Mood disorders produce changes in neurochemistry and brain structure. Patients with MDD have exhibited learning and memory deficits. In addition to changes in hippocampal volume, patients with MDD have been found to have elevated levels of peripheral and central inflammatory factors including IL-6 and TNFa. Microglial activity has been associated with atrophy and inflammatory signaling in brain regions affected by MDD. Given that patients with MDD display alterations in hippocampal circuits, we hypothesized that early life adversity would be characterized by increased protein expression of inflammatory markers, morphological changes in microglia and dynamic changes in cellular matrix activity in the hippocampus. In the present study, Sprague Dawley male and female pups were separated from PND 2 to PND 14 for three hours a day with and without indirect (in utero

and lactational) minocycline. A control condition of non- separated pups was maintained. First, we examined behavioral tasks during adolescence and found separated offspring spent more time in closed arms of an elevated plus maze. Second, we found preferential activation of RelA expression and other inflammatory markers in distinct compartments of the hippocampus via Western Blot. Next, to understand the functional connectivity of our findings, we used immunofluorecence to examine the morphology of Iba1 positive cells. Finally, cytoskeletal dynamics of microglia play an active role in the response to stress as we found alterations in cofilin-related proteins. Overall, our results may provide insight to the molecular mechanisms responsible for inflammation and cellular reorganization in cortico-limbic circuits related to MDD and early life adversity.

Disclosures: A.J. Betz: None. **M. Mirrione:** None. **K. Jones:** None. **L. Teliska:** None. **M. Szahaj:** None. **D. matinho:** None. **T. Zarin:** None. **J. Schurick:** None.

Poster

317. Stress-Modulated Pathways: Hippocampus

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 317.23/UU18

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH grant R01MH086828
NARSAD YI Award
NIH Grant T32 NS007375

Title: Strengthening of hippocampus-nucleus accumbens synapses underlies reward behavior and is deficient in depression

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Abstract: Rewards reinforce behaviors that promote survival. This creates strong evolutionary pressure to retain salient contextual information associated with these rewards. Changes in the drive to obtain rewards are observed in diseases such as addiction and depression. The neuronal circuits underlying the perception and processing of rewarding stimuli have been extensively examined, however, the requisite synapses and underlying neurophysiology involved in the encoding of contextual information within these circuits remains unknown. The hippocampus is a key brain region for processing and storing spatial information. It innervates the shell of the

nucleus accumbens (NAc), a structure that integrates information from multiple brain regions to process rewarding stimuli and convey signals to guide goal-oriented behaviors. The excitatory input from the hippocampus to the NAc is important for driving NAc activity, and modulation of the strength of this input may serve to regulate goal-oriented behaviors. Using *in vivo* electrophysiology and optogenetics, we demonstrate *in vivo* induction of long-term potentiation (LTP) at this synapse. Furthermore, this *in vivo* LTP is sufficient to drive conditioned place preference demonstrating an important role for plasticity at this synapse in the regulation of reward related behavior. We then used a chronic stress paradigm to induce depression-like behavior as measured by anhedonia. Using whole-cell electrophysiology, we observed a decrease in AMPA:NMDA ratio and LTP deficits specifically in D1-expressing medium spiny neurons in response to chronic stress. Additionally, exposure to chronic stress impaired hippocampus-NAc LTP-induced conditioned place preference. Taken together, this suggests that chronic stress weakens these synapses. The behavioral and electrophysiological changes induced by chronic stress exposure were rescued with antidepressant treatment. This work defines a specified neuronal circuit responsible for regulating contextual reward behavior and furthers our understanding of excitatory synaptic strength as a critical mediator of this process. Understanding the neuronal changes that underlie depression and antidepressant response will provide key insight into developing new, more effective treatments for this disorder.

Disclosures: T.A. LeGates: None. **M.D. Kvarta:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asulon Therapeutics. **J.R. Tooley:** None. **T.C. Francis:** None. **M. Lobo:** None. **M. Creed:** None. **S.M. Thompson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asulon Therapeutics.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.01/UU19

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSERC/ 402176
NSERC/ 05403
FRQS/ formation de maîtrise
NSERC/ BESC M

Title: Contribution of the nucleus basalis of Meynert to cerebral blood flow responses in the ipsilateral but not controlateral primary somatosensory cortex during nociceptive processing

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Abstract: Neurovascular coupling is a physiological process that involves a local hemodynamic response associated with surrounding neuronal activity. This coupling in mainly driven by glucose metabolism and the release of vasoactive agents, such as nitrite oxide. However, cerebral blood flow (CBF) is also regulated by the nucleus basalis of Meynert (NBM), which sends cholinergic projections to the cortex. Accordingly, the NBM regulates CBF independently of local neuronal activity in the cortex during somatosensory stimulation. However, the role of the NBM in CBF regulation during nociceptive stimulation associated with changes in mean arterial pressure has never been investigated. This is critical for neuroimaging of nociceptive and pain-related brain activity. Thus, the objective of this study was to investigate the contribution of the NBM to the CBF responses in the primary somatosensory cortex during nociceptive processing.
All experimental procedures were approved by the Université du Québec à Trois-Rivières animal care committee, and were in accordance with the guidelines of the Canadian Council on Animal Care. Experiments were conducted in 8 male Wistar rats under isoflurane anaesthesia (1.2%). After thinning the skull, cerebral blood flow of the entire cortex was examined using laser speckle contrast imaging. CBF responses to graded electrical stimulation of the right sciatic nerve was compared between intact conditions and after electrolytic lesion of the left NBM. For both conditions the stimulation protocol included 10 intensities ranging between 0.05 and 9.6 mA.
Electrical stimulation produced intensity-dependent increases in mean arterial pressure ($p<0.001$) and these changes were almost identical between the intact condition and after NBM lesion ($p=0.96$). In both conditions, electrical stimulation also produced intensity-dependent CBF responses ($p<0.001$) that were greater in the primary somatosensory cortex contralateral to the stimulation compared with the ipsilateral one ($p=0.004$). After NBM lesion, CBF responses were decreased in the primary somatosensory cortex ipsilateral to NBM lesion compared with the intact condition ($p=0.02$). However, CBF responses contralateral to NBM lesion were not significantly different between conditions ($p=0.46$).
These results indicate that NBM contributes to CBF responses to nociceptive stimulation in the ipsilateral but not controlateral primary somatosensory cortex and these effects are not confounded by changes in mean arterial pressure. This highlights the importance of NBM integrity for nociceptive and pain-related hemodynamic responses in the primary somatosensory cortex.

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Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.02/UU20

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: China Scholarship Council/University of Edinburgh
Alzheimer's Society

Title: Bilateral common carotid artery stenosis impairs glymphatic function

Authors: *M. LI[1], A. KITAMURA[1,2], J. BEVERLEY[1], J. KOUDELKA[1], J. DUNCOMBE[1], R. N. KALARIA[3], R. O. CARARE[4], J. J. ILIFF[5,6], K. HORSBURGH[1]
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Abstract: Cerebral hypoperfusion, by large vessel occlusion and stenosis is a key mechanism contributing to vascular cognitive impairment (VCI). Our previous work showed bilateral common carotid stenosis (BCAS), in a mouse model, leads to gliovascular disruption and increased vascular amyloid accumulation (Holland et al., 2015 and Salvadores et al., 2017). The paravascular pathway (glymphatic system) is a brain-wide pathway for waste clearance via the gliovascular network. It has been reported to be important in the removal of metabolic waste products and solutes such as amyloid-β and tau. We hypothesised that glymphatic function would be impaired in a model of carotid stenosis and further exacerbated in the presence of amyloid. Male wild-type and Tg-SwDI (a model of microvascular amyloid) mice were subjected to BCAS or sham surgery (n=7-10 per group), and at 3 months after hypoperfusion glymphatic function and resting cerebral blood flow (rCBF) were evaluated. We demonstrate that BCAS causes a regional reduction of paravascular cerebrospinal fluid (CSF) tracer influx in the dorsal lateral cortex (DLCTX) and CA1-DG molecular layer (CA1-DG) in parallel with reduced cerebral blood perfusion. To further investigate the mechanisms that may lead to these changes we measured, in a multiphoton study, the pulsation of cortical vessels and found a significant decrease in pulsation in pial arteries. This data suggest that carotid stenosis may influence VCI by an effect on vessel pulsation and impaired paravascular pathway.

Disclosures: M. Li: None. **A. Kitamura:** None. **J. Beverley:** None. **J. Koudelka:** None. **J. Duncombe:** None. **R.N. Kalaria:** None. **R.O. Carare:** None. **J.J. Iliff:** None. **K. Horsburgh:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

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Program #/Poster #: 318.03/UU21

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01NS078168
NIH Grant R01NS079737

Title: Noradrenergic modulation of neurovascular coupling in awake behaving mice

Authors: *Q. ZHANG[1], K. W. GHERES[2], P. J. DREW[1,3,4]
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Abstract: Hemodynamic signals are widely used to infer neural activity in functional brain imaging techniques (e.g., fMRI). Previous work (Huo et al., J. Neurosci., 2014) has shown that neural activity in the frontal cortex increases without corresponding changes in hemodynamic signals during locomotion, and we sought to mechanistically understand this decoupling. We hypothesized that neuromodulatory input, specifically a noradrenergic (NA) vasoconstrictory signal, interact with neural activity-driven vasodilation to shape the hemodynamic response. Here, we investigated the NA modulation of neurovascular coupling by measuring hemodynamic responses (intrinsic optical signal imaging) and neural activity (multi-laminar linear electrode arrays) to voluntary locomotion in awake, head-fixed mice. Noradrenergic tone was decreased or increased by systemic administration of antagonists of α1- (prazosin) and α2-adrenoceptors (atipamezole), respectively. Compared to vehicle controls, cerebral blood volume changes during locomotion were increased by prazosin in both the frontal and somatosensory cortices, while atipamezole decreases the amplitude the locomotion-related response in the somatosensory cortex. These results suggest that in addition to local vasodilatory signals released from neurons and astrocytes, changes in neuromodulatory tone (especially noradrenergic tone) play an important vasoconstrictory role in shaping hemodynamic signals during behavior. We are exploring the role of peripheral and central noradrenergic innervation on controlling the hemodynamic response using intracortical infusion of noradrenergic antagonists and performing an acute chemical sympathectomy. These results will elucidate the role of NA effects on hemodynamic signals.

Disclosures: Q. Zhang: None. **K.W. Gheres:** None. **P.J. Drew:** None.

Poster

318. Brain Blood Flow

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Program #/Poster #: 318.04/UU22

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01NS078168
NIH Grant R01NS079737

Title: Quantifying the neural and non-neuronal components of inter-hemispheric hemodynamic correlations

Authors: *K. L. TURNER[1,2], A. T. WINDER[2], P. J. DREW[1,2,3]
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Abstract: Hemodynamic signals in the brain are used to infer neural activity, and strong correlations in hemodynamic signals between bilateral cortical areas have been observed in the absence of a task (‘functional connectivity during the resting-state’). Understanding the relationship between these bilateral hemodynamic signals and the underlying neural activity is important for the interpretation of these hemodynamic signals. Previous work has proposed that hemodynamic signals are a sum of a neurally-evoked component and a putatively non-neuronal component. Importantly, the relative contributions of the neural and non-neuronal components depends on the behavioral state of the animal. Here we investigate the role of behavior and neural activity in sculpting bilateral hemodynamic signals. We used intrinsic optical signal imaging through chronically implanted thinned-skull windows to measure bilateral changes in cerebral blood volume in parallel with electrophysiological recordings in the somatosensory cortices of awake mice. We continuously monitored both animal motion and whisking behavior to classify behavioral state. We also stimulated the whiskers to compare the strength of neurovascular coupling in the evoked condition with neurovascular coupling in the resting state. To test the influence of the neural activity in driving bilateral hemodynamic correlations, we suppressed local neural activity in the somatosensory cortex of one hemisphere, allowing us to directly measure the strength of non-neuronal correlations between hemispheres. These experiments will elucidate the neural contribution to bilateral functional connectivity across behavioral states.

Disclosures: K.L. Turner: None. **A.T. Winder:** None. **P.J. Drew:** None.

Poster

318. Brain Blood Flow

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Program #/Poster #: 318.05/VV1

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Alzheimer's Association NIRG award (2016-NIRG-397149)
NIH/NINDS NS096997
NIH/NINDS F30 NS096868

Title: Pericyte structural plasticity in the adult mouse brain

Authors: *A. Y. SHIH[1,3], D. HARTMANN[4], A.-A. BERTHIAUME[2,4]
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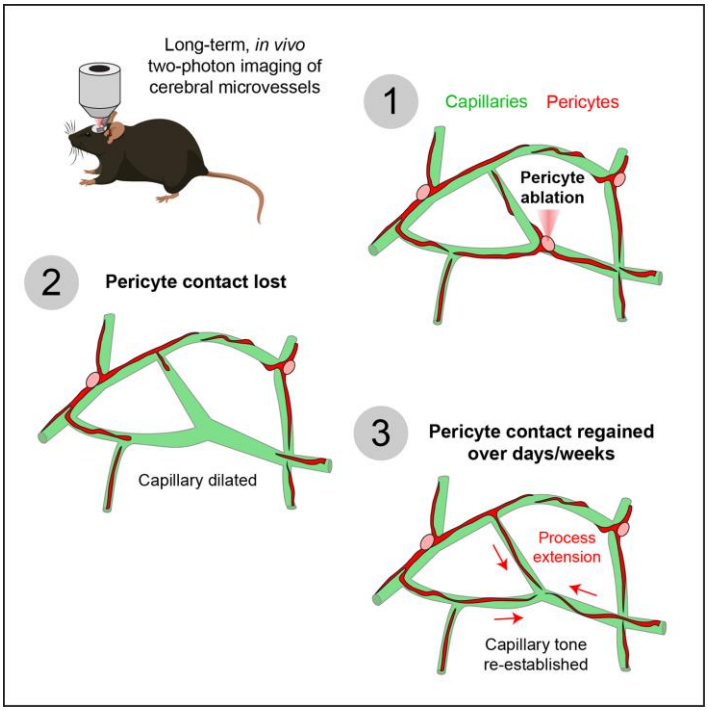
Abstract: Direct contact and communication between pericytes and endothelial cells is critical for maintenance of cerebrovascular stability and blood-brain barrier function. Capillary pericytes have thin processes that reach hundreds of micrometers along the capillary bed. The processes of adjacent pericytes come in close proximity but do not overlap, yielding a cellular chain with discrete territories occupied by individual pericytes. Little is known about whether this pericyte chain is structurally dynamic in the adult brain. Using *in vivo* two-photon imaging in adult mouse cortex, we show that while pericyte somata are immobile, the tips of their processes undergo extensions and/or retractions over days. The selective ablation of single pericytes provoked exuberant extension of processes from neighboring pericytes to contact uncovered regions of the endothelium. Uncovered capillary regions had normal barrier function, but were persistently dilated until pericyte contact was regained. Pericyte structural plasticity may be critical for cerebrovascular health and warrants detailed investigation.



Disclosures: A.Y. Shih: None. **D. Hartmann:** None. **A. Berthiaume:** None.

Poster

318. Brain Blood Flow

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Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: JSPS Grant-in-Aid for Young Scientists(B) 16K16652
JSPS Grant-in-Aid for Scientific Research(A) 18H03780
The VLSI Design and Education Center (VDEC), University of Tokyo, in collaboration with Cadence Design systems, Inc.

Title: A chronic blood-flow imaging device for a small animal's brain in a behavior experiment

Authors: *M. HARUTA[1], Y. KURAUCHI[4], A. KIMURA[2], Y. OHTA[6], T. NODA[3], K. SASAGAWA[3], T. TOKUDA[6], H. KATSUKI[5], J. OHTA[7]
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[5]Kumamoto Univ., Kumamoto, Japan; [6]Nara Institue of Sci. and Technol., Ikoma, Nara, Japan; [7]Nara Institue of Sci. and Technol., Ikoma, Japan

Abstract: Many studies on blood-flow of the cortical vascular that relates to that of the brain activity have been reported. However, it is difficult to continuously measure brain activity and blood-flow in a small animal. Wehave developed a chronic blood-flow imagingdevice for continuously observing brain activity and blood-flow in a small animal brain.We already succeeded to observe blood-flow on the brain surface using the green LEDs with an emission wavelength of 535 nm, at which one of the absorption peaks of hemoglobin in blood appears [1]. The developed device included a CMOS image sensor mounted on a small electronic substrate, a light source with green LEDs. This simple structure enabled us to measure brain blood-flow in a small animal. In this study, we have modified our previous device to perform a long-term measurement. We have improved devise's structure and developed an implantation method of a special chronic window in a small animal. The modified device measured the blood-flow changing with the LED light sources at a primary somatosensory cortex with stimulation. The new method allowed observation for more than one month in an animal. Next work, we will use this device to observe cerebrovascular disease in a behavioral experiment and evaluate of drug efficacy to the disease. All animal procedures conformed to the animal care and experimentation guidelines of the Nara Institute of Science and Technology. [1]M. Haruta, C. Kitsumoto, Y. Sunaga, H. Takehara, T. Noda, K. Sasagawa, T. Tokuda, J. Ohta, An implantable CMOS device for blood-flow imaging under freely moving experiments of rats, Jpn. J. Appl. Phys. 53(4S), pp.04EL05, 2014.

Disclosures: M. Haruta: None. **Y. Kurauchi:** None. **A. Kimura:** None. **Y. Ohta:** None. **T. Noda:** None. **K. Sasagawa:** None. **T. Tokuda:** None. **H. Katsuki:** None. **J. Ohta:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

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Program #/Poster #: 318.07/DP08/VV3

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: ERC Consolidator BrainMicroFlow 615102

Title: A new model for molecule delivery and clearance in brain microvascular system: Consequences of capillary occlusions in Alzheimer's disease

Authors: *M. BERG[1], O. BRACKO[2], Y. DAVIT[1], M. QUINTARD[1], N. NISHIMURA[2], C. B. SCHAFFER[2], S. LORTHOIS[1]
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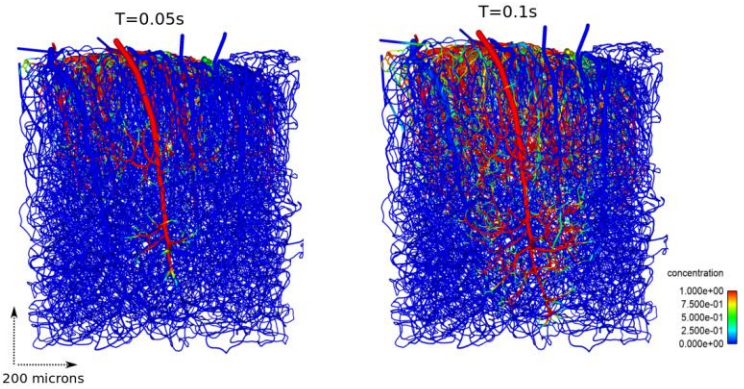
Abstract: The brain microvascular system is a key actor in Alzheimer's disease (AD) development. Indeed, a significant decrease of cerebral blood flow is the earliest biomarker of AD (Iturria-Medina Nat Com 2016).
In vivo TPLSM of cortical vasculature in APP/PS1 mice suggests the mechanism underlying the blood flow reduction is capillary occlusions. Leucocytes adhere to inflamed vessel walls and limit the flow (Cruz-Hernandez BioRxiv 2017).
The impact of capillary occlusions on blood flow has been quantified numerically in large (>10000 vessels) anatomical networks in humans and mice (Berg SFN 2017). The regional blood flow has been found to depend linearly with no threshold effect on the fraction of capillary occlusions, so that a small fraction of stalls (2-4%) yields a significant decrease in blood flow (5-12%).
Such flow decrease has a strong impact on nutrient delivery and waste clearance. That is why we devised a new model to study the effect of capillary stalling on molecule transport. The geometry of anatomical networks is too complex to use classic numerical approaches like finite elements. Instead, our model, inspired by pore-network approaches, reduces computational costs while capturing most of the underlying physics.
To derive this model, we apply upscaling methods (Davit Adv Wat Res 2013) to the 3D transport equations within each vessel to obtain 1D average equations along the axis. Contrary to previous models, this new formulation describes accurately radial concentration gradients, capturing effects like longitudinal dispersion.
We further use a Green's function formulation inpired by Secomb (ABE 2004) to calculate the concentration fields inside the tissue where diffusion and reaction occur. The coupling between vessels and tissues is modelled using a membrane condition (Fraser Micr 2015) representing the blood brain barrier.
This new molecule transport model is coupled with our previously validated blood flow model to examine the effects of capillary stalling on molecules delivery and clearance in transient and stationary regimes in anatomical networks.



Simulation of Intravascular transport of a passive tracer in a large mouse brain anatomical network (TPLSM post mortem acquisition, P.Tsai J. Neuroscience 2009).

Disclosures: M. Berg: None. **O. Bracko:** None. **Y. Davit:** None. **M. Quintard:** None. **N. Nishimura:** None. **C.B. Schaffer:** None. **S. Lorthois:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.08/VV4

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NASA Grant NNX13AD94G

Title: Head-down tilt as a model for intracranial pressure changes during spaceflight

Authors: *C. A. FULLER, E. L. ROBINSON, A. L. MCELROY, H. GOMPF, T. M. HOBAN-HIGGINS
Dept of Neurobiology, Physiol. & Behavior, Univ. of California, Davis, CA

Abstract: Introduction: In addition to the unweighting of the muscle and skeletal systems which normally counteract Earth's gravity, the microgravity environment of an orbiting spaceflight removes the hydrostatic pressure gradient, which produces a pronounced cephalic fluid shift. This study used the well-established rat hind-limb (HLS) suspension model to investigate the hypothesis that this fluid shift results in an increased intracranial pressure (ICP). Increased ICP could, in turn, underlie some of the ocular changes seen in astronauts during and following long-duration spaceflight. Methods: The HLS model, functionally equivalent to human head-down bedrest, was used to examine the relationship between cephalic fluid shifts, the regulation of intracranial pressure (ICP) and ophthalmic responses. In this model, a tail-suspension apparatus maintains the animal in a ~30° head down orientation. The forelimbs remain in contact with the floor and a pulley system allows the rat free access to all areas of the cage. Long Evans rats served as subjects for this project. Four groups of rats were studied to examine the effects of gender, age and hypercapnic exposure on the responses. In this presentation, we report on the results from rats 9 months of age at the start of the experiment. This group mimicked the age of the older astronauts studied in whom the prevalence of ocular changes was more prevalent. Subjects were studied for 180 days consisting of 90 days of HLS and then a 90-day post-HLS recovery period. An additional population of age-matched animals were similarly studied as cage controls. All animals had *ad lib* access to food and water. A 12:12 LD cycle was present. Biotelemetry (DSI) was used to record ICP, EEG, body temperature and activity. MRI imaging of the brain and eyes was performed at baseline and every 45 days thereafter. Intraocular pressure (IOP) was also measured. Ophthalmological measures included: OCT, fundoscopy, refraction and measurement of the length of the eyeball axis. Results and Conclusions: The 90-

day duration of the HLS was chosen to mimic an exploration class mission. A sustained small increase in ICP was seen during HLS. These observations agree with recent data collected from human subjects showing a small increase in ICP during spaceflight. Similarly, a small elevation of IOP was seen in the HLS subjects. MRI revealed reversible shifts in structures, including possible dilation of the optic nerve sheath and a dorsal shift in the location of the eyes. Differences in refraction, similar to those seen in astronauts, were also evident.

Disclosures: C.A. Fuller: None. **E.L. Robinson:** None. **A.L. McElroy:** None. **H. Gompf:** None. **T.M. Hoban-Higgins:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

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Program #/Poster #: 318.09/DP09/VV5

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH GrantNS100459
Foundation Leducq 16 CVD 05

Title: Regulating pericytes with optogenetics

Authors: *A. R. NELSON, Y. WANG, Z. ZHAO, B. ZLOKOVIC
Zilkha Neurogenetic Inst., USC, Los Angeles, CA

Abstract: Pericytes are essential for blood-brain barrier formation and maintenance, and perform multiple functions at the neurovascular unit including regulation of **1)** BBB permeability and bulk flow fluid transcytosis, **2)** capillary diameter, **3)** cerebral blood flow (CBF) velocity, **4)** angiogenesis (the formation of blood vessels from existing vessels) and subsequent microvascular stability and network architecture, **5)** phagocytotic clearance of toxic metabolites from the CNS, **6)** pro-inflammatory responses, e.g., leukocyte trafficking, and **7)** multipotent stem cell activity. However, whether or not pericytes are contractile cells has been a continuous debate dating back to 1873 when they were first described by Rouget as regularly arranged longitudinal amoeboid cells that have a muscular coat on capillaries. Here, we test the hypothesis that capillary level pericytes are contractile cells. To test this hypothesis, we developed a novel pericyte-specific Cre mouse using a double-promoter approach with both the *Pdgfrβ* and *Cspg4* promoters, crossed to either a Cre-dependent channelrhodopsin (ChR2) mouse with a YFP reporter gene, termed *Pericyte-ChR2*, or crossed to a Cre-dependent halorhodopsin (eNpHR3.0) mouse with a YPF reporter gene, termed *Pericyte-eNpHR3.0*. First, we confirmed that ChR2 and eNpHR3.0 are only expressed in pericytes by performing immunofluorescent staining with anti-CD13 antibody and which colocalized with the YFP reporter gene. Using the *Pericyte-ChR2* mice, we performed optogenetics experiments *in vivo* and found that stimulation of ChR2 caused

pericytes to contract and the underlying capillary to constrict. Using *Pericyte-eNpHR3.0* mice, we performed optogenetics experiments *in vivo* and measured changes to pericyte contractility and underlying capillary diameter.

Disclosures: A.R. Nelson: None. **Y. Wang:** None. **Z. Zhao:** None. **B. Zlokovic:** None.

Poster

318. Brain Blood Flow

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Program #/Poster #: 318.10/VV6

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant NS100459
NIH Grant AG039452
NIH Grant NS034467
NIH Grant AG023084
Foundation Leducq 16 CVD

Title: Development and validation of an open source software for brain perfusion imaging in rodents

Authors: *J. PRINCE[1], K. SHAH[1], M. D. SWEENEY[1], S. BARNES[2], M. T. HUUSKONEN[1], R. E. JACOBS[1], A. MONTAGNE[1], B. V. ZLOKOVIC[1]
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Abstract: Magnetic resonance imaging (MRI) can be used to image vascular dynamics, for instance, cerebral blood flow (CBF), to study normal brain physiology and pathophysiology with high temporal resolution. A technique to measure CBF established on MRI is dynamic susceptibility-contrast (DSC) perfusion, which comprises of intravenous injection of an exogenous contrast agent (CA), *i.e.*, gadolinium- or iron oxide-based compound. Various software packages do exist in the market, however, most of them only give relative/semi-quantitative CBF and CBV values. We insinuate a MATLAB program which is transfigured to a user-friendly interface, to convert the ΔR2* signal intensity recorded during a DSC scan into quantitative cerebral blood flow (CBF), cerebral blood volume (CBV), but also time-to-peak (TTP) and mean transit time (MTT) brain maps. We tested our DSC sequence and MATLAB program in chronic hypoperfusion (unilateral common carotid ligation) and Alzheimer's (*5xFAD*) mouse models. We found a severe CBF reduction (~-40-50%) in the ipsilateral hemisphere when compared to the contralateral side 24 hours post-carotid ligation. We also observed subtle regional CBF changes (~-10-30%) in 6-month-old Alzheimer's *5xFAD* mice compared to age-matched littermate controls in the primary somatosensory cortex, striatum, hippocampus and corpus callosum. Notably, we validated our DSC results in both models using

golden standard quantitative ^{14}C-iodoantipyrine (IAP) autoradiography using same exact animals for direct comparison. In conclusion, this is a unique perfusion user-interface which allows detection of subtle microcirculatory dysfunctions in the rodent brain. Moreover, our DSC method was corroborated using IAP method - a technique that takes about 3-4 weeks long for an *ex vivo* procedure contrary to a 2-min MR sequence for rapid DSC post-processing *in vivo*, which is also worthwhile for longitudinal studies. Finally, this software will be valuable not only in Alzheimer's Disease but also in Cerebral Small Vessel Disease and ischemic strokes involving vascular injuries and blood flow dysregulations.

Disclosures: J. Prince: None. **K. Shah:** None. **M.D. Sweeney:** None. **S. Barnes:** None. **M.T. Huuskonen:** None. **R.E. Jacobs:** None. **A. Montagne:** None. **B.V. Zlokovic:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.11/VV7

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Institutes of Health Grant R01NS101353

Title: Development of neural activity and neurovascular coupling in the somatosensory cortex of the awake mouse

Authors: *K. W. GHERES[1], P. J. DREW[2]
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Abstract: In the adult somatosensory cortex, behavior-driven increases in neural activity evoke large, spatially restricted changes in blood volume through arterial and venous dilations. However, as both human and rodent studies have shown neurovascular coupling can be weak, absent, or inverted in the juvenile brain we sought to understand how the stimulus evoked hemodynamic response matures during the postnatal period in mice. We investigated the underlying cellular mechanisms of neurovascular coupling in whisker barrel cortex using two-photon microscopy, intrinsic optical signal (IOS) imaging, and in-vivo extracellular electrophysiology. We found administration of the dilator isoflurane to P10 mouse pups was sufficient to induce arterial dilations, demonstrating arteries in the second postnatal week have resting muscle tone and are capable of dilating. In awake behaving animals, whisker stimulus increases neural activity in barrel cortex beginning in the second postnatal week, however, appreciable stimulus-evoked arterial dilations and blood volume increases do not appear until the third postnatal week, demonstrating an initial decoupling of the neurovascular relationship. After initiation of neurovascular coupling in the third postnatal week, increases in stimulus evoked

spike rates and local field potentials during the later juvenile period are matched by increases in stimulus evoked blood volume changes. This work suggests that prior to the third postnatal week, local neurons lack a fast acting mechanism to relay local neural activity to neighboring arteries, making it difficult to interpret hemodynamic signals in the developing brain.

Disclosures: K.W. Gheres: None. **P.J. Drew:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.12/VV8

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIMH R01 MH111438
NINDS R35 NS097265

Title: Extreme vasodynamics in cortex accompany REM sleep

Authors: *C. MATEO[1], D. KLEINFELD[2]
[1]Physics Dept, UCSD, La Jolla, CA; [2]Univ. of California at San Diego, La Jolla, CA

Abstract: Brain arterioles exhibit continuous dynamics, including changes in diameter linked to neuronal activity. We previously showed that slow (0.1 Hz) changes in the power of fast (gamma band) neuronal activity in the cortex of awake mice entrains the vasomotor activity of local arterioles and, consequently, modulates the oxygen supply to the parenchyma (Mateo et al. 2017). Here, we observed that the diameter of arterioles in the cortex undergo large phasic dilations that saturate at the maximum diameter of the vessels and last up to hundreds of seconds. The results from concurrently obtained electromyograms, local field potential measurements in cortex, behavioral monitoring, and assays of neuromodulators leads to the conclusion that this extreme dilation occurs when mice enter a rapid eye movement (REM) sleep phase. They persist as long as the REM sleep epoch and add to the wealth of phenomena that connect the sleep cycle with neuronal and metabolic changes (Petit and Magistretti, Neurosci 2016). We are currently exploring the source of this dilation. Vasoactive acetylcholine (ACh) and norepinephrine (NE) in subcortical neurons have been shown to have dramatic discharge pattern changes during sleep cycle (Boucetta et al. J Neurosci 2014). We monitored the volume transmission of ACh and NE with the use of implanted cell-based neurotransmitter fluorescent engineered reporters (CNiFERs) (Nguyen, Schroeder et al. Nat Neurosci 2010; Muller, Joseph et al. Nat Meth 2014). We find that ACh dramatically increases during REM sleep with a time lag of tens of s relative to the start of the large arteriole dilation. Local cortical ACh is therefore unlikely to be responsible for the onset of the arteriole dilation. The vasoconstrictor NE increases upon arteriole constriction and waking. We are currently measuring the activity of specific neuron populations

across vigilance states in superficial layers. Moving forward, we will use CNiFERs to probe dopamine and the neuropeptides NPY, orexin, and VIP, and other means to probe NO, during REM sleep. Changes in neuronal and vascular dynamics across brain states that may contribute to the restorative effects of sleep on cognition. Two hypotheses follow from our findings. One is the potential involvement of the dilation as a means to augment the clearance of metabolites in the brain during sleep (Xie et al. Science 2013). Toward this aim, we concurrently image the same vessel at different depths. A second hypothesis is that expansion of arteries increases oxygenation in the brain and compensates for metabolic load during REM sleep (Dash et al. Sleep 2012).

Disclosures: C. Mateo: None. **D. Kleinfeld:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

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Program #/Poster #: 318.13/VV9

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Wheaton College G.W. Aldeen Memorial Fund
Wheaton College Summer Research in Residence Program

Title: Effects of acute aerobic exercise on behavioral and prefrontal hemodynamic responses to a fatiguing cognitive task

Authors: *C. AUSENHUS[1], G. GOEBEL[1], K. HALLDIN[1], D. C. MONROE[3], B. HUNT[1], N. THOM[2]
[1]Applied Hlth. Sci., [2]Biol., Wheaton Col., Wheaton, IL; [3]Dept. of Neurol., UC Irvine, Irvine, CA

Abstract: Objectives: Despite having expended a significant amount of energy, people report lower levels of fatigue after exercise. We sought to explore the mechanisms that underlie this apparent paradox by measuring the effects of aerobic exercise on feelings of fatigue and prefrontal cortex (PFC) hemodynamic response during a fatiguing cognitive task. We hypothesized that exercise would reduce feelings of fatigue and improve task performance, changes that would be pronounced among those with elevated baseline fatigue, and partially explained by PFC hemodynamic response to the fatiguing task.
Methods: Healthy college students (16 males; 15 females) completed three lab visits: familiarization with graded exercise test, rest, and exercise sessions. A modified Paced Auditory Serial Addition Task (mPASAT) was administered before and after each Condition, with fNIRS recorded simultaneously. Self-reported fatigue, block-averaged reaction time weighted for accuracy (WRT) on the mPASAT, and block-averaged hemodynamic response (HbO, HbT, and HHb) were analyzed using an RM-ANOVA across Condition (Rest, Exercise), Time (Pre-, Post-

Condition), and Block (1, 2, 3), with Bonferroni corrections for multiple comparisons. Huyhn-Feldt was used to adjust F-values for differences in variance across Block levels. Pairwise comparisons were computed to decompose Block effects.
Results: Completing the mPASAT was fatiguing across Blocks independent of Condition and Time [$F(3,90)=55.77$, $p< 0.01$, $\eta^2=0.68$]. Fatigue increased across all blocks relative to pre-task baseline (all ps < 0.01). Weighted reaction time on the mPASAT decreased across Blocks independent of Condition and Time [$F(2,58)=16.42$, $p< 0.01$, $\eta^2=0.36$]. Pairwise comparisons revealed differences between blocks 1 and 2 ($p<.01$), blocks 1 and 3 ($p<0.01$), but not between blocks 2 and 3 ($p=0.11$). PFC hemodynamic responses to the mPASAT changed across Blocks independent of Condition and Time. There were significant effects of Block for HbO, HHb, and HbT [$F(2,44)=9.18$, $p<.01$, $\eta^2=0.29$; $F(2,44)=15.00$, $p<.01$, $\eta^2=0.41$; $F(2,44)=3.50$, $p=0.04$, $\eta^2=0.14$]. Pairwise comparisons revealed differences between blocks 1 and 2, 1 and 3, but not 2 and 3 for HbO (ps=.01, .02, 1.00) and HHb (ps=.01, .01, .78) and for blocks 1 and 2 for HbT (ps=.04, .18, 1.00)
Conclusion: These findings suggest that the mPASAT can be used to manipulate fatigue in a healthy sample of young adults in a laboratory setting. Contrary to expectations, exercise did not protect against the fatiguing effects of the task. The uncoupling of feelings of fatigue, performance, and PFC activity on a fatiguing task after exercise in this sample necessitate further exploration.

Disclosures: C. Ausenhus: None. **G. Goebel:** None. **K. Halldin:** None. **D.C. Monroe:** None. **B. Hunt:** None. **N. Thom:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.14/VV10

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: AHA 16PRE27600010
NIH NS100447

Title: Label-free measurement of flow speed in cortical blood vessels in mice using third harmonic generation microscopy

Authors: *N. RUIZ[1], S. AHN[2], C. B. SCHAFFER[2]
[2]Meinig Sch. of Biomed. Engin., [1]Cornell Univ., Ithaca, NY

Abstract: The measurement of blood flow speed in individual brain blood vessels of rodents is essential for understanding healthy and diseased state physiological processes. Two-photon excited fluorescence (2PEF) microscopy, which enables 3D, micrometer resolution *in vivo*

imaging of fluorescently-labeled structures deep into tissue, has emerged as a technique of choice for such measurements. To study vessel topology and function, the blood plasma is labeled by intravenously injecting high molecular weight dextran with conjugated fluorescent dyes. The red blood cells (RBCs) remain unlabeled, so they form dark patches whose motion can be tracked to quantify blood flow speed in individual vessels. While this approach has enabled detailed studies of blood flow in rodents, the penetration depth of 2PEF imaging restricts measurement to vessels in the top 0.5 mm of the cortex. Recently, the emergence of three-photon excited fluorescence (3PEF) microscopy has enabled imaging of blood vessels as deep as the hippocampus through the intact cortex in mice. Another nonlinear optical process called third harmonic generation (THG) occurs primarily at optical interfaces and can be resonantly enhanced by optical absorption peaks. For example, RBCs produce bright THG when excited with 1,300 nm light, due to the optical absorption peak of hemoglobin at 425 nm. In this study, we used 3PEF of FITC-dextran and THG from RBCs to quantify blood flow speed in arterioles, capillaries, and venules at depths of up to ~1 mm beneath the cortex. Because the THG signal is produced primarily from RBCs, while the 3EPF of FITC-dextran shows blood plasma, we were also able to quantify the width of the cell free layer adjacent to the vessel wall. Finally, we took advantage of the label-free nature of THG imaging to quantify the impact of injecting high molecular weight dextran on blood flow speed. We measured blood flow speed and tube hematocrit in the same vessels with and without FITC-dextran, and found a ~20% decrease in flow speed in arterioles and venules associated with the injection of ~100 µL of 5% w/v 2 MDa FITC-dextran (45 vessels across 4 mice). Interestingly, we did not observe slower flow speeds in capillaries and instead noted a ~35% decrease in tube hematocrit in capillaries associated with the injection of FITC-dextran (56 capillaries across 4 mice). With this study, we have shown the potential of THG as a label-free imaging approach for studying blood flow deep in the brain of rodents. In addition, the large changes in flow speed and hematocrit we observed with dextran injection suggest that careful consideration must be given when using this labeling strategy.

Disclosures: N. Ruiz: None. **S. Ahn:** None. **C.B. Schaffer:** None.

Poster

318. Brain Blood Flow

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Program #/Poster #: 318.15/VV11

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Canadian Institutes of Health Research (CIHR) – Frederick Banting and Charles Best Canada Graduate Scholarships
Cumming School of Medicine Graduate Scholarship, University of Calgary
Hotchkiss Brain Institute

Title: Tonic and bidirectional regulation of arteriole tone by astrocyte steady-state Ca^{2+}

Authors: *J. HAIDEY, G. R. GORDON
Univ. of Calgary, Calgary, AB, Canada

Abstract: Astrocyte-mediated neurovascular coupling has conventionally been examined in the context of transient neuronally-evoked calcium (Ca^{2+}) events triggering phasic changes in arteriole diameter. Our research group has recently demonstrated that driving astrocyte free endfoot Ca^{2+} to zero elicits prominent vasoconstriction in adjacent arterioles, suggesting that the basal, 'steady-state' astrocyte Ca^{2+} level maintains resting arteriole tone; thereby controlling brain blood flow tonically. However, it is unclear how subtle fluctuations in steady-state astrocyte Ca^{2+} may regulate vascular tone. Previous work has revealed that the resting astrocyte Ca^{2+} concentration ranges from ~70-130 nM, which may be altered by experience or disease. The objective of our investigation was to clamp astrocyte Ca^{2+} concentration both above and below resting levels, measuring any resulting changes in arteriole diameter and if so, determine if arteriole tone maintained a new, stable level. This was accomplished using two-photon fluorescence imaging and patch-clamp in acute cortical brain slices acquired from male Sprague Dawley rats (P21-30). We used various ratios of BAPTA and free Ca^{2+} to clamp astrocyte free Ca^{2+} at low (25 nM; n=7), near-resting (100 nM; n=5), moderate (250 nM; n=8), and high (750 nM; n=8) levels. Our preliminary data show that clamping astrocyte Ca^{2+} at either 25 nM or 750 nM increases arteriole tone (vasoconstriction), whereas clamping at 250 nM Ca^{2+} decreases arteriole tone (vasodilation), and each condition was met with a stable tone change that lasted a 10min recording. In contrast, both the 100 nM Ca^{2+} clamp solution and the EGTA control solution produced no substantial changes in arteriole diameter. Each Ca^{2+} clamp manipulation was met with a corresponding change in astrocyte Ca^{2+} fluorescence measured using Rhod-2. These results suggest that moderate deviations in astrocyte cytosolic free Ca^{2+} from resting levels stably set basal vascular tone in a bidirectional manner.

Disclosures: J. Haidey: None. **G.R. Gordon:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

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Program #/Poster #: 318.16/VV12

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R44 NS086343
NIH Grant 5R44AG043203

Title: GIRK channel direct activation with ML297 depresses a capsaicin-induced increase in microcirculatory blood perfusion in the rat cheek

Authors: *X. S. XIE[1], K. XIAO[1], C. PASCUAL[1], B. ZOU[1], W. CAO[1], C. LINDSLEY[2], C. WEAVER[2]
[1]Afasci Res. Laboratories, Afasci, Inc., Redwood City, CA; [2]Dept. of Pharmacol., Vanderbilt Univ., Nashville, TN

Abstract: A clinical experimental pain model and sensory response test utilizes capsaicin-induced neuroinflammatory pain in healthy volunteers. Functional imaging studies demonstrate that capsaicin induces central sensitization and suggests that these methods can potentially be used to guide the selection of effective analgesics for neuropathic pain in early drug development (Wanigasekera, et al., 2016). We attempted to "reverse" translate this clinical test into a preclinical assay and test the hypothesis that direct activation of G protein-gated inwardly-rectifying potassium (GIRK) channels can depress capsaicin-induced changes in microcirculatory blood perfusion in the rat cheek.
The total local tissue perfusion measured using Laser Doppler Imaging (Perimed Doppler) was stable for at least 30 min in individual rats. Due to large variation among individual rats, all perfusion levels (in an arbitrary value per a 1 min block) were normalized to the 10 min time point just prior to the topical cheek application of capsaicin (10 µL, 30µM in 70% ethanol). Tissue perfusion was gradually increased and reached a plateau level by 10 min and was maintained for another 10 min after capsaicin (but not ethanol alone) application under control conditions. Injection of ML297 (5 mg/kg, 0.4 mL I.V.), a direct GIRK channel activator, significantly inhibited capsaicin-induced enhancement of tissue perfusion. The peak effect was observed at approximately 7-min after drug application and tissue perfusion was 115.5%±9.3 compared to 183.2%±19.1 of vehicle control (n=9 for each group, $p<0.05$); whereas ML297 had no significant effects on the normal tissue perfusion with topical ethanol application (n=8, $p>0.05$). These results demonstrated that GIRK channel activation with ML297 preferentially depressed the capsaicin-induced perfusion increment. The objective measurement of capsaicin-induced tissue perfusion change and its response to drug treatment can be a powerful tool for analgesic evaluation in preclinical and early clinical proof of concept studies.

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Poster

318. Brain Blood Flow

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Program #/Poster #: 318.17/VV13

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: DFF – 6110-00210

Title: Precapillary sphincters on penetrating arterioles regulate brain capillary flow

Authors: *S. GRUBB, C. CAI, L. KHENNOUF, B. O. HALD, S. ZAMBACH, M. J. LAURITZEN
Univ. of Copenhagen, Copenhagen N, Denmark

Abstract: Research objective
In the brain, mural cells at the branch points of penetrating arterioles (PA) regulate blood flow to the capillary bed. Precapillary sphincters (PS) are mural cells encircling the initial segment of the PA branch and are well-known in mesenteric microcirculation and from numerous text-book examples of microcirculation, but their existence in other organs, including the brain, has been questioned. We provide evidence that they do exist in the mouse brain, and that they play a significant role in blood flow regulation.
Methods
We performed *in vivo* experiments in anaesthetized adult NG2-DsRed mice (male or female), which express DsRed in smooth muscle and pericytes under the NG2 promotor. The mouse was administered FITC-dextran i.v. to visualize branch points of PAs in layer 1-3 of the right barrel cortex by two-photon microscopy. We investigated the PS function by timelapses of dilatory responses during whisker pad stimulation and resonance line scanning to measure red blood cell (RBC) velocity through the PS. We also observed PS responses to cortical spreading depolarization.
Results
We found that PS exist in the mouse brain as mural cells encircling the initial segment of PA branches in layer 1-3. The PS was often followed by an expanded vessel lumen only sparsely covered by DsRed-positive cells which we named 'the bulb'. Under baseline conditions, the diameter of the PA lumen was 14±2 µm at the branchpoints (n=25). The diameter of the PS lumen (4±1 µm) was narrower than the bulb (8±1 µm), but comparable to the rest of the 1. order capillary (6±1 µm) (n=20-25, ±SD, one-way ANOVA). Upon whisker pad stimulation, the PS lumen dilated (26±3%) comparable to the rest of the 1. order capillary (28±3%) but more than the bulb (17±3%) or the PA (13±2%). In the minutes after stimulation, the PS lumen diameter narrowed (12±2%), sometimes only allowing plasma skimming. Line scanning revealed that RBCs pass quickly through the PS but when they enter the larger volume of the bulb they slow down, change to parachute form and line up, suggesting that the bulb might have a role in readying the RBCs for the capillary bed. During the early and late constriction phases of cortical spreading depolarization, the PS lumen also narrowed to a diameter where the RBCs in the capillary were either slowed or stopped, suggesting a bottleneck function of PS during hemodynamic changes evoked by cortical spreading depolarizations.
Conclusions
Precapillary sphincters exist in the mouse brain, and they actively regulate the blood flow by forming a bottleneck of vascular resistance at the very beginning of the capillary bed that can be released or tightened to match the nerve activity with blood flow.

Disclosures: S. Grubb: None. **C. Cai:** None. **L. Khennouf:** None. **B.O. Hald:** None. **S. Zambach:** None. **M.J. Lauritzen:** None.

Poster

318. Brain Blood Flow

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Program #/Poster #: 318.18/VV14

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Mindefonden for Alice Brenaa

Title: *In vivo* micro-puffing of ATP-sensitive potassium channel opener leads to brain capillary vasodilation

Authors: *S. A. ZAMBACH, C. CAI, M. LAURITZEN
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Abstract: Neurovascular coupling adjusts cerebral blood flow according to the metabolic needs of brain tissue. Cerebral blood flow is regulated by arteriolar smooth muscle cells, but new discoveries show that cerebral pericytes, contractile cells on capillary walls, actively regulate blood flow in capillaries, even prior to the upstream smooth muscle cells. However, it is still unclear what signaling pathway and channels of pericytes are involved in regulation of capillary diameter. Previous studies have shown that ATP-dependent potassium channels (Katp) are highly expressed in cerebral pericytes; while until now the regulation of blood flow by Katp channels have only been studied in vascular smooth muscle cells of big surface arteries of the brain. The aim of this study is to examine if pericyte Katp channels have the potential to modulate brain capillary blood flow in physiological state. Guided by two-photon microscopy, a glass micro-pipette containing Katp opener (pinacidil) was inserted and approached to the proximity of 1st, 2nd and 3rd order of capillary and penetrating arteriole in NG2DsRed mouse brain. Air pressure puffing of pinacidil in this local region was imaged by two-photon microscopy to study the vascular diameters. Vessel borders in two-photon time-series were calculated after ROI placement by an active contour algorithm. Vessels diameter increased (penetrating arteries mean = 4.83%, STD = 1.57%, 1st order capillary mean = 20.07%, STD = 2.07%, 2nd order capillary mean = 16.69%, STD = 2.1%, 3rd order capillary mean = 12.72%, STD = 6.98%) and stayed at a long-lasting plateau following puffing of pinacidil (n=9) compared to pre-puff baseline. Vasodilation of both 1st and 2nd order of capillaries were significantly larger than that of the penetrating arteriole. Control puffing of aCSF (n=3) showed small fluctuations of vessel diameter around the baseline. Preliminary data from 4D (continuous fast z-stack) scanning experiments showed similar results. This indicates that Katp channels are abundant in near arteriole pericytes and have ability to regulate pericyte contractile state and capillary blood flow.

Disclosures: S.A. Zambach: None. **C. Cai:** None. **M. Lauritzen:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.19/VV15

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Medical Research Council

Title: Investigating neurovascular coupling in the visual cortex and hippocampus of behaving mice using two-photon imaging

Authors: *K. SHAW[1], D. M. GRIJSEELS[2], O. BONNAR[2], K. BOYD[2], C. N. HALL[2]
[1]Psychology, [2]Univ. of Sussex, Brighton, United Kingdom

Abstract: In the healthy cortex, increases in neuronal signalling typically result in a local influx of oxygenated blood, via a process termed neurovascular coupling. The accurate interpretation of the relationship between neuronal activation and the cerebral vasculature, underpin blood oxygen level dependent (BOLD) functional MRI (fMRI), but are not yet fully understood. Some recent research has indicated that neurovascular coupling may be altered in subcortical regions. For instance, decreased fMRI signals were observed in caudate-putamen, despite increased neuronal activity (Mishra et al., 2011); and hippocampal BOLD signal has been demonstrated to show no correlation with local field potential (Ekstrom et al., 2009). Results such as these will have important implications for understanding fMRI data taken from subcortical brain areas, emphasising the need for further work which characterises neurovascular coupling throughout the entire brain. We used two photon imaging to chronically record from the visual cortex (V1) or hippocampus (HC) of awake, head-fixed mice. First, a craniotomy was performed on the skull covering the area of interest, for V1 a glass coverslip was inserted, and for HC the overlying cortex was aspirated and a cannula with glass coverslip implanted. Excitatory neuronal activity was measured using fluorescence changes of the genetically coded calcium indicator GCaMP6f under control of the Thy1 promoter. The red blood cell velocity and diameter changes of nearby blood vessels were simultaneously collected by labelling the lumen with intravenous Texas Red dextran. Laser Doppler flowmetry and optical spectroscopy were also used to gain additional haemodynamic information, such as blood flow, blood volume and oxygen metabolism measurements. Using these techniques, both the effects of sensory stimulation and of locomotion on neurovascular responses across brain regions are being elucidated. We have observed that local blood flow changes are small in hippocampus, relative to the amount of excitatory neuronal activity (and therefore energy use), and when compared to the neurovascular relationship in visual cortex. Thus, the BOLD signal may be a less sensitive proxy for underlying neural activity in the hippocampus than in visual cortex.

1 Mishra, A. M., et al. (2011). *J Neuroscience*, 31, 15053-15064.
2 Ekstrom, A., et al. (2009). *J Neurophysiol*., 101, 2668-2678.

Disclosures: K. Shaw: None. **D.M. Grijseels:** None. **O. Bonnar:** None. **K. Boyd:** None. **C.N. Hall:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.20/VV16

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: School of Psychology, University of Sussex

Title: Visual cortex neurons driving neurovascular coupling during visual stimulation and locomotion

Authors: *K. BOYD, K. SHAW, D. M. GRIJSEELS, C. N. HALL
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Abstract: Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging is used to measure changes in blood flow and extrapolate this to neuronal activity. However little is known about how activity of neuronal subtypes and BOLD signal are related, limiting the extent to which BOLD signal can be understood. Production of vasoactive molecules in pyramidal cells and several interneuron types has been linked to blood vessel dilation, and different cell populations are involved in neurovascular coupling (NVC) after whisker or basal forebrain stimulation[1]. However, we do not yet understand what cell types are involved in NVC during physiological behaviours, and how NVC might vary as neuronal activity changes. Studying visual cortex allows alteration of neuronal activity in different populations, while additionally allowing us to measure modulation by locomotion. We are investigating how changes to the presentation of a drifting grating affects pyramidal, SST and VIP cells in V1, while simultaneously recording diameter changes in proximal blood vessels throughout the vascular tree.
We use 2 photon imaging of V1 in awake transgenic mice expressing the genetically encoded calcium indicator GCaMP6f in specific subpopulations of neurons to measure changes in neuronal activity, and inject Texas Red dextran (70 MW) IV to visualise the vascular lumen. We present drifting gratings of varying contrast and size, aiming to modulate the balance of activity across different neuronal populations and relate changes of activity to vascular responses. Mice are free to run on a cylinder, allowing us to determine any effects of locomotion on the relationship between neuronal activity and vascular responses.
We compare the size of vascular dilations in response to stimulation to local calcium activity

next to that vessel and to population calcium, across different neuronal subtypes and vessel types (capillaries and penetrating arterioles). Our data suggest capillaries and arterioles both dilate to the same extent in V1. Excitatory neuronal activity is greater local to a vessel when that vessel dilates compared to when it does not respond, however SST activity local to a vessel does not seem related to whether that vessel dilates. The net population activity of SST cells does, however, correlate with the degree of vascular dilation. We are currently investigating how these responses vary with stimulus type and locomotion across the different cell types.
1.Lecrux, C., Hamel, E. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* **371**, (2016)

Disclosures: K. Boyd: None. **K. Shaw:** None. **D.M. Grijseels:** None. **C.N. Hall:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.21/VV17

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: AGS Young Clinician Scientist
Alcon Research Institute Young Investigator Award
RPB Unrestricted Award
NEI Core Grant P30EY014801

Title: Characterization of neurotransmitter receptors that mediate retinal neurovascular coupling

Authors: *A. L. GARCIA, M. N. TAPIA, D. MULLER, D. PELAEZ, S. K. BHATTACHARYA, L. E. VAZQUEZ
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Abstract: Neurovascular coupling and regulation of blood floow in the retina remains poorly understood. Our objective is to characterize VSMC cell surface receptors and downstream signaling pathways that regulate vascular tone to further understand neurovascular coupling in the retina. To achieve this aim, retinas from SMA-GFP transgenic (a.k.a. “OTO2-10”) mice, which express GFP under the acta2 promoter, were dissected and dissociated with papain into single cell suspensions. Confocal microscopy of SMA-GFP retinal flat mounts found GFP expression to be exclusive to the vascular tree. VSMCs were then purified by collecting GFP positive cells via fluorescence activated cell sorting (FACS) and submitted to liquid chromatography-mass spectrometry (LC-MS) to establish protein profiles of these cells. The purification of FACS cells was confirmed by western blot where we stained for alpha-smooth muscle actin (α-SMA). In addition, immunohistochemistry staining of retinal flat mounts with various targets identified by our exploratory LC-MS profile were used. A total of 6,175 proteins

were found in 3 biological replicates of SMA-GFP transgenic mice with 100 high confidence proteins (FDR < 0.01), 18 medium confidence proteins (FDR 0.01 - 0.05), and 6057 low confidence proteins (FDR > 0.05). The presence of identified VSMC cell surface receptors was examined by immunostaining retinal flat mounts. Neuronal and astrocytic coupling to VSMCs was examined by colocalization of NFH and GFAP to these receptors. We speculate that these interactions play a key role in the regulation of vascular resistance in the retina. These findings may shed light on the control of hyperemic responses in health and disease.

Disclosures: A.L. Garcia: None. **M.N. Tapia:** None. **D. Muller:** None. **D. Pelaez:** None. **S.K. Bhattacharya:** None. **L.E. Vazquez:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.22/VV18

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: National Institutes of Health Grants R01NS078168

Title: Dissecting the neural control of baseline and evoked vascular tone in the brain

Authors: *C. ECHAGARRUGA, P. DREW
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Abstract: Changes in local neural activity drive vasodilation and vasoconstriction of the cerebral vasculature, and these changes in the cerebral blood flow are essential for brain tissue health. While previous work has suggested that activity of interneurons is the primary drivers of arteriole diameter changes, the signaling mechanisms that control blood flow and arterial diameter are not completely understood. To test the role of neural activity in manipulating vascular tone, we used chemogenetics and pharmacology in the somatosensory cortex of awake mice, allowing us to bi-directionally manipulate neural activity in specific cellular subpopulations. We assayed changes in neural activity and vascular responses to voluntary locomotion using electrophysiology and two-photon microscopy. We found that modulating the activity of all neurons produced corresponding changes in resting and evoked arteriole diameters. However, while modulation of excitatory neurons produced changes in the electrophysiologically-recorded population activity, there were no corresponding changes in resting or evoked arterial tone. Decreasing the activity of nNOS-expressing neurons or inhibition of NO production both blocked the hemodynamic response to locomotion and impacted resting tone similarly. Due to the changes in vessel tone, ratiometric imaging of hemodynamic signals can give misleading results when measured across conditions where background neural activity

may change. Our results show that both baseline and evoked hemodynamics signals reflect the activity of a small set of neurons, not the average activity of entire neural population.

Disclosures: C. Echagarruga: None. **P. Drew:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.23/VV19

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NSF Grant 41537-61RH

Title: Neurovascular coupling can provide a driving force for glymphatic flow

Authors: *R. KEDARASETTI[1,2], C. ECHAGARRUGA[1,3], B. GLUCKMAN[2,1,3], F. COSTANZO[2,1,4], P. J. DREW[2,1,3]
[1]Ctr. for Neural Engin., [2]Engin. Sci. and Mechanics, [3]Biomed. Engin., [4]Dept. of Mathematics, The Pennsylvania State Univ., University Park, PA

Abstract: The brain lacks a traditional lymphatic system for clearance of metabolites. Recent work has suggested the existence of a "glymphatic system" where metabolites are removed from the brain's extracellular space by convective exchange between interstitial fluid (ISF) and cerebrospinal fluid(CSF) along the paravascular spaces around cerebral blood vessels. While there is some evidence that arterial pulsations can cause fluid movement, the driving mechanism for fluid circulation in the brain parenchyma is not fully understood. Also, there is no agreement on whether there is convective transport in the brain tissue. Due to experimental limitations, a better understanding of the movement of CSF and ISF in the brain requires computational modeling of the movement of these fluids and their interactions with the brain. Using a combination of computational modeling and in vivo two-photon microscopy, we investigate the nature of the movement of fluid in the perivascular space driven by vascular dilations and pulsations

Previous modeling work investigating the role of vascular pulsations in the glymphatic system has (unrealistically) treated the brain as a rigid structure that does not deform, when in fact brain tissue is very soft. We created a more realistic model of a blood vessel surrounded by a perivascular space and embedded in brain tissue, where the brain tissue can deform when pressure is applied. We use in-vivo two photon imaging in Thy1/YFP mice to measure the tissue deformation in the somatosensory cortex induced by vessel dilations and pulsation to verify the assumptions in our model.

When we extend previous computational models of flow in the perivascular space to account for deformation in the cerebral tissue in response to vascular motion, we find that there is no

significant fluid flow due to cardiac driven pulsations of arteries. Our results suggest that under biologically plausible conditions, movement of fluid in the brain is primarily driven by vasodilation. As vasodilation of arteries in the brain is coupled to increases in local neural activity, this mechanism would facilitate the exchange of CSF/ISF after the production of neural metabolic waste, providing another role for neurovascular coupling in maintaining brain health. Because functional hyperemia is very sensitive to anesthesia, our model can explain the sensitivity of CSF circulation to anesthesia. We are currently extending these models to simulate the brain as a porous, elastic solid that is saturated with fluid.

Disclosures: R. Kedarasetti: None. **C. Echagarruga:** None. **B. Gluckman:** None. **F. Costanzo:** None. **P.J. Drew:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.24/VV20

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant K25 HL131997
NIH Grant R01 NS095933

Title: Cerebral blood flow dynamics of the hemodynamic response function in human visual cortex

Authors: *J. KIM, A. TAYLOR, D. RESS
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Neural activity evoked by brief stimulation creates changes in cerebral blood flow (CBF) and oxygen uptake that together create the hemodynamic response functional response (HRF). We used arterial spin labeling (ASL) magnetic resonance imaging (MRI) to measure CBF responses in human cortex with high spatiotemporal sampling to understand the underlying CBF dynamics. **Methods**: Stimulus was a 2-s presentation of three round regions of 4-Hz flickering colored dots accompanied by bandpass filtered white noise, followed by a 32.5-s inter-stimulus interval. Dot regions appeared for 0.67 s at a random sequence of locations, each of which corresponded to a particular color and sound tone. Subjects were requested to push a button corresponding the presentation position. fMRI data was obtained on a 3T Siemens Trio scanner with a 32-channel head coil. Acquisition used an ASL sequence (PICORE/QUIPPS2 tagging scheme) on 25 quasi-axial slices with 2-mm voxels. TR was 2.5, so that alternating tag and control measurements were obtained every 5 s. We used a dithering method that varied the timing of the stimulus in four steps to improve temporal sampling to 1.25 s. We obtained a total of 4 runs of ASL measurements, each with16 events. In each session, we also measured the

fMRI HRF with simultaneous multi-slice echo-planar imaging (2 mm voxels, TR = 1.25 s) for 2 runs that obtained 12 events on the same prescription. **Results**: The audiovisual stimulus with its fast-paced task was effective in evoking strong CBF responses in visual cortex (Fig. A) that included an initial peak followed by an undershoot. Parameter analysis across subjects and ROIs quantified to magnitude and reliability of the undershoot (Fig. B). The timing of the peak and undershoot were also quantified and found to be stereotypical. Interestingly, we also found reliable variations of baseline flows across ROIs in visual cortex (Fig. C). **Conclusions**: We successfully obtained dynamics of CBF with ASL MR imaging. The result confirmed significant undershoot and stereotypical temporal response of the CBF evoked by brief neural activation.

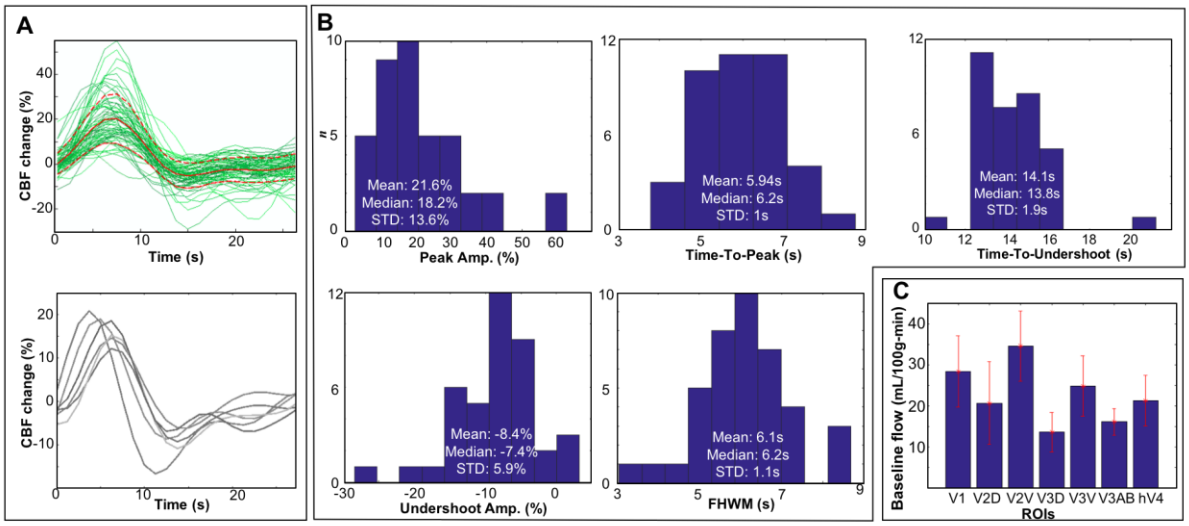

Fig. A) (upper) mean and standard deviation (red) of CBF responses across subjects and ROIs (green: individual data); (lower) examples of CBF within a subject for different ROIs. B) Histograms of CBF across subjects and ROIs. Distributions were obtained from bootstrapping data across subjects and ROIs. C) Flow baseline value for individual ROIs across subjects

Disclosures: J. Kim: None. **A. Taylor:** None. **D. Ress:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.25/VV21

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Canadian Institutes of Health Research
National Science and Engineering Council of Canada
Research Manitoba
Canada Foundation for Innovation
Winnipeg Health Sciences Centre

Title: Endothelial NMDA receptors are critical mediators of neurovascular coupling in awake behaving mice

Authors: *A. D. HOGAN-CANN[1,2], P. LU[1,2], C. ANDERSON[1,2]
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Abstract: Functional hyperemia (FH) ensures that active brain regions receive proportional delivery of blood flow. FH requires both local effects and coordinated upstream conduction of vasodilatory signals in an endothelium-dependent manner. There is strong literature consensus that this local response is mediated by neuronal N-methyl-D-aspartate (NMDA) receptors and nitric oxide produced by neuronal NO synthase (nNOS), or by inducing release of vasodilatory gliotransmitters from perisynaptic astrocytes with perivascular endfeet processes. However, neither of these mechanisms is endothelium-dependent, leaving neuro-endothelial coupling as a key conceptual deficit in understanding FH. We have observed that isolated middle cerebral artery segments free of neurons dilate in response to NMDA receptor agonists in a manner that requires functional endothelium and endothelial NOS. We also found that two-photon photolysis of caged astrocyte Ca^{2+} in mouse cortical slices led to NMDA receptor and eNOS-dependent vasodilation. The current study was designed to test the possibility that endothelial NMDA receptors participate in neurovascular coupling by measuring the hemodynamic responses in awake, head-fixed mice following sensory stimulation. To distinguish between neuronal and endothelial NMDA receptors we created conditional endothelial NMDA receptor loss of function mice that were characterized by greater than 50% loss of endothelial GluN1 (eGluN1) expression. Laser-Doppler flowmetry revealed that targeted whisker stimulation increased regional cerebral blood flow (CBF) in the somatosensory cortex of wild-type mice. This hyperemic response was dramatically impaired in eGluN1 deficient mice. Using two-photon microscopy, we measured vascular lumen diameter and red blood cell (RBC) velocity to better understand the dynamics of neurovascular coupling at the single vessel level in awake mice. In eGluN1 knockdown mice, the increase in lumen diameter and RBC velocity following whisker simulation was dramatically impaired relative to littermate controls. Spatial and temporal mapping of the vascular responses revealed signals that originated at cortical microvessels and were propagated throughout the vascular network to reach upstream pial arteries. Interestingly, pial vascular responses were unaffected by eGluN1 knockdown. These results suggest that eGluN1 loss of function reduces local vasodilatory effects while the upstream propagation of these signals is spared. Our results identify a novel mechanism of neuro-endothelial coupling by showing that endothelial NMDA receptors mediate activity-dependent, neurovascular signaling.

Disclosures: A.D. Hogan-Cann: None. **P. Lu:** None. **C. Anderson:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.26/VV22

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Support: Hotchkiss Brain Institute: Donald Burns and Louise Berlin Graduate Award in Dementia Research
Cumming School of Medicine: Medical Research Fund
Canadian Institutes of Health Research Foundation
Canada Research Council (Tier 2)
Hotchkiss Brain Institute: Brain and Mental Health

Title: Spatiotemporal dynamics of mural cell Ca^{2+} and tissue oxygenation in awake, behaving mice

Authors: *G. PERINGOD[1], L. YU[3], K. MURARI[3], G. R. GORDON[2]
[1]Dept. of Neurosci., [2]Dept. of Physiol. and Pharmacol., Hotchkiss Brain Institute, Univ. of Calgary, Calgary, AB, Canada; [3]Electrical and Computer Engin., Schulich Sch. of Engineering, Univ. of Calgary, Calgary, AB, Canada

Abstract: Arteriole smooth-muscle cells and contractile pericytes on pre-capillaries ("mural cells", collectively) respond to neural signals and are the ultimate end effectors in cerebral blood flow control. Basic excitation-contraction coupling rules for these cells stipulate that elevations in Ca^{2+} decrease blood flow, and that decrements in Ca^{2+} increase blood flow. Since the contractile activity of mural cells determine local oxygen delivery, they are directly linked to functional imaging modalities such as BOLD fMRI. However, the cerebral microvascular network exhibits complex intrinsic and extrinsic regulation, and experiences modulation both locally and at the network-level, to meet the energy demands of the brain. Little is known about the spatial dynamics of mural cell Ca^{2+} across the neocortex, or how faithfully tissue oxygenation tracks vascular Ca^{2+}, in vivo in conscious animals. Here, we developed a widefield imaging system that permits simultaneous measurement through intact bone of mural cell Ca^{2+}, blood volume and tissue oxygenation across the entire top of the cerebral cortex in awake, behaving mice exposed to whisker stimulation, volitional locomotor activity, or startle stimuli. We used Cre-Lox knock-in mice (PDGFRb-Cre x LSL-GCaMP6s), wherein a genetically-encoded calcium indicator is expressed in mural cells, to examine 'mesoscale' Ca^{2+} fluorescence signals from the vasculature. We observed these signals spread specifically from region-to-region across the neocortex in wave-like patterns, similar to previously-reported neuronal Ca^{2+} signals in the resting awake state. Unlike startle stimulation, which elicited a large bilateral reduction in Ca^{2+}, minimal whisker-stimulation elicited relatively localized signals of much

lower magnitude. In summary, our preliminary efforts highlight the use of PDGFRb-GCaMP6s animals to study vascular network functions through the skull in awake and active mice. Ongoing efforts seek to examine these signals in relation to intrinsic optical measures of hemodynamic activity during different behavioural states, and follow-up experiments will test whether any existing relationships are perturbed in mouse models of cerebrovascular dysfunction.

Disclosures: G. Peringod: None. **L. Yu:** None. **K. Murari:** None. **G.R. Gordon:** None.

Poster

318. Brain Blood Flow

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 318.27/WW1

Topic: F.06. Brain Blood Flow, Metabolism, and Homeostasis

Title: Cerebrovascular morphology and mechanics in rodent models of hypertension and heart failure

Authors: *C. ACOSTA, C. M. ANDERSON, H. ANDERSON
Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: There is growing evidence that heart failure (HF) is a risk factor for dementia and Alzheimer's disease (AD). In fact, HF patients often exhibit cognitive deficits, although the prevalence of AD in HF is unknown. Hypertension often precedes HF and in itself, is an independent risk factor for dementia. This may be related to the arterial wall remodeling, stiffening, and dysfunction that, by reducing lumen diameter, may compromise blood flow. Indeed, cerebrovascular remodeling leads to inadequate brain perfusion, and arterial stiffening is associated with dementia. We investigated cerebrovascular remodeling and stiffening as putative underlying mechanisms. Morphological and mechanical changes were characterized in middle cerebral arteries (MCAs) and penetrating arterioles (PAs) using genetic animal models of hypertension alone (spontaneously hypertensive rat, SHR) and hypertension associated with risk for HF (spontaneously hypertensive heart failure rat, SHHF). Vascular properties of isolated MCAs and PAs from Wistar Kyoto (WKY) and SHR, as well as, Sprague-Dawley (SD) and SHHF rats were measured by pressure myography. SHHF MCAs exhibited eutrophic remodeling, as evidenced by increased media-lumen ratio (15.9±2 vs. SD 8.9±0.5, $p<0.05$) and unchanged media cross-sectional area (mCSA). An increasing trend in the latter, however, resulted in a growth index of 44%, suggesting hypertrophic growth was in process. SHHF MCAs also exhibited mechanical changes in terms of stiffening and reduced compliance *(*vs. SD, *$p<0.01$).* In contrast, smaller, downstream PAs in SHHF exhibited solely eutrophic remodeling (increased media-lumen ratio (*$p<0.01$*) in the absence of any change (significant or trend) in mCSA. SHHF PAs experienced less arteriolar wall stress (0.003±0.0001 vs. SD 0.004±0.0001,

p<0.01) and were less compliant (13.1±0.8 vs. SD 9.3±0.5, *p<0.01*). SHHF PAs were significantly stiffer (0.07±0.01 vs. SD 0.04±0.002, *p<0.01*) due to greater wall component stiffness (23.9±4 vs. SD 10±0.6, *p<0.01*). Similar to SHHF, SHR PAs exhibited eutrophic remodeling (*p<0.01*) and were exposed to reduced stress on their arteriolar walls (0.0028±0.0001 vs. WKY 0.004±0.0001, *p<0.01*). However, in contrast to SHHF, SHR PAs were significantly more compliant (8.2±0.1 vs. WKY 11.2±0.09, *p<0.01*), less stiff (0.03±0.002 vs. WKY 0.04±0.002, *p<0.01*), and had unchanged wall component stiffness. This study identified eutrophic remodeling in both SHHF and SHR PAs, as well as, changes in mechanical properties that may be protective against HF and HF-induced dementia in SHR but are absent in SHHF.

Disclosures: C. Acosta: None. **C.M. Anderson:** None. **H. Anderson:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.01/WW2

Topic: F.10. Food Intake and Energy Balance

Title: Effects of food maternal restriction on palatable food consumption of the offspring in preadolescence and adulthood in rats

Authors: *E. BARRIOS DE TOMASI, A. E. MARTÍNEZ-MARTÍNEZ, J. JUAREZ
Inst. De Neurociencias, Jalisco, Mexico

Abstract: Food maternal restriction has morphological and functional implications in the central nervous system of the offspring, like a decrease in the hormone leptin, changes in the conformation of the hypothalamus and in the disposition of dopaminergic receptors. Preadolescence is another vulnerable period, in which the early exposure to rewarding substances, such as the ingestion of drugs or alcohol, as well as palatable food consumption, can facilitate the dependence in adulthood. On this basis, it is important to know how food restriction during the fetal period affects the consumption of appetizing food in preadolescence, considering that both are sensitive periods for the development of obesity in adulthood. We used 16 pregnant Wistar female rats, which were divided into a control group and a restriction group. The control group was given food and water *Ad libitum* throughout the gestation period and the restriction group had access to 50% of the standard food that consumed by the control group (gestation day 10-22). During the lactation period, both groups had free access to standard food. At postnatal day (PD) 25 offspring were assigned to four groups: Control males (MCN), control females (HCN), restriction males (MRS) and restriction females (HRS). From PD 28 to 39, they were exposed to high-caloric food and standard food ad libitum for 24hrs/12 days. From PD 70 to 98, the four groups were again exposed to the consumption of high-caloric and standard meals for 28 days following the criteria above mentioned. We observed that the rats exposed to the maternal

food restriction had a higher percentage of weight gain at the end of the high-caloric food access in preadolescence and adulthood, despite there were no differences in food consumption between control and restriction group. Males had a greater percentage of weight gain and a higher consumption of standard food in both ages, however, the females had the highest consumption of high-caloric food in adulthood. Results suggest that the maternal food restriction generates changes in the metabolism of offspring rats but no in the preference for high-caloric foods, generating a greater long-term weight gain that could be affected by leptin and sex hormones, particularly estrogens, which would serve as a protective factor for females that result in a lower body weight gain than males.

Disclosures: E. Barrios De Tomasi: None. **A.E. Martínez-Martínez:** None. **J. Juarez:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.02/WW3

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant G12 MD007601
NIH Grant R01 DK47320
NIH Grant P20 GM113134

Title: Selenoprotein M promotes hypothalamic leptin signaling and thioredoxin antioxidant activity

Authors: *T. GONG[1], A. C. HASHIMOTO[1], V. S. KHADKA[2], M. J. BERRY[1], M. W. PITTS[1]
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Abstract: Abstract
Selenoproteins are an essential class of proteins involved in redox signaling and energy metabolism. However, the means by which selenoproteins influences energy homeostasis is enigmatic, as the functions of many selenoproteins are not clearly established. Selenoprotein M (SELENOM), an ER-resident oxidoreductase bearing structural similarity to thioredoxin (TXN), is among those yet to be fully characterized. This protein is highly expressed in hypothalamic regions involved in leptin signaling and has been previously linked to energy metabolism, as *Selenom*$^{-/-}$ global knockout mice develop adult-onset obesity. Moreover, it was recently shown that ablation of hypothalamic selenoprotein synthesis impedes leptin signaling. Herein, we performed a series of studies using i*n vivo* and *in vitro* models to investigate the specific influence of SELENOM on hypothalamic leptin signaling. Microarray analysis was also conducted in parallel to the identify genes and pathways most affected by SELENOM

deficiency. Collectively, our findings conclusively demonstrate that SELENOM is a positive regulator of both leptin signaling and thioredoxin antioxidant activity in the hypothalamus.

Disclosures: T. Gong: None. **A.C. Hashimoto:** None. **V.S. Khadka:** None. **M.J. Berry:** None. **M.W. Pitts:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.03/WW4

Topic: F.10. Food Intake and Energy Balance

Support: NRF-2016K2A9A1A06945430
NRF-2017R1D1A1B03031216
2015M3A9E7029173

Title: Pigment epithelium-derived factor regulates energy balance via adipose triglyceride lipase in the brain of mice

Authors: M.-G. SONG[1], H.-J. KIM[1], B.-Y. JIN[1], N.-H. HA[1], H.-J. LEE[1], S.-H. CHOI[1], *D.-H. KIM[2]
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Abstract: Pigment epithelium-derived factor (PEDF) known as an antiangiogenic and neurotrophic factor, plays a role in the regulation of lipid metabolism and insulin sensitivity in humans and rodents. However, its role in energy balance remains unclear. In this study, we investigated central role of PEDF in the regulation of energy balance and its underlying mechanism in mice. We monitored food intake, energy expenditure and weight gain after administering PEDF into the third ventricle (ICV) of C57BL/6 mice and compared activities of energy sensors including AMP-activated protein kinase, acetyl-CoA carboxylase (ACC), and signal transducer and activator of transcription 3 (STAT3) in the mediobasal hypothalamus by western blot. We performed a conditioned taste aversion test in mice to identify whether ICV administration of PEDF was associated with non-specific illness. In addition, we investigated a role of adipose triglyceride lipase (ATGL), a receptor of PEDF, in central PEDF-induced anorexia by using ATGListatin, an ATGL inhibitor, and ATGL knockout mice. ICV administration of PEDF significantly decreased food intake and weight gain with no change in energy expenditure compared to control and it was not associated with non-specific illness. ICV administration of PEDF increased hypothalamic ACC and STAT3 activities compared to control, implying an involvement of lipid sensing and leptin signaling in central PEDF-induced anorexia. Consistently, PEDF had a synergic effect with leptin on the regulation of energy balance in the

brain of mice. In addition, central PEDF-induced anorexia was reinstated by pretreatment with ATGListatin and it was attenuated in ATGL knockout mice compared to wild-type mice. Taken together, these results suggest a central role of PEDF via ATGL in the regulation of energy balance in mice.

Disclosures: M. Song: None. **H. Kim:** None. **B. Jin:** None. **N. Ha:** None. **H. Lee:** None. **S. Choi:** None. **D. Kim:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.04/WW5

Topic: F.10. Food Intake and Energy Balance

Support: NIH Intramural Research Program (NIDDK)

Title: Why do mice overeat high-fat diets? how high-fat diet alters the regulation of daily caloric intake in mice

Authors: *J. A. LICHOLAI[1], K. P. NGUYEN[2], W. C. FOBBS[3], C. J. SCHUSTER[4], M. A. ALI[5], A. V. KRAVITZ[1]
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Abstract: The obesity epidemic is a multifaceted problem with a range of health problems and associated costs. Over-eating is thought to contribute to weight gain and obesity, however the factors involved in over-eating are not well understood. *Ad libitum* high-fat diets (HFDs) spontaneously increase caloric intake in rodents, which correlates positively with weight gain. However, it remains unclear why rodents overeat HFDs. Here, we investigated how changing the proportion of diet that came from HFDs altered total daily caloric intake in mice. Mice were given *ad libitum* chow supplemented with 25%, 50%, or 90% of their daily caloric need from HFD. We hypothesized that HFD may interfere with satiety mechanisms, such that additional calories would be required for mice to become sated on HFD. If true, we predicted that the total calorie intake would increase as we increased the proportion of daily calories from HFD. Contrary to our hypothesis, however, HFD supplements did not increase total daily caloric intake, even when 90% of their daily calories were obtained from HFD. Importantly, these same mice increased their daily caloric intake when given *ad libitum* HFD. We concluded that HFD appropriately engages satiety signaling, yet mice over-eat HFD in spite of satiety. A follow up experiment confirmed that sated mice consumed 50% of their daily calories from HFD in 30

minutes. These results suggest that over-eating of HFD may be driven by hedonic mechanisms, and not by impairing mechanisms that regulate daily caloric intake.

Disclosures: J.A. Licholai: None. **K.P. Nguyen:** None. **W.C. Fobbs:** None. **C.J. Schuster:** None. **M.A. Ali:** None. **A.V. Kravitz:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.05/WW6

Topic: F.10. Food Intake and Energy Balance

Support: FIR RBFR12DELS_003

Title: Central effects of peripherally administered oleoylethanolamide in rats subjected to surgicalsubdiaphragmatic vagal deafferentation

Authors: *J. B. KOCZWARA[1], A. ROMANO[1], C. A. GALLELLI[1], E. K. AZARI[2], A. MANSOURI[3], M. ARNOLD[3], S. GAETANI[1]
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Abstract: Oleoylethanolamide (OEA), a PPAR-alpha agonist, is a mediator of satiety. After peripheral administration, OEA induces c-Fos (a marker for neuronal activation) in areas of the central nervous system (CNS) involved in the control of eating behavior, such as the nucleus of the solitary tract (NST) and the area postrema (AP) in the brainstem, as well as the paraventricular (PVN), supraoptic (SON) and ventral tuberomammillary (vTMN) nuclei in the hypothalamus. Moreover, the OEA-induced behavioral and neurochemical effects were abolished after lesion of the noradrenergic projections that originate in the brainstem and project to the hypothalamus. Although previous reports suggested an involvement of visceral vagal fibers in mediating OEA effects, recent findings demonstrate that abdominal vagal afferents are not necessary for the anorectic effect of OEA. In fact, OEA is able to decrease food intake both in rats that underwent a subdiaphragmatic vagal deafferentation (SDA), a surgical procedure that eliminates all abdominal vagal afferents but spares about 50% of the vagal efferents, and in SHAM-operated controls. Thus, the aim of the present work was to further elucidate the role of abdominal vagal afferents in mediating OEA's effects on the CNS. In particular, we aimed to investigate the effects of OEA administration (10 mg/kg, i.p.) on the expression of c-Fos and dopamine-β-hydroxylase (DBH, a marker of noradrenergic neurons) within the NST and AP, and on the expression of c-Fos in areas of the hypothalamus involved in the control of eating. To this end, we subjected male rats to SDA or SHAM (control) surgery. Two hours after OEA or vehicle administration, the rats were sacrificed and brains were collected. By using

immunohistochemistry, we assessed c-Fos and DBH expression patterns in the NST, the AP, and in the hypothalamus. Consistent with the behavioral results, OEA increased c-Fos expression in the NST and in the AP in both SHAM and SDA rats. Moreover, SDA did not alter DBH expression in these areas. In the hypothalamus, in line with the behavioral results, OEA increased c-Fos expression in the PVN and the vTMN, even though in the latter nucleus the increase did not reach statistical significance. Interestingly, in the SON, the OEA-induced increase in c-Fos expression was blunted by the SDA surgery, suggesting a direct involvement of vagal afferents in the activation of this nucleus. Overall, our findings indicate that vagal afferents, which are not necessary for the satiety effect of OEA, are also not necessary for most of the neurochemical changes induced by i.p. OEA, although appear to mediate the OEA-induced activation of the SON.

Disclosures: J.B. Koczwara: None. **A. Romano:** None. **C.A. Gallelli:** None. **E.K. Azari:** None. **A. Mansouri:** None. **M. Arnold:** None. **S. Gaetani:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.06/WW7

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant DK063040

Title: Leptin receptor-expressing neurons in the nucleus of the solitary tract receive input from capsaicin-sensitive C-type vagal afferents

Authors: *D. NEYENS[1], S. M. APPLEYARD[2]
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Abstract: Leptin is a hormone that regulates energy homeostasis and reduces food intake. The nucleus of the solitary tract (NTS) in the hindbrain is an important hub of integration for signals controlling food intake, including incoming vagal afferents carrying satiety information from the gastrointestinal tract that enter via the solitary tract (ST). Leptin receptors (LepRs) are expressed on both vagal afferents and NTS neurons, and direct injections of leptin into the NTS reduce food intake. Previous work from our lab showed that LepR expressing neurons receive glutamate inputs from ST afferents, including cholecystokinin (CCK) sensitive afferents. In addition, leptin increases ST activation of action potentials in LepR neurons; however, the phenotype of these ST inputs has not been fully characterized. ST afferents can be myelinated (A-type) or unmyelinated (C-type) fibers, with C-type fibers shown to contribute to satiety reflexes. Here we use capsaicin (a TRPV1 agonist and activator of C-type fibers) to determine whether C-type

afferents activate LepR neurons. We also determined whether LepR neurons have ST-evoked asynchronous inputs characteristic of C-type afferents. We used patch-clamp electrophysiology in horizontal brain slices to measure ST-evoked synchronous excitatory postsynaptic currents (eEPSCs) and asynchronous events as well as spontaneous glutamate inputs (sEPSCs). We targeted LepR neurons in the NTS using a transgenic mouse line that expresses Cre-dependent td-Tomato driven by the leptin receptor promoter (LepRCre-tdTom). The majority of LepR neurons examined received both monosynaptic and polysynaptic inputs from ST afferents as well as spontaneous glutamatergic inputs. All LepR neurons tested also displayed asynchronous activity, characterized by a large but transient increase in sEPSC count during the 100 ms following ten 50 Hz stimulations of the ST (average 15 fold-increase ± 3, n = 11). In addition, bath application of 1 μM capsaicin dramatically increased sEPSC frequency in all cells (n = 11). Furthermore, capsaicin reduced the amplitude of ST-evoked EPSCs by 76% (n = 6, $p < .005$), likely due to depletion of glutamate as has been shown previously for other NTS neurons. Taken together with our previous finding that CCK activates these neurons, these data suggest that NTS LepR neurons receive direct inputs from C-type sensory afferents involved in satiety reflexes.

Disclosures: D. Neyens: None. **S.M. Appleyard:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

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Program #/Poster #: 319.07/DP10/WW8

Topic: F.10. Food Intake and Energy Balance

Support: NIH SPARC Program (1U18TR002205-01)

Title: High-throughput analysis of nodose ganglion cell responses to abdominal stimuli in the ferret

Authors: *D. M. MILLER[1], A. C. NANIVADEKAR[2], S. FULTON[5], A. A. MCCALL[1], L. WONG[6], J. OGREN[6], G. CHITNIS[6], B. MCLAUGHLIN[6], L. E. FISHER[3], B. J. YATES[4], C. C. HORN[7]
[1]Otolaryngology, [2]Swanson Sch. of Engineering, Dept. Bioengineering, [3]Physical Med. and Rehabil., [4]Dept Otolaryngology, Univ. of Pittsburgh, Pittsburgh, PA; [5]UPMC Hillman Cancer Ctr., Stephanie Fulton, Pittsburgh, PA; [6]Micro-Leads Inc, Boston, MA; [7]Med., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Background: Thousands of nodose ganglion (NG) neurons act as gatekeepers of abdominal organ sensory information and play critical roles in metabolic and feeding disorders, gastrointestinal (GI) diseases, and inflammatory conditions. Here, we report our first experiments to assess the simultaneous signaling from this neuronal population, using 32-channel electrode

arrays. There were three study objectives: (1) determine the stability of multiple single-unit responses from the ferret nodose ganglion during several hour duration *in vivo* electrophysiology studies; (2) measure the activation patterns to abdominal vagus nerve electrical stimulation; and (3) assess the phenotypes of these neurons to prototypical stimulation, such as gastric distension. **Methods**: All animal experiments were approved by the University of Pittsburgh IACUC. Acute experiments were performed in 6 anesthetized ferrets, using inhalational isoflurane or urethane (ip) anesthesia. A 32-chan 4x8 Utah Electrode Array (Blackrock Microsystems, UT) was inserted in the nodose ganglion using a pneumatic inserter. A balloon-catheter was advanced into the stomach through a small incision on the lateral edge of the gastric fundus; 5, 10 and 20 ml volumes of saline were infused into the balloon to provide distension. Nerve cuff electrodes (Micro-Leads Inc.) were placed on the ventral abdominal vagus trunk. Initial single-unit activity was classified online using Ripple LLC's Trellis software. **Results**: Ganglionic single-unit activity was successfully recorded from the NG for up to 9.5 hours after insertion of the microelectrode array. Approximately 72 single, discriminable units were recorded, yielding 12-13 units per ferret. In two ferrets, we found that approximately 40% of units were sensitive to gastric distention. Of the gastric sensitive units, some units only responded at higher volumes of saline infusion. **Conclusions**: These results show the feasibility to record multiple single-unit responses from the ferret nodose ganglia. A subset of neurons were responsive to gastric distension. Other cells, some activated by abdominal vagus electrical stimulation, could provide additional modalities, such as GI chemical detection and metabolic signals from the liver and pancreas. Future effort could focus on the design of vagus electrical stimulation therapy to modulate specific components of vagal sensory transmission to treat obesity and GI disease.
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Disclosures: D.M. Miller: None. **A.C. Nanivadekar:** None. **S. Fulton:** None. **A.A. McCall:** None. **L. Wong:** A. Employment/Salary (full or part-time):; Micro-Leads Inc. **J. Ogren:** A. Employment/Salary (full or part-time):; Micro-Leads Inc. **G. Chitnis:** A. Employment/Salary (full or part-time):; Micro-Leads Inc. **B. McLaughlin:** A. Employment/Salary (full or part-time):; Micro-Leads Inc. **L.E. Fisher:** None. **B.J. Yates:** None. **C.C. Horn:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

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Program #/Poster #: 319.08/WW9

Topic: F.10. Food Intake and Energy Balance

Support: AMC Fellowship (2015)
Netherlands Diabetes Fonds (2015.82.1826)

Title: Human hypothalamic microglia and POMC neurons are differently affected by anti-diabetic treatment in type 2 diabetic patients

Authors: *M. KALSBEEK, S. E. C. WOLFF, I. V. MILANOVA, N. L. KORPEL, C.-X. YI
Academic Med. Center, Amsterdam, Amsterdam, Netherlands

Abstract: Hypothalamic dysfunction plays a key role in the development of obesity, type 2 diabetes mellitus (T2DM) and other metabolic disorders, which casts a huge burden on modern day society. Our previous studies showed that mice on a long-term obesogenic diet not only become morbidly obese, but also a robust decrease of the appetite-curbing pro-opiomelanocortin (POMC) expressing neurons and an increase of microglial activity in the hypothalamic arcuate nucleus. In humans, a similar decrease of hypothalamic expression of POMC was found in T2DM patients. Whether microglia activity is also affected in the hypothalamus of T2DM patients, and whether anti-diabetic treatments can reverse these changes remains unknown.
In this project, we set out to investigate in human hypothalamus the findings from the rodent studies. We've collected human post-mortem hypothalamic brain tissue from 20 control subjects and 40 subjects diagnosed with type 2 diabetes. Investigation of the medical records confirmed these diagnoses, as T2DM subjects had significantly higher HbA1c (glycated hemoglobin) levels compared to control. Immunohistochemistry was used to visualize microglia and POMC neurons in the hypothalamic infundibular nucleus (equivalent to the arcuate nucleus in rodents). Interestingly, male T2DM subjects who had not received insulin treatment showed significantly lower hypothalamic POMC expression compared to control males, while in T2DM males who had received insulin treatment, the POMC expression was similar to the level of control subjects. Intriguingly, none of these changes were found in female subjects. Furthermore, we did not find differences in microglia expression when subjects were compared based on their received insulin treatment. However, microglia expression was significantly lower in T2DM subjects who had received metformin treatment compared to those who had not received metformin treatment and control, these decreases were found in both males and females. Our data suggest that insulin has a clear gender specific effect on POMC neurons, while the impact of metformin on microglia is not gender-dependent. The mechanism behind these observations will be further studied.

Disclosures: M. Kalsbeek: None. **S.E.C. Wolff:** None. **I.V. Milanova:** None. **N.L. Korpel:** None. **C. Yi:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.09/WW10

Topic: F.10. Food Intake and Energy Balance

Support: CONACYT No. 24335

Title: Insulin contributes to the development of hyperalgesia in overweight ovariectomized rats

Authors: *O. A. JARAMILLO-MORALES[1], J. V. ESPINOSA-JUÁREZ[2], A. ALEJO-MARTÍNEZ[3], L. MENA-VALDÉS[3], F. J. LÓPEZ-MUÑOZ[3]
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Abstract: Several studies have reported that menopause causes a greater perception to painful stimuli and an increase in adipose tissue, which promotes a greater body weight gain compared to men. Additionally, it is known that weight gain is related to changes in the perception of pain; however, its mechanism is not clear. Objective. The aims of this study were to analyze the behavioral responses of hypoestrogenic overweight Wistar rats to thermal stimuli and to analyze the glucose and insulin levels in this population. Methods. Animals with hypoestrogenism induced by bilateral ovariectomy were used. Animals received either a hypercaloric diet (30% sucrose) or regular water with standard laboratory food *ad libitum* for 4 weeks; the thermal nociception and body weight were measured during this period. Four weeks after treatment, the glucose and insulin levels and the abdominal fat weight were measured in both groups. Nociception was assessed using the "Plantar test". Results. Overweight ovariectomized Wistar rats displayed significantly higher body weight and abdominal fat weight than did the control group. A hyperalgesic response was observed in animals fed sucrose. Thermal latency was also significantly decreased during the 4th week in these animals compared to that of controls. There were no differences in glucose levels, but the insulin levels were altered between groups. Conclusions. Our data indicate that increased body weight, abdominal fat and increases in insulin levels are associated with the hyperalgesic responses observed in ovariectomized overweight female rats.

Disclosures: O.A. Jaramillo-Morales: None. **J.V. Espinosa-Juárez:** None. **A. Alejo-Martínez:** None. **L. Mena-Valdés:** None. **F.J. López-Muñoz:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

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Program #/Poster #: 319.10/WW11

Topic: F.10. Food Intake and Energy Balance

Support: Lafayette College

Title: Characterization of the relationship between phenotype, diet, and mitochondrial function in a *Drosophila* model of epilepsy

Authors: S. GENEUS, A. CAREY, *E. R. REYNOLDS
Program in Neurosci., Lafayette Col., Easton, PA

Abstract: Drosophila mutants known as “bang-sensitive” have been utilized as models for neurological conditions including epilepsy, sensorineural deafness, and age-dependent neurodegeneration. These mutants also have a shortened lifespan. While the mechanisms producing these phenotypes are unique to each strain, some of the gene products suggest mitochondrial dysfunction as a possible underlying cause. Diet is an important factor in determining energetics. For example, a ketogenic diet has been shown to be an effective treatment for refractory epilepsy in humans, and diet can manipulate lifespan. We wanted to more clearly define the connection between diet, mitochondrial function and phenotype in this fly model system. Bang-sensitive mutant strains were reared on a standard molasses, yeast and cornmeal (MYC), which is a low protein/high carbohydrate diet, or a protein-rich yeast sugar (YS) diet. The mutants display a lower percentage of seizures on the YS food, but also reduced viability and lifespan. Several biochemical methods were utilized to define the effects of diet. Cytochrome oxidase (CO) in mutants is reduced as compared to wildtype, with increased CO levels in all flies raised on the YS food. In this case, alterations in mitochondrial function correlate with improvement in epilepsy phenotype. In addition, citrate synthase activity and other metabolic indicators suggest that both the mutant phenotype and diet interact in complex ways to produce the defects in excitability and aging.

Disclosures: S. Geneus: None. **A. Carey:** None. **E.R. Reynolds:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

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Program #/Poster #: 319.11/WW12

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant R01 DK104363
NIH grant R01 NS050465/

Title: Precision medicine: Genetic predisposition to fructose consumption in diverse mouse strains

Authors: *Z. YING[1], G. ZHANG[1], H. BYUN[1], Y. ZHAO[1], X. YANG[1], F. GOMEZ-PINILLA[1,2]
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Abstract: The escalating prevalence of metabolic syndrome (MetS) poses a significant public health threat worldwide. Fructose consumption is a major risk for MetS and influences a cascade

of genes that can regulate long-term response to metabolic and neurological disorders (Meng et al., BioMedicine, 2016). MetS predisposes individuals to neurological and psychiatric disorders; however, there is a large range of individual variability. To explore mechanisms involved in the genomic variability in the metabolic predisposition to fructose, genetically diverse mice C57/B6 (B6), DBA and FVB, were fed with 8% fructose for 12 weeks. Fructose-fed DBA mice gained significantly higher amount of body weight and glucose intolerance from the 4th to the 12th week compared to control group, while B6 and FVB showed no differences. Increases in fat mass were only observed in DBA mice, elevated insulin levels were found in DBA and FVB mice, while cholesterol levels were uniquely elevated in B6 mice. RNA sequencing was used to investigate the effect of fructose on the transcriptional profiles of liver, adipose and hypothalamus tissues. Consistent with the differences in phenotype changes, different strains showed distinct patterns of transcriptional and pathway perturbations in a tissue specific manner. Among pathways altered in the liver by fructose, fatty acid and cholesterol metabolic pathways were prominent in B6 mice, while DBA mice showed unique over-representation of pathways related to PPAR signaling pathway. In adipose tissue, pathways are more related to fatty acid metabolism and oxidation in B6 mice, whereas no metabolic pathways were found to be enriched for differential genes in DBA and FVB mice. In hypothalamus tissue, only B6 showed significant enrichment for pathways involved in protein folding, pancreatic secretion and fatty acid beta-oxidation. Using network modeling, we predicted potential key regulators of fructose response such as Fgf21 and Sqle in liver, Cav1and Dpp4 in adipose tissue, and Fmod in hypothalamus. Our findings provide molecular evidence into the mechanisms by which individuals respond differently to the effects of fructose or other environmental factors. Results provide important insight for the design of individualized preventative and therapeutic strategies against MetS or other disorders.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

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Program #/Poster #: 319.12/WW13

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant P60 AA06420
NIH Grant T32 AA007456
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NIH R25 HL084692
AA015566

Title: Expression of functional leptin receptors in the anterior insular cortex: Sexually dimorphic behavioral and metabolic correlates

Authors: *S. R. SPIERLING[1], S. N. PUCCI[2], D. KIRSON[2], A. L. SCOTT[2], S. T. M. REHAN[2], C. A. WILLIAMS[2], S. Y. FANG[2], M. ROBERTO[3], E. P. ZORRILLA[3]
[1]The Scripps Res. Inst., La Jolla, CA; [3]Dept. of Neurosci., [2]The Scripps Res. Inst., LA Jolla, CA

Abstract: Receptors for leptin, an adipocyte hormone originally identified for its role in regulating hypothalamic energy balance circuits, also are synthesized in many extra-hypothalamic brain regions where their functions remain largely uncharacterized. Via TaqMan qPCR, we found that LepR mRNA expression is expressed in the anterior insular cortex of young adult male and female Wistar rats (n=49) at levels about half those expressed in the arcuate nucleus of the hypothalamus. Male rats had significantly greater LepR mRNA expression (~1.5-2-fold) in the anterior insula vs. female rats. Twelve weeks of continuous access to a palatable, high-sucrose diet that increased adiposity tended to increase LepR mRNA levels, but not significantly (p=0.08), with intermittent, long access (24 hr/day, 3 days/week) rats intermediate. However, we identified sexually dimorphic correlations of LepR expression levels with behavioral and metabolic endpoints: in female rats (n=30), independent of diet schedule, greater insular LepR expression in the insula correlated with greater operant fixed-ratio food self-administration (r=0.45, p<0.02) and less nocturnal energy expenditure (r=-0.42p<0.03), measured by indirect calorimetry. In contrast, in males (n=19), greater insular LepR expression correlated with greater diurnal energy expenditure (r=0.49, p<0.05) and was not directly related to food self-administration (r=-0.37). In males, but not females, insular LepR expression also directly and strongly correlated with initial adiposity (% body fat) before diet schedules (r=0.73, p<0.001). A functional role for insula LepR receptors was supported by whole-cell voltage- and current- clamp slice electrophysiological studies, in which bath leptin application (~60 nM) elicited rapid excitatory effects on glutamatergic neurons in the anterior insular cortex. Collectively, the results suggest a functional role and sexual dimorphism of LepR in anterior insula circuits, with levels of expression relating to appetitive behavior, adiposity, and whole-body metabolism. Mechanistic understanding of this novel extra-hypothalamic, leptin-responsive circuit may further understanding of leptin's physiologic and pathophysiologic roles in interoception and higher-order cognitive and motivational processes relevant to obesity and disordered eating.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.13/WW14

Topic: F.10. Food Intake and Energy Balance

Title: Taste preferences in male and female rats after soda consumption

Authors: *K. S. CURTIS, D. SISCO, M. JACOBS
Dept. Pharmacol & Physiol, Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK

Abstract: Our previous work showed no effect of chronic soda intake on body weight in male rats. The goal of the present study was to further evaluate the effect of soda consumption on body weight in male and female rats, and to determine whether soda consumption altered preferences for salt and sucrose taste solutions. Adult ovariectomized (OVX) female rats given estradiol benzoate (EB; n = 5) or oil vehicle (OIL; n = 5), and adult male rats (n = 8) had 2-hr access to store-brand soda for 4 days/week on alternate weeks for 4 weeks, with water only on the other weeks. At the end of each week, rats were given 2-bottle tests (0.5 M NaCl and water or 0.05 M sucrose and water) to assess preferences for the taste solutions. Intake of each solution was measured after 2 hours, and a preference score was calculated (intake of taste solution/total intake). EB- and OIL-treated OVX rats drank similar amounts of soda during the experiment; male rats, which weighed more, drank more soda. Soda intake did not affect body weight in EB-treated rats, but reduced the typical weight gain in both OIL-treated rats and male rats. Although EB-treated rats drank less sucrose in 2-bottle tests after soda access, all rats consumed very little water. Thus, the preference for sucrose taste was not affected by soda access in either OIL- or EB-treated OVX rats, or in male rats. In contrast, salt taste preferences were reduced after soda access in both OIL- and EB-treated OVX rats, as well as in male rats; however, only EB-treated rats preferred salt taste without soda access. Interestingly, all groups increased water intake during the salt and water 2-bottle tests after soda access. Thus, while intermittent access to soda does not increase body weight, it selectively alters taste preferences, particularly in females with estrogen. This effect may be associated with soda-induced changes in central reward circuitry. Levels of dopamine in the Nucleus Accumbens were slightly increased after access to soda and levels of the dopamine metabolite, HVA, were significantly increased. Together, these data suggest that access to soda alters the preference for tastes associated with high calorie/high sodium food by altering dopaminergic activity in the Nucleus Accumbens, which ultimately may facilitate the consumption of these unhealthy foods.

Disclosures: K.S. Curtis: None. **D. Sisco:** None. **M. Jacobs:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.14/XX1

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant RO1 DK047320-22

Title: Role of selenium utilization in hypothalamic control of energy metabolism

Authors: *D. TORRES, M. W. PITTS, A. C. HASHIMOTO, M. J. BERRY
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Abstract: Selenium (Se) an essential trace element known mainly for its antioxidant properties is critical for proper brain function and may also play an important role in whole-body energy metabolism. Dietary Se is incorporated into selenoproteins in the form of the unique amino acid selenocysteine (Sec), which requires its cognate selenocysteine-tRNA (Trsp) to be synthesized. Whole-body knockout (KO) of Sec lyase (Scly), a critical participant in selenium recycling, increases susceptibility to developing metabolic syndrome (MetS) in mice. Scly KO mice also have decreased expression of several selenoproteins in the hypothalamus, a key regulator of energy homeostasis. The purpose of this project is to elucidate the mechanisms underlying the link between disrupted hypothalamic selenium utilization and the associated metabolic disturbances. Agouti-related peptide (Agrp)-positive neurons are a nutrient-sensing hypothalamic sub-population that promote positive energy balance. Reduced sensitivity to the anorexigenic hormone leptin in Agrp neurons has been linked to energy dyshomeostasis. We generated a mouse line with Cre-driven Agrp neuron-specific Scly KO (Scly-Agrp KO mice) to determine the contribution of these neurons to the MetS phenotype observed in whole-body Scly KO mice. Preliminary characterization suggests Scly-Agrp KO mice have increased body weight and feeding behavior, as well as reduced glucose tolerance. We also generated Agrp-neuron specific Trsp KO mice (Trsp-Agrp KO mice) to evaluate ablation of selenoprotein synthesis within these neurons. Trsp-Agrp KO mice had reduced body weight and improved glucose sensitivity. These results may be due to impaired leptin signaling within Agrp neurons.

Disclosures: D. Torres: None. **M.W. Pitts:** None. **A.C. Hashimoto:** None. **M.J. Berry:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

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Program #/Poster #: 319.15/XX2

Topic: F.10. Food Intake and Energy Balance

Support: FAPESP Grant 2015/20198-5
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Title: Characterization of leptin-receptor expressing cells of the arcuate nucleus of hypothalamus during sexual maturation

Authors: *T. T. ZAMPIERI, T. M. BOHLEN, L. C. LANA, R. FRAZÃO
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Abstract: Previous studies have demonstrated that GnRH and kisspeptin neurons are under higher presynaptic inhibitory tonus in prepubertal animals, suggesting that the release of this neural restrain may represent an essential step for puberty onset. Considering the importance of the hormone leptin as a permissive factor for puberty onset and maintenance of the reproductive functions, we investigated whether leptin receptor expressing (LepR) neurons in the ARH exhibit morphological or electrophysiological changes during development. LepR-Cre/tdTomato-reporter or wild-type female mice were used to study LepR cell morphology or activity. Sexual maturation was assessed daily by determining the age at the vaginal opening and at the first occurrence of vaginal cornification (first estrus). Animals were selected for experiments at different ages: 8-12 days (prepubertal), 38-42 days (pubertal) and 60-90 days (adult). Brain sections were processed to perform histological quantification of ARH LepR neurons and measurement of neuronal area (μm). ARH micropunches were obtained and processed for LepR gene expression. Additionally, whole-cell patch-clamp recordings of brain slices were performed to evaluate spontaneous inhibitory and excitatory postsynaptic currents (sIPSC and sEPSC), resting membrane potential (RMP) and leptin responsiveness of ARH LepR neurons throughout the development. Our results demonstrated that the number of LepR neurons increased in the rostral ARH during development, whereas the number of LepR neurons in the caudal ARH remained unchanged. The mean neuronal area of LepR expressing cells in the ARH was similar in all ages evaluated. In addition, LepR gene expression was similar during development. Interestingly, the frequency of sEPSC and sIPSC was significantly decreased in ARH LepR neurons of prepubertal female, compared to prepubertal and adult mice, despite no differences in the mean sEPSC or sIPSC amplitude. Unexpectedly, leptin induced no changes in RMP, input resistance or the frequency of action potential in ARH LepR neurons of female mice. In conclusion, our findings indicate that LepR expressing neurons in the ARH have a lower excitatory and inhibitory presynaptic tonus, which is increased during puberty and adulthood. Suggesting that puberty may be follow by a significant change in the presynaptic tonus of different neural populations involved in the sexual maturation.

Disclosures: T.T. Zampieri: None. **T.M. Bohlen:** None. **L.C. Lana:** None. **R. Frazão:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.16/XX3

Topic: F.10. Food Intake and Energy Balance

Support: Royal Society UK

Title: Inhibition of mitochondrial fission in the dorsal vagal complex of the brain prevents hyperphagia in high fat diet fed rats

Authors: *B. PATEL, L. NEW, J. DEUCHARS, B. FILIPPI
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Abstract: Worldwide obesity has more than doubled since 1980, with over 600 million cases in 2014. Obesity can lead to many adverse metabolic effects of the cardiovascular and endocrine systems and in the brain. In rodents, the dorsal vagal complex (DVC) of the brain regulates glucose homeostasis and controls food intake through insulin signalling. A 3-day high fat diet (HFD) has shown to induce insulin resistance thus affecting the DVC's ability to regulate glucose metabolism and food intake, though exact mechanistic effects of this are still unknown. HFD feeding is associated with an increase in mitochondrial fission in the DVC. Mitochondrial fission is regulated by dynamin related protein 1 (Drp1), and an increase in Drp1 activity in the DVC has shown to inhibit the insulin signalling pathway. Adenoviruses expressing a constitutively active form of Drp1 (S637A), a dominant negative form of Drp1 (K38A) and a GFP expressing control were injected into the nucleus of the solitary tract (NTS) of the DVC. Our data has shown, rats expressing Drp1-S637A in the DVC, do not decrease food intake in response to an acute insulin treatment, compared to the GFP controls. Confirming that increases in mitochondrial fission results in impaired insulin sensitivity. Furthermore, we found that after 14 days, Drp1-S637A expressing rats were hyperphagic and had an overall increase in body weight and fat accumulation. Following this, we determined if inhibition of Drp1 can restore insulin sensitivity in HFD fed (insulin resistant) rats. Acute insulin treatment, decreased food intake in the HFD fed Drp1-K38A expressing rats, but not in the HFD fed GFP expressing rats, confirming that inhibition of Drp1 can restore insulin sensitivity. In addition, chronic inhibition of Drp1, resulted in a decrease in food intake, body weight and fat accumulation.

Disclosures: L. New: None. **J. Deuchars:** None. **B. Filippi:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

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Program #/Poster #: 319.17/XX4

Topic: F.10. Food Intake and Energy Balance

Support: JSPS KAKENHI Grant Number 15H05624

Title: Hypothalamic neuronal circuits regulating hunger-induced taste modification

Authors: O. FU[1,2], Y. IWAI[1], *T. MISAKA[1], Y. MINOKOSHI[2], K. NAKAJIMA[2]
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Abstract: Gustatory system plays a critical role in sensing appetitive and aversive taste stimuli for evaluation of food quality. Although taste sensitivity and taste preference are known to change depending on internal state such as hunger, the mechanistic insight remains unclear. Here we show that neuronal mechanism regulating hunger-induced taste modification in the mouse brain.

Starved mice exhibit increased sensitivity for sweet taste and tolerance for aversive taste, respectively (C57/BL6J mice, male, 10 weeks, n=6). As Agouti-related peptide (AgRP)-expressing neurons located in the arcuate nucleus of the hypothalamus (ARC) play a key role in driving hunger by sending inhibitory inputs towards multiple brain regions. we thus investigated whether optogenetic stimulation of AgRP neurons (AgRP-ires-Cre mice expressing ChR2 in AgRP neurons, male, 10 weeks, n=6) lead to the taste modification. Selective activation of AgRP neurons projecting to the lateral hypothalamus (LH) but not other brain regions recapitulated the hunger-induced change in taste sensitivities.

Immunohistochemical analysis indicates AgRP neurons connect to parts of the glutamatergic Vglut2-expressing neurons in the LH. We thus evaluated the role of these neurons in taste sensitivities. Chemogenetic inhibition of $Vglut2^{LH}$ neurons (Vglut2-ires-Cre mice expressing inhibitory DREADD, hM4Di in $Vglut2^{LH}$ neurons, male, 8~16 weeks, n=7) changed taste sensitivities as observed under physiological hunger. By contrast, activation of $Vglut2^{LH}$ neurons (Vglut2-ires-Cre mice expressing excitatory DREADD, hM3Dq in $Vglut2^{LH}$ neurons, male, 8~16 weeks, n=6) completely cancelled the hunger-induced phenotype.

$Vglut2^{LH}$ neurons send dense projections to the lateral septum (LSI), the anteriordorsal nucleus of thalamus (AD), and the lateral habenula (LHb), we conducted pathway-selective chemogenetic inhibition experiments to identify the key area on the taste modification. Interestingly, $Vglut2^{LH}$ projection in the LSI only increased sensitivity for sweet taste. By contrast, $Vglut2^{LH}$ projection in the LHb decreased tolerance for aversive taste.

In summary, we found that 1) hunger-induced taste modification is caused by activation of the LH-projecting AgRP neurons and the following inhibition of $Vglut2^{LH}$ neurons and that 2) the two differential inhibitory circuits ($AgRP^{ARC}$-$Vglut2^{LH}$-LSI and $AgRP^{ARC}$-$Vglut2^{LH}$-LHb) regulate sensitivity for sweet taste and tolerance for aversive taste, respectively. These hypothalamic circuits for taste modification would be important for optimizing feeding behavior under an energy deficit.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

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Program #/Poster #: 319.18/XX5

Topic: F.10. Food Intake and Energy Balance

Support: NIH R01DC013904

Title: Roux-en-Y and vagotomy increase DNA fragmentation in vagal afferent neurons of rats within 24h

Authors: *D. M. MINAYA CABA[1], A. TURLEJ[1], S. C. FARUQUE[1], V. LACMANOVIC[1], A. JOSHI[1], A. HAJNAL[2], P. M. DI LORENZO[3], K. CZAJA[1]
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Abstract: Roux-en-Y gastric bypass (RYGB) is one of the most effective long-term weight loss treatments for obesity. Although the effects of RYGB on the gut-brain vagal connection are largely unknown, prior studies have shown that RYGB triggers a degenerative response in vagal afferents similar to the response observed after subdiaphragmatic vagotomy (VAX). However, these observations have only been recorded several weeks after the procedure. The aim of this study was to investigate the short-term effects of RYGB and VAX on plasticity of vagal afferents in the nodose ganglia (NG) and Nucleus Tractus Solitarius (NTS) in male and female rats. Sprague-Dawley rats underwent RYGB, VAX, or sham surgery. Twenty-four hours later, animals were sacrificed and NG and NTS were collected. Neuronal cell damage was determined by TUNEL assay. Inflammation was determined by quantifying the fluorescent staining against the ionizing calcium adapter binding molecule 1 (IBA 1). Reorganization of vagal afferents was evaluated by fluorescent staining against Isolectin 4 (IB4). Results of the study revealed that RYGB and VAX significantly increased DNA fragmentation in vagal neurons in the NG of male and female rats. In males, RYGB and VAX decreased the density of vagal afferents projecting to the NTS. RYGB did not trigger microglia activation in the intermediate NTS, but VAX increased microglia activation. RYGB and VAX decreased microglia activation in the rostral NTS. In females, RYGB decreased the density of vagal afferents projecting to the intermediate NTS. However, we observed an increase in fibers projecting the rostral NTS. In contrast, VAX did not affect the density of vagal fibers projecting to NTS. RYGB decreased microglia activation in the NTS, but we did not observe an inflammatory response after VAX. The changes observed in vagal presynaptic projections to the NTS indicate that RYGB and VAX surgery induce rapid neuronal damage in the NG. Furthermore, the current data suggests that reorganization of vagal afferents and the inflammatory response previously reported in the NG and NTS ten days after RYGB and VAX surgery develop progressively over that time course.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.19/XX6

Topic: F.10. Food Intake and Energy Balance

Title: The physiological effects of PYY is dependent upon time of day

Authors: M. J. MARONI, K. M. CAPRI, A. V. CUSHMAN, I. K. MONTEIRO DE PINA, M. H. CHASSE, *J. A. SEGGIO
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Abstract: Food consumption during the inactive periods, which is common for individuals experiencing circadian disruption, have been liked to metabolic diseases, including Type-2 diabetes mellitus and obesity. Recent studies show that restricting food intake during the active period only can attenuate or reverse these metabolic problems in animal models. One hormone which plays a large role in food consumption patterns is PYY, a hormone released by the hindgut after food consumption which interacts with NPY2 receptors in the hypothalamus to modulate hunger. This study aimed to uncover the circadian variation of food consumption and the secretion of hormones related through metabolism through supplementation of PYY 3-36 in male CD-1 mice under a standard 12:12 LD cycle. In the first part of the study, blood was collected from 12 hour fasted mice at ZT 0, ZT 6, ZT 12, and ZT 18, and the amount of PYY 3-36 were measured. In the second part, mice were fasted for 12-hours; afterwards, they were given an injection of PYY 3-36 or saline at the aforementioned zeitgeber times and were given food to determine the levels of food consumption and hormones observed under each injection type and time point. Endogenous fasting levels of PYY 3-36 exhibit time of day differences, peaking at ZT 6. PYY 3-36 is most effective at suppressing food intake and body weight, compared to saline injected controls, when injected during the subjective night than the subjective day. Interestingly, PYY3-36 led to overall increases in glucose levels and disrupted the circadian glucose response to a meal after a fast. Injections of PYY 3-36 also led to an overall reduction of insulin regardless of time of day. These results illustrate that the effectiveness of PYY 3-36 in modulating food consumption and hormone secretion is dependent upon the time of day given.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.20/XX7

Topic: F.10. Food Intake and Energy Balance

Title: Sex differences and similarities in stress-induced eating behavior

Authors: *N. CLAUSS
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Abstract: Stress-induced consumption of highly palatable (HP) food could be one potential pathway from stress to obesity. However, it is unclear whether males engage in stress-induced eating to a similar extent as females (e.g. Grunberg & Straub, 1992; Zellner et al., 2007). The current study hypothesized that exposing male and female participants to sex-specific stressors would lead to similar levels of stress-induced consumption of HP food between sexes.A preliminary power analysis indicated a sufficient sample size would be 165 participants. Participants were 167 undergraduate students recruited from a southern United States university, a majority of whom were female (52.6%), Caucasian (73.10%), and between the ages of 18-21 (92.6%) Participants were randomly assigned to one of three conditions: achievement stress, social rejection, and control. Participant heart rate and post-condition food intake were measured. A two-way between-groups ANOVA was conducted to explore the impact of sex and experimental condition (achievement, social rejection, control) on stress (as measured by respiratory Sinus Arrhythmia). There was a significant interaction effect for sex and experimental condition (F [2, 159] = 6.73, $p < .01$). Males demonstrated higher stress after an achievement stressor (MD = -.88, SE, .34, p = .01, $C;_{.95}$[-1.56, -.20]), and females demonstrated higher stress after a social rejection stressor (MD= -1.05, SE = .40, p = .01, $C;_{.95}$[-1.85, -.25]). A two-way between-groups ANOVA was conducted to explore the impact of sex and sex-specific laboratory stressor on HP food consumption (HPFC). The interaction between sex and amount of HPFC was not statistically significant. However, there was a main effect for condition (F [2, 157] = 4.23, $p < .01$). Post-hoc comparisons demonstrated that males and females both consumed a significant amount of HP food after either the social rejection or the achievement condition than they did after the control condition. For female participants, HPFC was also associated with current menstrual cycle such that overall consumption of HP food was significantly increased among females in the luteal phase, and consumption of specifically HP salty food was significantly greater among females in the ovulation phase. Given the finding that RSA provided an accurate measure of stress that resulted in stress-induced eating, it is possible that biofeedback could be used to reduce instances of stress-induced consumption of non-nutritious, hyper-energetic foods. The preliminary result that females HPFC may be influenced by menstrual cycle could have implications for the role of hormones in stress-induced eating behavior.

Disclosures: N. Clauss: None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.21/XX8

Topic: F.10. Food Intake and Energy Balance

Title: single cell resolution hindbrain neuronal dynamics reveal convergent appetitive and consummatory processes in both hunger and thirst

Authors: *R. GONG[1], S. M. STERNSON[2]
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Abstract: Feeding and drinking behavior are comprised of sequential appetitive and consummatory phases. Interoceptive neurons that monitor energy or hydration state can be used to artificially induce hunger or thirst states in order to examine circuits responsible for need-based behaviors. Activation of AGRP neurons or SFO^{Nos1} neurons can induce seeking and consumption of food or water, respectively. To identify brain areas sensitive to both AGRP neuron and SFO^{Nos1} neuron activation, we used optogenetic activation of these neurons and determined brain areas that contain Fos-immunoreactivity after acute activation. Stimulation of AGRP neurons or SFO^{Nos1} neurons induced strong Fos expression in both lateraldorsal tegmental area (LDTg) neurons and neurons in the pre locus coeruleus (preLC). Cre-dependent trans-synaptic anterograde herpes simplex virus starting from AGRP neurons also labeled neurons in these areas, raising the possibility that these regions play an important role in feeding and drinking behavior. To investigate these regions, we developed a stable cellular-resolution endoscopy calcium imaging method in the hindbrain that stabilizes unwanted hindbrain movement so that we could readily obtain neuronal dynamics in freely moving mice. We found that GABGAergic neurons are highly correlated with locomotoer activity, indicating a role in food- and water-seeking behaviors; whereas glutamergic neurons are strongly modulated during the consummatory phase. Thus two independent populations of neurons in these adjacent brain regions actively take part in the sequential appetitive and consummatory phases of hunger and thirst behaviors. Collectively, these data show the convergence of circuits regulating hunger and thirst in hindbrain areas that respond to locomotion and consummatory behaviors.

Disclosures: R. Gong: None. **S.M. Sternson:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.22/XX9

Topic: F.10. Food Intake and Energy Balance

Title: Mast cells-derived histamine regulates liver ketone body production via oleoylethanolamide-mediated signaling

Authors: *A. MISTO[1], A. BASIT[2], G. PROVENSI[3], V. VOZELLA[2], M. PASSANI[4], D. PIOMELLI[5]
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Abstract: The fatty acid ethanolamide, oleoylethanolamide (OEA), is a lipid mediator that regulates feeding and stimulates lipolysis and fatty acid oxidation in adipocytes and hepatocytes through activation of nuclear peroxisome proliferator-activated receptor type-alpha (PPAR-α). Fasting is accompanied by a substantial elevation in liver OEA levels, but the biochemical mechanism and physiological implications of this effect are unknown. The neurotransmitter histamine plays an important role in the control of feeding behavior and contributes to the anorexic effects of systemically administered OEA. In the present study, we describe an unprecedented paracrine mechanism that regulates fasting-induced ketogenesis through stimulation of OEA signaling in the liver. Histidine decarboxylase-null ($HDC^{-/-}$) mice, mast cell-deficient ($C57BL/6J\text{-}Kit^{W\text{-}v}/J$) mice, $NAPE\text{-}PLD^{-/-}$ mice and their wild-type littermates (all males) were subjected to three different conditions: a) free feeding (FF); b) 12 h food deprivation (FD) and c) 1 h refeeding after food deprivation (RF). Histamine (0.45 μmol or 0.9 μmol in sterile saline) was slowly injected into the liver using an insulin syringe (injection volume 0.1 mL). 30 min later, the mice were killed and their livers were collected. H_1 antagonist fexofenadine (10 mg/kg), H_2 antagonist famotidine (10 mg/kg), H_3 antagonist ciproxifan (3 mg/kg) and H_4 antagonist JNJ7777120 (20 mg/kg) were administered by intraperitoneal injection 1 h before tissue harvest. Alpha-fluoromethylhistidine (α-FMH), a suicide inhibitor of HDC, was administered by intracerebroventricular infusion (1 μg/μl in physiological saline). Endogenous OEA, N-oleoyl-PE, oleic acid and histamine levels were quantified by liquid chromatography/mass spectrometry (LC/MS) analyses and ketone body production was measured in plasma and liver samples using a colorimetric assay kit. We found that: 1) a 12-h fast stimulates mast cells to release histamine into the hepatic portal circulation; 2) the biogenic amine travels to the liver, where it activates G protein-coupled H_1 histamine receptors, which

activate in turn OEA biosynthesis; 3) this signaling cascade enhances fasting-induced ketogenesis, without affecting lipolysis or other responses to food deprivation. Note that disabling histamine-dependent OEA signaling, either genetically or pharmacologically, cuts down overall ketone body production in fasting mice by approximately 50%. The results reveal an unexpected role for histamine in the control of bioenergetics homeostasis, and suggest that dysfunctions in histamine-dependent OEA signaling might contribute to metabolic disease.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

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Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant DK104897

Title: Ventral hippocampus ghrelin elevates meal size via interactions with gut-derived satiation signals

Authors: *A. N. SUAREZ[1], C. LIU[2], E. NOBLE[3], A. CORTELLA[1], S. E. KANOSKI[1]
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Abstract: In addition to classic gastrointestinal-hindbrain pathways that control meal size, emerging findings reveal that higher-order brain substrates influence satiation processing as well. Our recent findings show that the gut-derived "hunger" hormone ghrelin acts in the ventral subregion of the hippocampus (vHPC) to not only stimulate conditioned aspects of feeding but also increase spontaneous meal size. Here we investigate whether vHPC ghrelin signaling elevates meal size through interactions with vagally-mediated within-meal satiation signals, including the intestinal hormone cholesystokinin (CCK) and mechanical distension of the stomach. Results show that a dose of vHPC ghrelin that is subthreshold for feeding effects alone attenuates the satiating efficacy of both peripheral CCK administration and gastric distension following methylcellulose gavage. To determine the descending neural pathways potentially mediating these effects, we utilized a multisynaptic virus-based tracing method to identify multi-order neural pathways from the vHPC (CA1) to the dorsal vagal complex (DVC) in the hindbrain. Results identify the lateral hypothalamic area as a relay connecting the vHPC to the DVC. We conclude that vHPC ghrelin signaling increases meal size through interactions with gut-derived vagally-mediated satiation signals and that these effects may occur through a newly identified descending pathway connecting the vHPC to the caudal brainstem via the lateral hypothalamic area.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

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Topic: F.10. Food Intake and Energy Balance

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McNair Foundation

Title: Basal forebrain excitatory neurons suppress appetite

Authors: *J. PATEL[1], K. UNG[2], J. SWANSON[3], A. M. HERMAN[2], E. HANSON[3], B. R. ARENKIEL[4]
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Abstract: Hypothalamic circuits that regulate feeding, dynamically respond to the perception of food, and function to govern consummatory behaviors. How sensory information is processed and relayed to the hypothalamus, and how such circuits function towards regulating feeding related behavior remains largely unknown. Here, we investigated a subset of excitatory neurons that reside in the mouse basal forebrain, a structure that has previously been implicated in appetite suppression and have uncovered a potent role for this circuit node in regulating feeding behavior through food avoidance mechanisms. Utilizing in-vivo microendsocopy and cell-type specific expression of GCaMP6m, we identified a group of basal forebrain excitatory neurons selectively activated by food odor presentation. Chronic activation of basal forebrain excitatory neurons resulted in severe hypophagia that ultimately led to starvation and death. Moreover, we found that basal forebrain excitatory neurons receive monosynaptic cholinergic inputs, and project to the lateral hypothalamus. Optogenetic activation of both basal forebrain excitatory neuron cell-bodies and targeted lateral hypothalamic projections confirmed that this extrahypothalamic circuit node functions in the observed reduced food intake. We also discovered that this acute hypophagic phenotype was in part due to avoidance behavior towards food and food-related stimuli. Together, our data highlight a role for the basal forebrain as a potent integrator of sensory information, capable of governing consummatory behaviors in response to the perception of food.

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Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.25/XX12

Topic: F.10. Food Intake and Energy Balance

Support: R01DK113445
5T32NS061764

Title: Essential and sex-specific effects of mGluR5 in the ventromedial hypothalamus facilitating glucose and lipid homeostasis

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Abstract: Brain-derived neurotrophic factor (BDNF) and its receptor TrkB promote neuronal survival, differentiation and synaptic plasticity and play required roles in the central regulation of energy and glucose balance. Indeed, mice with global central BDNF depletion ($BDNF^{2L/2LCk\text{-}cre}$) exhibit excessive feeding, obesity, insulin resistance and hyperglycemia. Furthermore, *Bdnf* was identified as one of the top loci linked to obesity susceptibility in humans. The ventromedial hypothalamus (VMH), an energy and glucose balance-regulating center containing anorexigenic and glucose sensing neurons, is an important site of BDNF action. Accordingly, VMH neurons in $BDNF^{2L/2LCk\text{-}cre}$ mutant mice exhibit diminished excitatory drive and selective deletion of *Bdnf* in this region triggers obesity and the associated metabolic syndrome. To gain insight into the underlying mechanisms, we conducted an analysis of the transcriptome of VMH cells of control and $BDNF^{2L/2LCk\text{-}cre}$ mice and found that metabotropic glutamate receptor 5 (mGluR5) was significantly downregulated in male and female mutants. Because mGluR5s play paramount roles in excitatory synaptic plasticity in other brain regions, we hypothesized that they might facilitate energy and glucose balance control acting downstream of BDNF in the VMH. To test this, we examined the effect of deleting mGluR5 in $SF1^{+}$ neurons, which in the brain are exclusive to the VMH. We found that this deficit produced alterations in glycemic control, insulin sensitivity and lipid metabolism without affecting body weight in mutant ($mGluR5^{f/f:SF1\text{-}cre}$) females but not in male mice. Alterations in synaptic physiology and in the intrinsic excitability of $SF1^{+}$ neurons and diminished sympathetic tone were observed exclusively in $mGluR5^{f/f:SF1\text{-}cre}$ females and underlie these metabolic abnormalities. Notably, the beneficial effects of estrogen on glucose balance control are blunted in $mGluR5^{f/f:SF1\text{-}cre}$ females. To ensure

scientific rigor, all experiments involved appropriate use of controls, power analysis to determine cohort size and statistical analysis to determine significant differences. Collectively, these findings indicate a novel an essential role of mGluR5 in female VMH facilitating estrogen signaling, neuronal activity, glucose homeostasis and lipid metabolism. They also inform mechanisms underlying the reported higher risk of insulin resistance and metabolic disorders in post menopausal women.

Disclosures: M. Rios: None. **M. Panessiti:** None. **D. Ameroso:** None. **A.N. Rock:** None. **J.L. Maguire:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.26/XX13

Topic: F.10. Food Intake and Energy Balance

Support: Japan Early-Career Scientists Grants 2618K16225

Title: PTP1B deficiency enhances leptin action to improve glucose homeostasis in IDDM

Authors: *Y. ITO[1,2], R. BANNO[2,3], H. YAGINUMA[2], K. TAKI[2], A. MIZOGUCHI[2], M. SUGIYAMA[2], T. TSUNEKAWA[2], H. TAKAGI[2], H. ARIMA[2]
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Abstract: Recent researches showed that intracerebroventricular (ICV) administration of leptin could normalize blood glucose levels (BG) in rodent models of insulin-dependent diabetes mellitus (IDDM). As a mechanism by which leptin improves glucose homeostasis in IDDM, central leptin is supposed to enhance glucose uptake in both brown adipose tissue and soleus muscle via the activation of sympathetic nervous system. Protein tyrosine phosphatase 1B (PTP1B) negatively regulates leptin signaling via the direct dephosphorylation of Jak2 and have been implicated as an important regulator of energy homeostasis. On the other hand, it is still unclear whether PTP1B affect the leptin action in IDDM. In the present study, we investigated the role of PTP1B in leptin action for treating IDDM by using PTP1B deficient (KO) mice. At first, wild-type (WT) and KO mice were intraperitoneally injected with 150 mg/kg streptozotocin (STZ) to generate IDDM model for each study group. After 1 week of the procedure, the BG at the end of dark cycle were monitored in IDDM mice every third day. We also measured BG in mice received two kinds of treatment. One is to implant mice subcutaneously with an osmotic mini-pump providing leptin (20 μg/day) or saline systemically, and the other is to implant with the pump in the same way, which was connected to ICV cannula to enable continuous infusion

of leptin (0.25 μg/day) or saline only centrally. STZ treatment significantly increased BG in both WT and KO mice compared to control mice, but the BG was significantly lower in KO mice compared to WT mice. Systemic or central leptin treatment decreased BG in WT mice, although the BG was still significantly higher than those in control mice. In contrast, in KO mice both kinds of leptin treatment decreased BG to almost same levels as control mice. No differences were detected in body weight and food intake between genotypes. These results suggest that PTP1B deficiency enhanced leptin action in the brain to improve blood glucose levels in IDDM and may provide a potential approach for treating IDDM.

Disclosures: Y. Ito: None. **R. Banno:** None. **H. Yaginuma:** None. **K. Taki:** None. **A. Mizoguchi:** None. **M. Sugiyama:** None. **T. Tsunekawa:** None. **H. Takagi:** None. **H. Arima:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.27/XX14

Topic: F.10. Food Intake and Energy Balance

Title: A fully implantable, closed-loop wireless recording and stimulation system for the treatment of obesity

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Abstract: Over the past several decades, obesity has grown into a major global epidemic. In the United States, more than two-thirds of adults are now overweight and one-third is obese [1]. Unfortunately, the current available treatments for obesity are often ineffective, and do not treat the underlying pathology. Moreover, therapies for these conditions are limited by our inability to understand and control the network of neuronal circuitry, in particular **vagus afferent fibers**, that regulate energy homeostasis [1]. Meal cessation is to a large extent mediated by feedback from the gut to the brain. Distension of the stomach, the absorption of nutrients and the release of satiety hormones (GLP-1, peptide YY, and cholecystokinin) cells can activate the vagus nerve that then signals the nucleus tractus solitarius (NTS) in the hindbrain [2]. Neurons in NTS then relay signals to the parabrachial nucleus (PBN) and other nuclei to suppress feeding [3]. Because the **vagus** is a major origin of satiation signals, it is a logical place to intervene to treat obesity. Furthermore, several studies indicate that the vagus becomes insensitive to satiation signals in obese animals. Consequently, the ability to bypass this obesity-induced insensitivity and experimentally activate the vagus has significant potential [4]. However, a human nodose ganglion contains 100,000 neurons which can innervate many different internal organs [5]. Therefore, cellular level control of nerves is crucial to this pursuit. In addition, there is no way to

directly record the activity of vagal neurons in awake mice, which can provide real insights into how satiety information is processed. Thus, all the experiments that suggest that the vagus becomes insensitive to nutrients and hormones in response to obesity are indirect [4]. Here, we propose soft, miniaturized implantable battery-free wireless device that can offer exceptional spatial/temporal resolution, optogenetic stimulation, and capabilities in wireless recording. These innovative and disruptive technologies allow experiments that examine subtypes suppressing feeding, thereby identifying a signaling pathway that could regulate food intake to treat obesity. Here, we use adult male mice (C57/BI6 background) for experiments and inject AAV9-Syn-DIO-ChrimsonR-TdTomato virus into nodose ganglion to infect vagus nerve.

1. Wu *et al. Cell 137*:1225-1234, 2009.
2. De Lartigue, *et al. Mol Metab 3*: 595-607, 2014.
3. Morton *et al. Nature Rev Neurosci* 15(6):367-78, 2014.
4. Carter *et al. Nature* 503:111-114, 2013.
5. Famm *et al. Nature 496*:159-161. 2013.

Disclosures: W. Kim: None. **C. Campos:** None. **R.D. Palmiter:** None. **S. Park:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.28/YY1

Topic: F.07. Autonomic Regulation

Support: NIH Grant HL116387

Title: Regulation of pancreatic islet oxytocin by autonomic nervous system agonists

Authors: J. S. WESTWRIGHT[1], A. SZETO[2], *A. HELLER[2], P. M. MCCABE[2], A. J. MENDEZ[3]
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Abstract: Objective: The neuropeptide oxytocin (OT) is a well-established regulator of reproductive processes that has gained recent attention as a modulator of social behavior. Peripheral effects of OT are classically thought to result from central release, yet OT and its receptor have also been detected in peripheral tissues, including the endocrine pancreas. OT has been implicated in glycemic control and metabolism, but regulation of its release from pancreatic islet cells is not well understood. OT release in the central nervous system is modulated by classical neurotransmitters such as norepinephrine (NE). Similarly, autonomic nervous system (ANS) derived NE and acetylcholine (ACH) are known to play a role in pancreatic metabolic processes (e.g. insulin and glucagon secretion). Thus, the present study examined whether ANS

agonists modulate OT secretion in pancreatic islet cells in vitro, and whether OT influences insulin secretion.
Methods: Isolated human or rat pancreatic islets or mouse MIN6 cells (a cancerous, pancreatic beta-islet cell line) were primed in low glucose media for one hour, then subsequently incubated in media containing low (3 mM) or high (20 mM) glucose with or without NE or ACH (10 µM). Secretion of OT and insulin were quantified by enzyme-linked immunosorbent assay (ELISA). To evaluate the effect of OT on glucose-stimulated insulin secretion, rat pancreatic islets were incubated with low or high glucose in the absence or presence of 1nM OT.
Results: In the presence of high or low glucose, NE significantly increased secretion of OT from islet cells. Ten µM NE decreased and 10 µM ACH increased insulin secretion from the mouse beta-cell line MIN6 and human islets, consistent with previous research. In the presence of high glucose, incubation with OT significantly increased insulin secretion from rat islets.
Conclusions: Treatment with NE, regardless of glucose concentration, stimulated release of OT from pancreatic islets. These results suggest that OT secretion from the endocrine pancreas may be regulated by the ANS. Furthermore, OT enhances insulin secretion in the presence of high glucose. Future experiments will evaluate the relationship between pancreatic OT and insulin to determine whether OT, directed by the ANS, may act as a secondary system to optimize glycemic control in times of challenge.

Disclosures: J.S. Westwright: None. **A. Szeto:** None. **A. Heller:** None. **P.M. McCabe:** None. **A.J. Mendez:** None.

Poster

319. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 319.29/YY2

Topic: F.07. Autonomic Regulation

Support: National Research Foundation of Korea

Title: The comparative study on anatomical and functional innervation between parasympathetic nervous system and liver in mouse and human

Authors: *D. CHEON, C. NAMKOONG, H. J. CHOI
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Abstract: The liver is innervated by both the sympathetic and the parasympathetic nerve system. Human liver parasympathetic nerves are well characterized in neuroanatomical pattern in the human liver is unknown. In the present study, we investigated the parasympathetic innervation of human and mouse liver by passive tissue clearing method for 3D-images. We were optimize passive clearing method and immunofluorescent labelling of parasympathetic neurons in human

liver and mouse tissue. In addition to visulaising of parasympathetic nerve in liver. We performed liver passive clearing and immunohistochemistry analysis to confirm 3D-anatomical interaction of parasympathetic neurons and hepatocytes. The images show complex and dense neuronal circuit in the liver. We next investigated the role of parasympathetic in regulation of liver glucose metabolism by chemogenetic methods using DREADDs (designer receptors exclusively activated by designer drugs). We confirm that our chemogenetic virus and mouse model is working by electrophysiology of DMV neurons showing that CNO activates the neurons. Acute activation of neurons in DMV region results in increasing hepatic lipogenesis and gluconeogenesis. These results suggest that specific activation/inhibition of parasympathetic neurons to might be involved in the regulation of lipid and glucose metabolism.

Disclosures: D. Cheon: None. **C. namkoong:** None. **H.J. choi:** None.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.01/YY3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: National Natural Science Foundation of China (81403502)
General Research Fund of Research Grants Council of Hong Kong (17124418)

Title: Metabolomic and structural brain connectomic evidence validating traditional Chinese medicine diagnostic classification of major depressive disorder

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Abstract: Major depressive disorder (MDD) is a highly heterogeneous mental illness. Further classification may help characterize its heterogeneity. The purpose of this study was to examine metabolomic and brain connectomic associations with traditional Chinese medicine (TCM) diagnostic classification of MDD. Fifty unmedicated depressed patients were classified into Liver Qi Stagnation (LQS, n = 30) and Heart and Spleen Deficiency (HSD, n = 20) subtypes according to TCM diagnosis. Healthy volunteers (n = 28) were included as controls. Gas chromatography-mass spectrometry (GC-MS) and diffusion tensor imaging were used to detect serum and urinary metabolomic profiles and whole-brain white matter connectivity, respectively. In metabolomic analysis, 28 metabolites were identified for good separations between TCM subtypes and healthy controls in serum and urine samples. While both TCM subtypes had similar

profiles in proteinogenic branched-chain amino acids and energy metabolism-related metabolites that were differentiated from healthy controls, the LQS subtype additionally differed from healthy controls in multiple amino acid metabolites that are involved in the biosynthesis of monoamine and amino acid neurotransmitters. Several metabolites are differentially associated with the two subtypes. In connectomic analysis, The LQS subtype showed significant differences in multiple network metrics of the angular gyrus, middle occipital gyrus, calcarine sulcus, and Heschl's gyrus when compared to the other two groups. The HSD subtype had markedly greater regional connectivity of the insula, parahippocampal gyrus, and posterior cingulate gyrus than the other two groups, and microstructural abnormalities of the frontal medial orbital gyrus and middle temporal pole. The insular betweenness centrality was strongly inversely correlated with the severity of depression and dichotomized the two subtypes at the optimal cutoff value with acceptable sensitivity and specificity. These results suggests that the LQS subtype may represent an MDD subpopulation mainly characterized by abnormalities in the biosynthesis of monoamine and amino acid neurotransmitters, closer associations with stress-related pathophysiology, and aberrant connectivity of the audiovisual perception-related temporal-occipital network, whereas the HSD subtype is more closely associated with hyperconnectivity and microstructural abnormalities of the limbic-paralimbic network. Certain metabolomic and connectomic variables are potential biomarkers for TCM diagnostic subtypes which is perhaps an alternative classification for depressive disorders.

Disclosures: Z. Zhang: None. **L. Liu:** None. **H. Zhang:** None. **X. Xu:** None.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.02/YY4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Shanghai Sailing Program(18YF1402400)

Title: A genetic insight into the pathogenesis of depression from gene set enrichment analysis

Authors: *D. DAI[1,2], N. MA[2], Q. ZHOU[1], Z. LIU[2], J. FENG[2,3]
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Abstract: Background: Depression as a heterogeneous disorder, results from a complex interaction between vulnerability genes and environmental factors. Genome-wide association study (GWAS) has greatly facilitated the understanding of genetic basis of depression.

Distribution of depression-related genes in the human brain is not clear yet, which can be very informative to identify key brain regions and genetic mechanism underlying the altered brain functions in depression.
Methods: Based on GWAS results of major depressive disorder (MDD) from the Psychiatric Genomics Consortium, we obtained MDD-related genes within a 50Kb distance of SNPs with significant effects on the developing of MDD (p value <0.001). ABAEnrichment R package was applied to MDD-related gene get enrichment analysis. GO (Gene Ontology) enrichment analysis was performed by R package clusterProfiler to identify biological processes, molecular functions and cellular components regulated by those MDD-related genes. At last, a region of interest (ROI) to voxel analysis was conducted to identify any voxels that differently connected to paracentral lobule (posterior part) between 282 depressed patients and 254 healthy subjects (two-sample t-tests, AlphaSim correction threshold of p value < 0.05).
Results: Those MDD-related genes were found to be significantly enriched in three human brain regions (p value <0.05). Anterior orbital gyrus and habenula, which have been both implicated in reward processing and depression, were identified to be enriched with MDD-related genes. To our surprise, posterior part of paracentral lobule representing body sensory information was indicated as the brain region with most significant enrichment expression of MDD-related genes. Those three regions were all found in the right part of the human brain. ROI analysis indicated altered functional connectivity between paracentral lobule with some brain regions including putamen and thalamus in depressed patients.
Conclusion: Paracentral lobule, anterior orbital gyrus and habenula might get involved in the pathogenesis of depression via disrupted reward processing, especially for the somatosensory information. The altered functional connectivity may underlie the structural and functional abnormality of putamen and thalamus in depressed patients, indicating paracentral lobule might involve in reward processing related subcortical dysfunction in depression. Together with the gene set enrichment analysis, we pointed out key brain regions in the pathogenesis of depression.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.03/YY5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Phyllis and Jerone Lyle Rappaport Fellowship
NIMH Grant F32 MH106262
NIMH Grant 5R01 MH095809

Title: Frontoinsular network markers of current and future adolescent mood health

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Abstract: *Objective:* Depression and other mood disorders frequently emerge in adolescence, pointing to this life stage as a critical period for such disorders. The identification of biomarkers in adolescence that can reliably assess and predict depression is a vital step towards enhanced treatment of these conditions. The current study aimed to identify frontoinsular biomarkers for assessing and predicting mood health in an adolescent sample, using task-based neuroimaging. *Method:* The sample consisted of adolescents (n=42, ages 14-19) exhibiting high variance in severity of depressive symptoms. All participants completed a baseline neuroimaging session, which utilized an emotional executive functioning task. A subset of participants (n=28) completed a two-week follow-up, comprised of a daily diary report of negative affect and a final report of depressive symptom severity. Regression analyses tested associations between task-based functional connectivity in frontoinsular networks and measures of current or future mood health. Additional analyses examined associations between task performance and measures of anxiety and rumination, as well as associations between those measures and functional connectivity. *Results:* Frontoinsular task response was correlated with multiple dimensions of poor mood health, including current and future depressive symptom severity, as well as future intensity and variability of negative affect. Specifically, these indications of increased mood difficulties were associated with hyperconnectivity between insula and midline or temporal regions of the default network, and hypoconnectivity between insula and lateral prefrontal regions of the frontoparietal network. Associations between future mood health and frontoinsular activity were significant controlling for baseline symptoms, demonstrating the complementary utility of these biomarkers alongside other measures of risk. *Conclusion:* Frontoinsular connectivity appears to be a promising target of investigation for its potential therapeutic relevance for mood disorders.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.04/YY6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NRF-2016M3C7A1914448
KAIST G04150045
Samsung SRFC-TC1603-06
NRF-2017R1C 1B 2008972
IITP 2017-0-00451

Title: Impaired reinforcement learning signal representation in depression

Authors: *S. HEO[1], Y. KIM[3], Y. SUNG[2], E. KANG[2], S. LEE[2]
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Abstract: Decision making is guided by two distinct systems: Model-Based (MB) and Model-Free (MF) system. Previous studies revealed that depressed individuals show impaired performance in reinforcement learning task. However, the neural mechanism underlying these abnormal decision making is not well understood. To address this, we analyzed neural response underlying decision making in depressive people using machine learning method. We especially focus on frontopolar prefrontal cortex (FPC) and interior lateral prefrontal cortex (ilPFC), areas known to integrate MB and MF systems. Twenty eight participants performed a two-stage Markov decision task, which is designed to drive one strategy over the other during the task and fMRI images were acquired. Based on the computational model (Lee 2014), we calculated the underlying signals such as MB/MF reliability (how much subjects rely on each system during the task) and Pmb (how much probability is finally assigned to each system). To understand the depression effect on information processing in FPC and ilPFC, we conduct two analysis: General Linear Model (GLM) and Multi Voxel Pattern Analysis (MVPA). GLM results show that information about integration of two systems (maximum value of the MB, MF reliability) is significantly less represented in FPC and left ilPFC as depression scale increases. On the other hand, MVPA results indicate that MF reliability and Pmb information is more clearly represented in these areas as people get more depressed. In summary, our findings indicate that proper integration of two reinforcement learning systems is impaired in depression, and this might be due to the elevated sensitivity of MF system in depression.

Disclosures: S. Heo: None. **Y. Kim:** None. **Y. Sung:** None. **E. Kang:** None. **S. Lee:** None.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.05/YY7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Pritzker Neuropsychiatric Research Consortium

Title: Distribution and quantification of neuropeptide processing enzyme mRNA in the hippocampus of postmortem depressed subjects

Authors: *M. WASELUS[1], A. MEDINA[1], C. A. TURNER[1], W. E. BUNNEY, Jr[2], R. M. MYERS[3], A. F. SCHATZBERG[4], J. D. BARCHAS[5], F. S. LEE[5], H. AKIL[1], S. J. WATSON, Jr[1]
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Abstract: Neuropeptides are one of a number of substrates that have been implicated in the pathophysiology of major depressive disorder (MDD). Unlike the biosynthesis of classical neurotransmitters, neuropeptides undergo a series of processing steps to release active neuropeptide(s) from their larger, inactive precursors. The first enzymatic step in this process is carried out by proprotein/prohormone convertases (PCs), which typically cleave inactive peptide precursors C-terminal to paired basic amino acid residues (e.g., Lys/Arg). Two members of this family, PC1/3 and PC2, are stored in secretory granules and act on peptide precursors processed within the regulatory secretory pathway. We have previously shown that PC1/3 and PC2 expression levels are decreased at the level of the anterior hippocampus of MDD subjects when compared to non-psychiatric control subjects. At the level of the posterior hippocampus, MDDs had decreased 7B2 (a modulator of PC2) expression compared to controls, and together with findings in the anterior hippocampus suggest a dysregulation in the initial peptide processing steps in MDD. Here, we extend these studies to examine expression of two additional peptide processing molecules that function subsequent to the PCs in the generation of active neuropeptides: carboxypeptidase E (CPE) and peptidyl-glycine alpha-amidating monooxygenase (PAM). CPE is the primary carboxypeptidase involved in the biosynthesis of regulated secretory pathway neuropeptides, is broadly distributed in the brain and functions in mature secretory granules to remove C-terminal basic residues on intermediate cleavage products previously generated by PCs. PAM is a bifunctional molecule and sole known enzyme responsible for peptide amidation which is required for full functionality of around half of known neuropeptides. In this study, frozen 10µm sections through the hippocampus of MDD and non-psychiatric control subjects were processed for *in situ* hybridization using radiolabeled cRNA probes for CPE or PAM. Quantitative measurements of CPE or PAM mRNA expression using ImageJ are currently ongoing in the anterior and posterior hippocampal formation (HF). Initial evaluation of the distribution of CPE and PAM mRNA indicates that both are expressed in all regions of the HF, with CPE more abundantly expressed than PAM, consistent with previous studies carried out in the rat. Together with our previous findings, we anticipate that differences in the expression of CPE and/or PAM will contribute to a more thorough understanding of the molecular and anatomical specificity underlying the dysregulation of neuropeptides in the postmortem HF of depressed individuals.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.06/YY8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: National Institute of Mental Health MH 048063

Title: Depression and brain network profiles of the hippocampus and the prefrontal cortex in patients with borderline personality disorder: A focus on episodic memory

Authors: *T. J. ATTISHA[1], T. D. MERAM[1], A. Z. CHOWDURY[1], E. KALLABAT[1], P. SOLOFF[2], V. A. DIWADKAR[1]
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Abstract: Background: Borderline Personality Disorder (BPD) is characterized by impulsivity, mood instability and suicidality (Paris, 2005). Major depressive disorder (MDD) is frequently comorbid (Yoshimatsu et al., 2014), yet, how MDD affects the brain's connectivity profiles in BPD patients is unknown. We investigated this in the context of a hippocampal episodic memory paradigm, known to reliably distinguish BPD from controls (Soloff et al., 2015). We were interested in understanding how network profiles during Encoding of, and Recognition for affective valenced images (Lang et al., 2008) are modulated by valence.
Methods: 36 BPD patients (BPD_{MDD+}=15) underwent fMRI (3.0 T Siemens Trio) during which subjects performed the episodic memory task using images from the International Affective Pictures System (IAPS). Subjects were required to remember pictures (Encoding), after which memory for those pictures was tested (Recognition). fMRI data were processed using standard methods (SPM8). Network profiles of the Hippocampus (Encoding) and the dorsolateral prefrontal cortex (dlpfc, Recognition) were estimated using Psychophysiological Interaction (PPI) (Friston et al., 1997, p<.05, cluster level). Separate second level analyses were created (one for each seed). In each, Group (BPD_{MDD+} vs. BPD_{MDD-}) and Valence (-ve, +ve, neutral) were factors.
Results: a) Negatively valenced pictures: BPD_{MDD+} showed *decreased* hippocampal modulation of the supramarginal gyrus, and *decreased* dlpfc modulation of the rolandic operculum, fusiform and superior temporal pole. b) Positively valenced pictures: BPD_{MDD+} showed *decreased* hippocampal modulation of the superior temporal gyrus and middle temporal gyrus, and

decreased dlpfc modulation of the caudate nucleus and anterior cingulate gyrus. In contrast, BPD_{MDD+} showed *increased* hippocampal modulation of the insula and temporal lobe, and *increased* dlpfc modulation of the mid occipital gyrus. c) Neutral valence: The effects were singularly different. BPD_{MDD+} showed increased hippocampal modulation of the frontal middle gyrus and superior frontal lobe, and increased dlpfc modulation of the supramarginal gyrus and frontal medial orbital gyrus.
Discussion: During both encoding and recognition, negative *and* positive valences interfere with brain network profiles in BPD_{MDD+}. Depression appears to interfere with affective context dependent processing, leading to patterns of hypo-connectivity during memorial processing. Our results are generally consistent with the idea (from metaanalyses of rsFC) that MDD is characterized by hypo-connectivity (Kaiser et al., 2015).

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.07/YY9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: This project is supported by the Radboud University Medical Center including a grant from the Psychiatry Foundation.

Title: Association between depression and perseveration during reversal learning across samples of healthy individuals and psychiatric patients

Authors: *S. C. BROLSMA[1,2], J. N. VRIJSEN[2], E. VASSENA[1], A. H. SCHENE[2], R. COOLS[1,2]
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Abstract: Adaptive decision making depends on a balance between goal-directed and habitual behaviors. Excessive focus on the habitual system leads to compulsive behavior, a symptom of several psychiatric disorders. A typical failure of the habitual system is perseveration, i.e. the inability to modify behavior based on feedback. In depression, rumination is thought to be a general manifestation of perseveration. In the healthy population there is large variability in the severity of depressive symptoms. However, the relationship between such variability and habitual behavior has never been investigated. In this study we hypothesized that perseveration, as an index of habitual behavior, correlates with severity of depressive symptoms.
To this end, we administered a probabilistic reversal learning task to a group of young

participants selected randomly from the normal population (study 1, n=78, ages 18-35) and to a heterogeneous group of psychiatric patients with depression, anxiety, autism, ADHD, or multiple disorders (study 2, n=208, ages 18-78). The task consisted of a series of choices between two stimuli. In 70% of the trials (80% for study 2), choice of one stimulus led to positive feedback, and choice of the other stimulus to negative feedback. Participants learnt these contingencies, and chose the stimulus that was most often correct. At some point in the task, and unbeknownst to participants, these contingencies reversed. After reversal, participants were required to switch, and select the previously incorrect stimulus. Failing to switch resulted in a perseveration error. Perseverative errors were counted when participants committed at least two consecutive errors in the reversal phase.
The results of study 1 showed a positive correlation: Participants with higher depressive symptom scores committed more perseverative errors. This was not the case for errors committed in the acquisition phase. Study 2 replicated this effect: Patients with more severe depressive symptoms also committed more perseverative errors (with no difference for acquisition errors). Critically, this effect was selective for depressive symptoms; anxiety, autism and ADHD symptom scores did not correlate with perseveration.
These findings demonstrate that severity of depressive symptoms is associated with compulsive, perseverative responding across samples of healthy individuals and psychiatric patients.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.08/YY10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant P20 GM103645
NIH Grant R01 EY012793

Title: Luxotonic signals in human frontal-polar cortex: A possible substrate for effects of light on mood

Authors: *J. N. SANES[1,2,3], S. SABBAH[1,2], R. WAUGH[1], M. S. WORDEN[1,2], D. M. BERSON[1,2]
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Abstract: A distinctive component of retinal output encodes absolute light intensity (irradiance) in the visual environment. This derives largely from melanopsin-expressing *intrinsically photosensitive retinal ganglion cells (ipRGCs)*. These cells innervate multiple subcortical targets and drive diverse physiological effects of light including circadian entrainment, pupillary reflexes, neuroendocrine and sleep modulation, along with retinal and visual brain development. In mice, unnaturally rapid light cycles (7 hr period) trigger depression-like symptoms, but this effect is abolished if ipRGCs are selectively killed (LeGates et al. 2012, Nature 491:594). New evidence suggests that the light cycle effects on mood may be mediated by a circuit linking ipRGCs through a thalamic region abutting the lateral habenula (the perihabenular nucleus), which then projects to the medial prefrontal cortex (Fernandez et al. 2017, ARVO meeting). To determine whether a similar light-intensity-dependent functional pathway affects human frontal cortex, we used BOLD functional MRI (3T Siemens Prisma, 2 mm isotropic voxels) to explore whole-brain activation patterns in response to full-field diffused light stimuli of four light intensities (10.2, 12.1, 13.1, and 13.8 log photons cm^{-2} s^{-1}; 30 sec epochs). Sustained monotonic increases in the fMRI signal were detected throughout visual cortex, including striate cortex and extrastriate regions as far anterior as the occipital border of the occipital-parietal sulcus. We also found strong luminance-dependent modulation in the frontal-polar cortex (frontopolar gyrus). The most anterior regions of the frontal-polar cortex exhibited persistent monotonic increases in activation with increasingly bright diffuse light. A second region, posteriorly adjacent to the first and including the subgenual medial prefrontal cortex, exhibited monotonic *reductions* in fMRI signal as a function of light intensity. These cortical regions have been implicated in mechanisms of major depression. We conclude that environmental light intensity modulates activity of certain regions of limbic neocortex. This circuit may contribute to diverse emotional and hedonic responses to environmental light, including seasonal affective disorder, mood elevation by phototherapy, a preference for well-lit spaces, and aversion to excessive light. Animal studies suggest that ipRGCs and the dorsomedial limbic thalamus are critical elements of this neural circuit. Preliminary results show evidence for photic activation of thalamic regions near the habenula, but a targeted regional analysis is needed and the possible role of ipRGCs remains to be tested.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

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Program #/Poster #: 320.09/YY11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: 2014 Friends of BrainHealth Distinguished New Scientist Award to NH
2017 Friends of BrainHealth Distinguished New Scientist Award to LH
2015 Think Ahead Group Research Award to LH

Title: Connectivity differences with subgenual anterior cingulate cortex during self-referential processing in depressed and healthy participants

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Abstract: Cognitive theories of depression posit a key role for negative, or depressive, self-referential thought. A network of brain regions at rest have been associated with depressive and neutral self-referential processing in persons diagnosed with depression. One such region, subgenual anterior cingulate cortex (sACC) is a hub in this network and is implicated in sad emotion in both depressed and healthy controls (HCs). What is currently unknown is whether patterns of sACC functional connectivity are altered in depressed persons during actual depressive and neutral self-referential processing. We assessed which regions are most strongly connected with sACC during depressive and neutral self-referential processing using functional magnetic resonance imaging to assess the functional connectivity (FC) between this region and the rest of the brain in individuals diagnosed with a current Major Depressive Episode (MDE) and HCs during a depressive and neutral self-referential processing task (DST and NST, respectively). 15 participants with MDE and 21 HCs completed DSTs and NSTs during scanning. Participants viewed either a neutral (e.g., “I like to eat meat”) or a depressive (e.g., “I have no friends”) self-referential statement and indicated whether that statement was representative of him or her by button press. Left Brodmann area (BA) 25 (encompassing sACC) was used as the seed region, and whole-brain, voxel-wise correlations (p=.005, k=30) were calculated. MDE individuals had higher FC compared to HCs between sACC and insula and middle temporal gyrus during DST. During DST, HCs had higher FC between sACC and the cuneus, superior frontal gyrus (BA 6), parahippocampal gyrus, and medial prefrontal cortex (mPFC; BA 10) than MDE individuals. During NST, MDE individuals had higher FC between sACC and dorsolateral PFC (DLPFC; BA 46) and mPFC than HCs. HCs during NST had higher FC between sACC and posterior and anterior cingulate, parahippocampal gyrus, superior temporal gyrus, and mPFC. These results suggest that HCs utilize neutral self-referential processing (mPFC) regions when engaging in
both depressive and neutral self-referential processing, while different regions are utilized by individuals within an MDE. Further, individuals with MDE require use of cognitive control regions (e.g., DLPFC) during NST, reflecting a possible increased need to control for depressive self-referential thought during neutral self-referential processing. Differing connectivity patterns between MDE individuals and HCs in self-referential processing could underlie the abnormal self-referential thought that occurs in MDE.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

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Program #/Poster #: 320.10/YY12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant 5U01MH108148-03

Title: Towards a more useful heritability scale for genetic studies in depressive disorders: Comparison of trait and state depression scales in depressed and healthy men and women in a human population isolate

Authors: *M. KVARTA[1], E. HONG[2]
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Abstract: Our understanding of the genetic basis of mood disorders, including depression, is incomplete. In genetic studies, defining the phenotype by diagnosis may miss risk-allele carriers without depressive disorders, forcing a continuum of symptom profiles and severities into a dichotomy. Future patients could be erroneously included as healthy controls, as first mood episodes can occur later in life. Furthermore, although quantitative assessments of mood have gained more attention, many depression studies in humans rely on assessments that are heavily weighted towards recent or current state of mood, generally using scales designed to identify recent or active mood episodes. Whether this approach can fully capture the genetic vulnerability for depression remains to be seen. We hypothesized that quantitatively detected symptoms of depression would identify a trait that may track with vulnerability for depressive disorders and is also significantly heritable. The Maryland Trait and State Depression Scale (MTSD) measures existence of depression "state" (i.e., symptoms within the last 7 days) and depression "trait" (i.e., symptoms experienced in lifetime excluding the last week). We administered the MTSD to a sample of Old Order Amish and Mennonites (OOA/M) with large family pedigrees. The OOA/M is a population isolate with high environmental homogeneity and a prevalence of mood disorders similar to that of the general population. Heritability was estimated using the variance components method implemented with SOLAR-Eclipse software. This is an ongoing study. Preliminary analysis was performed on currently available data from 309 individuals, including patients with mood disorders and their healthy family members. We found that the heritability estimates of the both lifetime depression trait score ($h2 = 0.47$, s.e. = 0.13, $p = 0.00004$) and current depression state score ($h2 = 0.48$, s.e. = 0.13, $p = 0.000026$) showed similar and highly significant heritability estimates. Unlike current depression reporting, lifetime depression assessments are prone to memory errors and other related confounds. The finding of a strong

heritability in the trait score is encouraging, suggesting additional effort is warranted to determine whether trait depression may serve as an additional quantitative depression endophenotype that could be a valuable tool to supplement the diagnosis phenotype in human depression studies.

Disclosures: E. Hong: None.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.11/DP11/YY13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant F31MH109257
NIH Grant R01MH095807
NIH Grant R01MH101479

Title: Habenula connectivity in adolescent mental illness

Authors: *B. A. ELY[1], J. G. XU[2], V. GABBAY[3,4]
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Abstract: Introduction: Adolescence is a critical period in development when many psychiatric illnesses, including major depressive disorder (MDD), first emerge. Converging evidence suggests that the habenula (Hb), a small nucleus bordering the dorsomedial thalamus, plays an important role in MDD, particularly the symptom of anhedonia. In animal models, the Hb inhibits dopaminergic reward signaling by the ventral tegmental area (VTA) and downstream nucleus accumbens (NAc). Task fMRI studies indicate a similar Hb response profile in healthy humans (Lawson 2014), which is disrupted in MDD (Lawson 2017). Building on our recent findings of highly significant resting-state functional connectivity between the Hb and VTA in healthy young adults (Ely 2016), independently corroborated at 3T (Hesu 2016) and 7T (Torrisi 2016), we examined Hb connectivity with the VTA, NAC, and whole brain during the critical, emergent stages of psychiatric illness. **Methods:** We recruited 49 adolescents with psychiatric diagnoses (primarily MDD and anxiety disorders) and 15 healthy controls. Subjects completed a semi-structured diagnostic interview with a clinician and questionnaires to assess depression severity (BDI), anhedonia levels (TEPS), and anxiety symptoms (MASC). Human Connectome Project (HCP)-style MRI was performed on a 3T Siemens Skyra, including 0.9mm isotropic T1w and T2w anatomical scans and a resting-state fMRI scan (2.3mm isotropic, TR=1s, 600 volumes). Data were preprocessed using the HCP minimal preprocessing pipelines (Glasser

2013) and denoised using ICA-FIX, CompCor (5 WM + 5 CSF PCA components), 5mm FWHM spatial smoothing, and bandpass (0.1-0.01Hz) filtering. Functional connectivity was modeled using the CONN toolbox (ROI-to-ROI) and Connectome Workbench + FSL PALM (ROI-to-whole-brain). **Results:** Consistent with our previous findings, we observed highly significant Hb connectivity with the VTA ($p<10^{-8}$) and NAc ($p<10^{-6}$) in the full sample, as well as the dorsal anterior cingulate cortex (ACC), bilateral insula, and early sensory cortices in the whole-brain analysis ($p_{FWE}<0.05$). In the full sample, anhedonia severity was positively correlated with Hb-VTA connectivity ($r=0.29$, $p_{uncorrected}=0.042$), while anxiety scores were negatively correlated with Hb-NAc connectivity ($r=-0.29$, $p_{uncorrected}=0.044$) only in the clinical sample. **Conclusions:** Our findings indicate that Hb connectivity with key reward regions (i.e. VTA, NAc, ACC) develops early in life, and moreover that connectivity within these pathways may be associated with anhedonia and anxiety severity during adolescence, supporting the potential role of the Hb in the onset of mental illness.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.12/YY14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R21MH106775

Title: An EEG-fMRI-TMS system for investigating BOLD response to alpha phase-locked TMS

Authors: *Y. LIN[1], J. FALLER[1], J. DOOSE[2], G. T. SABER[2], J. R. MCINTOSH[1], R. I. GOLDMAN[4], M. S. GEORGE[3,5], P. SAJDA[1], T. R. BROWN[2]
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Abstract: Pulsing transcranial magnetic stimulation (TMS) in synchrony with endogenous brain rhythms may have greater effects on both local and distributed neural activity than non-synchronized stimulation with this change being of possible clinical significance. To better understand the mechanisms that underlie treatment efficacy, we developed an instrument that can trigger synchronized stimulation at a target phase via real-time processing of the electroencephalogram (EEG) while concurrently recording hemodynamic response at high spatial resolution via functional magnetic resonance imaging (fMRI). EEG was recorded and

processed at a sampling rate of 488Hz. For phase tracking and prediction, the prefrontal alpha oscillation was recovered using a finite impulse response filter (order 50) on the spatial average of four left frontal EEG electrodes (FP1, AF3, F3 and F7). Subsequently, a sine model was fit onto a time window that was extracted from 307 to 102ms before the most recently acquired EEG sample. Fitting was accomplished by minimizing root mean squared error (RMSE) via nonlinear optimization for the free amplitude, frequency and phase parameters. RMSE was then computed for phase and amplitude between the model prediction and the signal in a test window from 102 to 0ms prior to the same reference point as before. If the RMSE values for the test window were below fixed conservative thresholds, the time point for the next target-phase in the alpha rhythm was predicted up to 123ms in the future and a pulse event was registered once the predicted time had passed. Triggering was always followed by a refractory period of 5s, in which new EEG data was preprocessed but sine fitting and triggering remained disabled. To establish a performance baseline, the system was first tested outside the scanner with eleven healthy subjects, where the system was able to mark a phase target of 90 degrees at a mean phase error of 0.8 degrees (standard deviation: 45.4). During subsequent tests on three healthy subjects where fMRI data was recorded concurrently, all EEG data processing was preceded by real-time gradient artifact removal. Phase prediction accuracy was found to be comparable to recordings outside the scanner. The performance achieved by this instrument will allow us to probe causal hypotheses relating the phase of ongoing endogenous oscillations to behavior and the TMS induced BOLD response.

Disclosures: Y. Lin: A. Employment/Salary (full or part-time):; Columbia University in the City of New York. **J. Faller:** A. Employment/Salary (full or part-time):; Columbia University. **J. Doose:** A. Employment/Salary (full or part-time):; Medical University of South Carolina. **G.T. Saber:** A. Employment/Salary (full or part-time):; Medical University of South Carolina. **J.R. McIntosh:** A. Employment/Salary (full or part-time):; Columbia University. **R.I. Goldman:** A. Employment/Salary (full or part-time):; University of Wisconsin–Madison. **M.S. George:** A. Employment/Salary (full or part-time):; Medical University of South Carolina. **P. Sajda:** A. Employment/Salary (full or part-time):; Columbia University. **T.R. Brown:** A. Employment/Salary (full or part-time):; Medical University of South Carolina.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.13/YY15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Intramural Program

Title: Resting state oscillatory power and amotivation in depressed patients

Authors: *C. S. GALIANO, J. R. GILBERT, A. C. NUGENT, E. D. BALLARD, C. A. ZARATE
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Abstract: Lack of motivation is known to be a common symptom of depression. For example, a recent exploratory factor analysis of common depression rating scale scores from a group of depressed patients identified amotivation as a potential depression biotype, suggesting that the use of this unidimensional construct might lead to more precise treatment and greater response efficacy (Ballard et al., 2018). However, little is known about the brain circuitry supporting amotivation in depression. Given this limited knowledge, we sought to investigate the relationship between amotivation scores and magnetoencephalographic (MEG) oscillatory power changes in the delta, theta, alpha, beta, gamma, and high gamma bands during rest. Resting-state MEG data were acquired using a 275-channel CTF system (VSM MedTech Ltd.) in 1 to 2 sessions from 29 depressed subjects after an intravenous infusion of both ketamine hydrochloride (0.5 mg/kg) and a placebo saline infusion. A factor score from an exploratory factor analysis reflecting amotivation was calculated for each participant and was composed of items from the Beck Depression Inventory (BDI) (Ballard et al., 2018). A linear mixed effects model in AFNI was used to calculate the relationship between oscillatory power and amotivation scores. There was a significant association between gamma and high gamma power and amotivation scores in left middle occipital cortex (MOC), such that a loss of power in both gamma and high gamma in MOC during rest were associated with increased amotivation scores (gamma: $F=15.4$, $p<0.05$ fwe-corrected; high gamma: $F=23.0$, $p<0.01$ fwe-corrected). No other significant power differences were associated with amotivation in the other frequency bands explored. These findings provide MEG evidence of the distinct role of the MOC in amotivation. More generally, baseline activity in MOC has been shown to predict treatment response in depressed patients for both an emotion working memory task (Furey et al., 2013) and a selective attention task with emotion modulation (Furey et al., 2015). Our findings add to this by demonstrating that reduced resting-state gamma power within this region is associated with increased amotivation scores. Importantly, several MEG studies have demonstrated that ketamine induces spontaneous gamma power within cortical networks (Cornwell et al., 2012; Shaw et al., 2015), suggesting that increased cortical excitability within the MOC might lead to improvements in motivation following ketamine administration.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.14/YY16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH grant K01MH099232

Title: Neural signatures of genetic and socioeconomic risk for psychiatric illness

Authors: *M. A. COLLINS, K. M. ANDERSON, R. CHIN, A. J. HOLMES
Dept. of Psychology, Yale Univ., New Haven, CT

Abstract: Genetic and environmental factors, including socioeconomic status and social support, influence risk for psychiatric illness. Affective illness is marked by subtle neuroanatomical shifts across multiple aspects of association cortex. However, there remains a pressing need to understand the interplay between genetic and environmental factors and their effects on brain anatomy that accompany risk for illness onset. The current study utilized structural magnetic resonance imaging (MRI) data to assess the associations linking the thickness of cortical gray matter with social and economic factors in a population-based sample (n=7,785) of individuals ages 44-73 from the UK Biobank study, including a subset who presented with a lifetime history of psychiatric illness (n=2,585). Variables of interest included a derived composite measure of the quality and frequency of social interactions, as well as the Townsend Index, which assesses economic deprivation based on community factors. Multiple linear regression models were used to predict cortical thickness from 1) economic deprivation, 2) social impairment, 3) polygenic risk for major depressive disorder (MDD), and 4) the interaction of economic deprivation and genetic risk for depression. Across the sample, variables of interest were associated with a shared pattern of reduced cortical thickness in regions including cingulate and prefrontal cortices and the insula. Cortical thinning in these regions was linked to the interaction of polygenic risk for MDD and economic deprivation, even after accounting for the main effects of both variables. This interaction demonstrated that genetic risk for depression had a stronger relationship with cortical thinning in more economically disadvantaged individuals, that the combination of genetic risk and high levels of economic deprivation may amplify differences in brain anatomy associated with psychiatric illness. A similar, yet more robust, anatomical profile was evident in individuals with a history of psychiatric illness. These data suggest a continuous relationship between genetic, psychosocial, and structural correlates of psychiatric illness that is evident across the general population and enhanced in individuals with a current or past diagnosis.
**This research has been conducted using the UK Biobank Resource under Application Number 25163.*

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

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Program #/Poster #: 320.15/YY17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIGMS: P20GM121312
The William K. Warren Foundation

Title: Latent cytomegalovirus infection associated with white matter abnormalities: A diffusion tensor imaging study

Authors: *M. BERGAMINO[1], B. N. FORD[1,2], K. TEAGUE[4], J. BODURKA[1,5], C. J. JARRETT[1], R. H. YOLKEN[6], M. P. PAULUS[1], J. SAVITZ[1,3]
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Abstract: Major Depressive Disorder (MDD) is associated with impaired adaptive immunity, increasing vulnerability to infectious diseases, including those caused by cytomegalovirus (CMV), a member of the human herpesvirus family. After initial infection, CMV can persist in myeloid cells as well as in the central nervous system (CNS), and is reactivated by stress and other immunosuppressive conditions. There is growing awareness that repeated reactivation of CMV has negative sequelae including premature immunoscenesence that accentuates the inflammation associated with aging. This investigation aimed to determine whether MDD individuals who are CMV positive (CMV+) show evidence of CNS changes that have been associated with inflammation.
A free-water algorithm was used to correct the raw diffusion tensor imaging (DTI) data to quantify extracellular free water (FW), a putative marker of neuroinflammation and FW-corrected fractional anisotropy (cFA), an index of white matter (WM) integrity, in 242 individuals with MDD (64% F, age = 34±11, 56% CMV+) and 49 healthy controls (HC, 55% F, age = 33±11, 41% CMV+). Anti-CMV IgG antibodies were quantified using a commercially-available solid-state array.
After controlling for age and sex, there was a higher prevalence of CMV in the MDD group versus the HC group that trended significant (p=0.064, adjusted OR=1.82, 95% CI: 0.97-3.47). After controlling for age, there was a significant main effect of CMV serostatus on FW with

higher values in CMV+ subjects (regardless of diagnosis) in several WM locations (p<0.05 Threshold-Free Cluster Enhancement corrected), including the anterior thalamic radiation (bilateral), the corticospinal tracts (bilateral), the cingulate gyri (bilateral), longitudinal inferior fasciculus (L), uncinate fasciculus (L), middle cerebral peduncle, splenium of corpus callosum, and posterior corona radiata (L). Similarly, lower cFA was found in CMV+ subjects (regardless of diagnosis) in all of the above regions with the exception of the corticospinal tracts. There was no main effect of diagnosis or interaction between diagnosis and CMV serostatus for either the FW or the cFA analyses.
The results provide support to the hypothesis that CMV infection may have neuroinflammatory effects that impact WM integrity. However, contrary to our hypothesis, this effect may not be limited to the MDD group. The results should be considered preliminary given the cross-sectional design and the relatively smaller number of HCs which may have limited the power to detect a diagnosis-by-serostatus interaction.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.16/YY18

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: William K Warren Foundation

Title: Both medicated and unmedicated subjects with Mood and Anxiety Disorders show dysregulated interoceptive processing

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Abstract: Major depressive disorder (MDD) is among the most disabling conditions worldwide, yet only about 1 out of 3 patients remit after treatment with a first-line antidepressant. Recent study from our institute has revealed that individuals who are unmedicated with MDD show abnormal activity in the insula when processing interoceptive information (Avery et al., 2014). However, it is unclear whether medication status contributes to altered interoceptive processing. To address these questions, 261 adults underwent fMRI while performing a task requiring interoceptive attention to visceral sensations or exteroceptive attention in a visual target detection condition. Participants were recruited as part of the Tulsa 1000 (Victor et al., 2018), a naturalistic longitudinal study of treatment seeking individuals with mental health conditions including

mood/anxiety, substance use, and eating disorders as well as healthy controls. Exclusion criteria for the T1000 included bipolar disorder, schizophrenia, history of significant brain trauma, and neurological disorders. Additionally, this study includes only participants from the first 500 recruited who met criteria for mood/anxiety disorders (MA, PHQ-9 ≥ 10 or OASIS ≥ 9, n=217) and healthy controls (HC, n=44), but not substance use or eating disorders. MA participants were divided into medicated (MA-med, n=146) and unmedicated (MA-unmed, n=71) groups based on whether or not they were currently taking psychotropic medications. fMRI data were acquired on two identical GE Discovery MR750 3T scanners. A whole-brain voxel-wise analysis was conducted to examine group differences in the interoceptive (heart and stomach) versus exteroceptive (target) conditions using AFNI. Results show both MA-unmed and MA-med had decreased contrast in the dorsal-mid insula compared to healthy controls (voxel-wise $p<0.005$), but the two MA groups did not differ from each other. Using the dorsal-mid insula ROI defined by the above whole brain voxel-wise analysis, the average contrast values were extracted for each subject. Then, only within the MA group, we tested separately for linear effects of PROMIS Anxiety and PROMIS Depression. This revealed significant negative effects for both Anxiety ($p=0.0024$, $R^2=0.043$) and depression ($p=0.016$, $R^2=0.027$). Taken together, these findings indicate that individuals with MDD show altered interoceptive processing, which is independent of medication status. Future studies will need to investigate whether the dorsal mid-insula could be an anatomical treatment target for depression. This work was supported by the William K Warren Foundation.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.17/YY19

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: HSØ2015052

Title: Attentional Bias Modification alters fMRI response towards negative stimuli in depression

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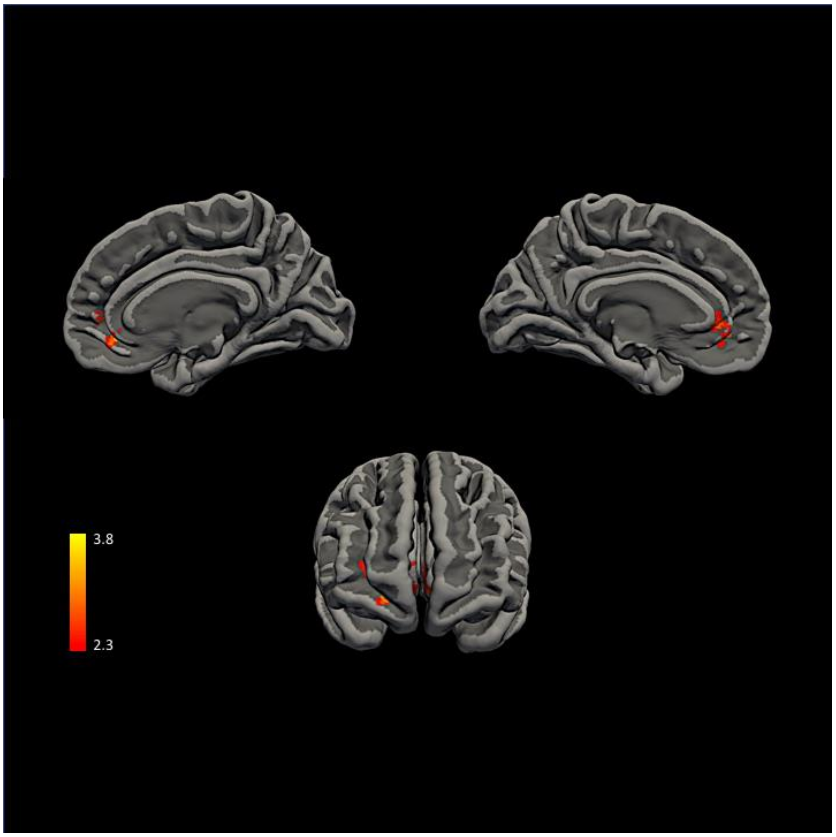
Abstract: Background Modification of attentional biases (ABM) in residual depression may lead to more adaptive emotion perception and emotion regulation reflected in changes in brain activity. There are growing efforts to characterize the neural underpinnings of ABM in depression, but task related emotion processing has so far not been investigated in a larger sample.
Methods A total of 134 previously depressed individuals with residual symptoms were allocated to 14 days of ABM or placebo in a pre-registered RCT followed by an fMRI modified emotion perception task.
Results ABM was associated with reduced amygdala and anterior cingulate cortex (ACC) activation compared to placebo during negative images. Response within the insular cortex was associated with the induction of positive affective biases following ABM and with improvement in symptoms.
Conclusions ABM training has an early effect on brain function within circuitry associated with emotional appraisal and the generation of affective states.



Disclosures: E.G. Hilland: A. Employment/Salary (full or part-time):; Diakonhjemmet Hospital. **N. Landrø:** A. Employment/Salary (full or part-time):; University of Oslo. **C. Harmer:** A. Employment/Salary (full or part-time):; University of Oxford. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Johnson and Johnson Inc, P1 vital and Lundbeck. **M. Browning:** A. Employment/Salary (full or part-time):; University of Oxford. B. Contracted

Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; P1 vital, Lundbeck. **L. Maglanoc:** A. Employment/Salary (full or part-time):; University of Oslo. **R. Jonassen:** A. Employment/Salary (full or part-time):; University of Oslo.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.18/YY20

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: 2R37MH068376
Kaplen Fellowship on Depression

Title: Computational phenotyping of brain-behavioral relationships underlying approach-avoidance decision making in major depressive disorder

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Abstract: Adaptive decision making requires balancing the reward and aversiveness associated with outcome of choices. Non-human primate studies have implicated a circuit linking pregenual anterior cingulate cortex and striatum in such processes, which are also altered in affective disorders such as Major Depressive Disorder (MDD), but the underlying mechanisms remain understudied. Computational psychiatry methods can be used to improve diagnostics and classification and to infer mechanisms underlying mental illness. Here we apply computational modeling of dynamic decision processes to extract latent parameters that relate brain activities to behavioral output, and to assess how they are altered in MDD. We use hierarchical Bayesian parameter estimation of the drift diffusion model (HDDM) to infer decision processes that explain choices and response time distributions during approach-avoidance conflict in healthy controls and patients with MDD. We further extracted BOLD-activation from regions of interest in ACC and striatum and analyzed the impact of their trial-to-trial variation on latent decision processes. Preliminary results indicate that variation in reward and aversiveness, and in neural activity tracking these quantities, are predictive of decision parameters, and that these are altered

in MDD. A machine learning classifier based on brain-behavior model parameters was shown to be diagnostic of patient status beyond that afforded by using raw behavioral data alone.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.19/YY21

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Cortical reorganizations for the recovery from depressive state after spinal decompression surgery

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Abstract: Background: Depressed mood following neuronal damage not only impedes functional recovery, but negatively affects quality of life for many patients. Depressed patients with cervical myelopathy often show improvement in both mood and motor function following spinal decompression surgery; however, the neural mechanism underlying this psychological benefit from the surgery remains unclear. The aim of this study is clarifying the brain sites that relates to the alleviation of depression following the spinal decompression surgery. **Methods:** We compared the brain activity of cervical myelopathy patients (n = 6) with those of healthy controls (n = 5) using functional magnetic resonance image (fMRI). In the second step, we analyzed the fMRI data to find the brain region(s) that correlated with depression severity (n = 12: six preoperative patients and six postoperative patients). Then we compared preoperative with postoperative imaging data from patients. **Results:** Spinal decompression surgery alleviated depression and diminished the activity of anterior cingulate cortex (ACC). Simultaneously, the activity of the supplementary motor area (SMA), which was enlarged in myelopathy patients compared with controls, was diminished following the surgery. **Conclusion:** Traditionally, surgical indications for myelopathy are determined by the severity of sensorimotor symptoms without considering psychological symptoms. We anticipate our results will lead to more informed surgical decisions for cervical spondylosis myelopathy.

Disclosures: M. Sawada: None. **T. Nakae:** None. **T. Munemitsu:** None. **M. Hojo:** None.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.20/YY22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R56MH109600-01

Title: Resting state cortical frequencies in human EEG are differentially associated with negative cognition in adults with and without a history of major depressive disorder

Authors: *A. ALARIO[1], J. LABRADA[3], R. STEWART[3], N. R. GRIFFIN[2], J. J. ALLEN[4], C. BEEVERS[3], D. M. SCHNYER[5]
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Abstract: Major depressive disorder (MDD) is characterized not only by mood disturbances, but also by persistent negative thoughts. In addition to these disturbances, extensive research has examined alterations in the frequencies of brain electrical activity associated with MDD, such as alpha band (8-12Hz) activity recorded at rest. Greater alpha activity in the frontal left hemisphere relative to the right (frontal alpha asymmetry; FAA) is associated with current MDD as well as prior history of MDD. Alternatively, the relationship between frontal alpha patterns and the negative cognition associated with MDD has not been explored in full detail. This study recruited 216 adults from the Austin community who participated in two identical laboratory sessions 1 week apart. Of the 216, 156 are included in the present report due to incomplete data sets. Participants were recruited so that depression severity would be normally distributed. Diagnosis of current and past psychopathology was determined through clinical interviews by research assistants. The current analysis examines data collected on Day 1, including a period of resting EEG where the participants alternated between eyes open and closed every 1 minute for a total of 8 minutes of recording. To measure negative attention bias, a standard dot-probe task with sad face stimuli was performed without EEG. Trial level bias scores estimated attention bias directed towards sad stimuli relative to neutral stimuli. 64-channel EEG data was preprocessed to remove artifacts and eye-movements and then re-referenced using a current source density (CSD) reference. A Fast Fourier Transform was utilized to determine frequency power in the alpha band. FAA scores were calculated by subtracting log transformed right less log transformed left total alpha power. The present study determined that frontal left alpha power positively correlates ($r = 0.17$, $p = 0.03$) with attention bias towards sad faces. Additionally, a history of MDD correlates with low FAA scores particularly for the F8-F7 electrode pair locations, indicating greater left hemisphere alpha activity than the right when with a history of

MDD. More severe depressive symptom severity measured with Beck Depression Inventory-II negatively correlated ($r = -0.22$, $p = 0.04$) with FAA scores but only for those with a history of MDD. The current results indicate that alpha band power is associated both with depressive symptoms, previous history of MDD, and negative attention bias. Future analyses will focus on test-retest reliability and the relationships with other frequencies.

Disclosures: A. Alario: None. **J. Labrada:** None. **R. Stewart:** None. **N.R. Griffin:** None. **J.J. Allen:** None. **C. Beevers:** None. **D.M. Schnyer:** None.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.21/YY23

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Austrian Science Fund P 27141
Austrian Academy of Sciences 24384

Title: Investigation of the effect of electroconvulsive therapy on monoamine oxidase A expression in treatment resistant depression using positron emission tomography

Authors: *G. GRYGLEWSKI, P. BALDINGER-MELICH, C. PHILIPPE, G. M. JAMES, C. VRAKA, L. SILBERBAUER, L. NICS, T. VANICEK, A. HAHN, M. MITTERHAUSER, W. WADSAK, M. HACKER, S. KASPER, R. FREY, R. LANZENBERGER
Med. Univ. of Vienna, Vienna, Austria

Abstract: Background: Electroconvulsive therapy (ECT) constitutes one of the most effective antidepressant therapies and is being applied routinely in patients with limited response to approved psychopharmacological treatment options. Despite the consistent observation of increases in hippocampal volumes and neurotrophic factors, the mechanism warrants further investigation [1]. In our previous study, a decrease in serotonin 1A receptor binding potential in many brain areas could be observed following an ECT series in depression [2]. As monoamine oxidase A (MAO-A) was found to be increased in major depression [3] and is a molecular target for several antidepressants, we investigated if ECT affects its expression in patients with treatment resistant depression (TRD). **Methods**: 16 patients (12 female, aged 46±9 years) with unipolar depression according to DSM IV and a Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) score ≥ 23 (mean 25±3) were included. All patients underwent adequate treatment trials with at least two antidepressant or augmentative drugs and had a stable medication for at least 10 days prior to measurements. Two PET measurements were carried out prior to ECT and one after a series of at least 8 right unilateral ECT treatments applied three times a week. The target

specific tracer [^{11}C]harmine was injected and quantification of MAO-A distribution volume (V_T) was carried out in PMOD using Logan plots and metabolite-corrected arterial input functions. **Results**: Depressive symptoms decreased significantly to 10.8±4.5 HAM-D following ECT treatment ($p<0.001$). Repeated measures ANOVA did not indicate significant changes in MAO-A V_T in any brain region studied at any time point, neither in voxel-wise nor regions of interest analysis. Whole-brain MAO-A V_T was 18.3±4.3, 18.1±4.2 and 17.8±3.7 at PET session 1, 2 and 3, respectively. **Conclusion**: In the current naturalistic sample of TRD patients undergoing ECT we could not observe any effects on MAO-A expression in the brain. A potential limitation may be that all patients included were medicated and treatments were applied only unilaterally. Our findings indicate that the mechanism underlying the efficacy of ECT is not associated with a downregulation of the MAO-A enzyme. Furthermore, these results may provide a rationale for the use of MAO-inhibitors as an independent treatment option after completion of ECT treatment.
References: [1] Sartorius A. et al. 2016 Eur Neuropsychopharmacol. Mar;26(3):506-17 [2] Lanzenberger R. et al. 2013 Mol Psychiatry. Jan;18(1):93-100 [3] Meyer JH. et al. 2006 Arch Gen Psychiatry. Nov;63(11):1209-16

Disclosures: G. Gryglewski: None. **P. Baldinger-Melich:** None. **C. Philippe:** None. **G.M. James:** None. **C. Vraka:** None. **L. Silberbauer:** None. **L. Nics:** None. **T. Vanicek:** None. **A. Hahn:** None. **M. Mitterhauser:** None. **W. Wadsak:** None. **M. Hacker:** None. **S. Kasper:** None. **R. Frey:** None. **R. Lanzenberger:** None.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.22/DP12/YY24

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Prediction of rTMS treatment outcome in depression: A machine learning approach

Authors: *J. CORLIER, A. C. WILSON, I. A. COOK, A. F. LEUCHTER
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) for the treatment of Major Depressive Disorder (MDD) is commonly administered to the left dorsolateral prefrontal cortex (LDLPFC) at 10 Hz with response rates of 30-50%. Although it is an effective treatment, many patients do not benefit and it is not fully understood what distinguishes responders from non-responders.
The goal of this study was a) to identify qEEG-biomarkers that would allow us to predict clinical outcome for rTMS treatment and b) to investigate the underlying physiological characteristics.

Specifically, we used a machine learning approach to classify responders and non-responders to 30-sessions of rTMS treatment, based on the electroencephalogram (EEG) from pre- and post-1st rTMS session. We successfully applied this approach to a large patient sample (N = 112) receiving either a unilateral left (UL) or bilateral (BL) rTMS treatment and also to more homogeneous cohorts split according to treatment type. We compared the performance of 3 predictors: coherence, envelope correlation, and a newly developed biomarker, alpha dynamic response (αDR). Features for these biomarkers represented connections between stimulation sites and all other channel locations (783 total features). First, we show that responders and non-responders have significantly different probability distributions of change in connectivity (Kolmogorov-Smirnoff test $p = 0.008$). While responders were more likely to decrease overall coherence and envelope correlation, they were also more likely to increase αDR from pre- to post- 1st session TMS than non-responders. The features with largest T-statistic value comparing the two groups were found to connect regions of the fronto-parietal control network. Secondly, the elastic net models were best for envelope correlation and αDR with an area under receiver operating curve (AUC) over 80% for internal and over 60% for external cross-validation. Model performance was further improved in the homogenous cohorts UL and BL, which is potentially more generalizable within the respective population.
Overall, we propose a way of predicting rTMS clinical outcome based on 1st session EEG, which can help optimize clinical routine and practice.

Disclosures: **A.C. Wilson:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **I.A. Cook:** A. Employment/Salary (full or part-time):; University of California Los Angeles. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Neosync, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroSigma. F. Consulting Fees (e.g., advisory boards); Artica Health, Cereve, NeuroDetect, HeartCloud. **A.F. Leuchter:** A. Employment/Salary (full or part-time):; University of California Los Angeles. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Brain Biomarkers Analytics LLC, Neosync, Inc. F. Consulting Fees (e.g., advisory boards); Neosync, Inc, Ionis, Inc., ElMindA. Other; Neuronetics, (DoD) Department of Defense, Neurosigma, CHDI.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.23/DP13/ZZ1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The relationship among individual alpha frequency, stimulation frequency, and clinical outcome of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder

Authors: *A. LEUCHTER[1], J. CORLIER[1], A. C. WILSON[1], I. COOK[1], L. L. CARPENTER[2]
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]Brown Univ., Providence, RI

Abstract: rTMS for treatment of Major Depressive Disorder (MDD) is commonly administered to left dorsolateral prefrontal cortex (DLPFC) at a frequency of 10 Hz. 10 Hz stimulation leads to response rates of 30-50%, but many patients do not benefit. 10 Hz is the center frequency of the alpha (α) band, which plays a central role in linking the activity of brain regions within resting state networks (RSNs). The range and peak frequency of α oscillations, however, vary across individuals. This variability suggests that tuning stimulation within each patient's individual α frequency (IAF) may better engage RSNs and enhance treatment outcomes. We examined the relationship among IAF, stimulation frequency, and treatment outcome in 137 patients undergoing clinical rTMS treatment for MDD. All patients received 10 Hz rTMS stimulation administered to left dorsolateral prefrontal cortex (DLPFC) at the beginning of treatment: 70 subjects continued with only 10 Hz stimulation at left DLPFC, while 67 subjects received left DLPFC rTMS treatment at 10Hz or other types of rTMS treatment for the majority of their treatment sessions.
We examined the absolute value of the numerical difference between patients' IAF and the 10Hz stimulation frequency in relation to clinical outcome. This difference was significantly correlated with percentage change in depression severity from baseline to rTMS treatment session 30 in patients who received 10 Hz stimulation for all or most of their treatment course($P < 0.02$), but not those who received treatment at other frequencies for most of their treatment. In the 10-Hz stimulation group, the responders and non-responders had significantly different IAF probabilities (Kolmogorov-Smirnoff test $p = 0.008$). Notably, the responders were almost twice as likely to have an IAF close to 10 Hz (within 1 Hz distance) than the non-responders ($p = 0.73$ vs $p = 0.41$), with a median distance of 0.48 Hz between the two groups). These findings indicate that a patient's IAF is an important factor to consider in selecting a stimulation frequency for patients receiving rTMS treatment for MDD.

Disclosures: **A. Leuchter:** A. Employment/Salary (full or part-time):; University of California, Los Angeles. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Brain Biomarker Analytics LCC, Neosync, Inc.. F. Consulting Fees (e.g., advisory boards); Neosync, Inc., Ionic, Inc., ElMindaA. Other; Neuronetics, Department of Defense, Neurosigma, CHDI. **J. Corlier:** A. Employment/Salary (full or part-time):; University of California, Los Angeles. **A.C. Wilson:** A. Employment/Salary (full or part-time):; University of California, Los Angeles. **I. Cook:** A. Employment/Salary (full or part-time):; University of California, Los Angeles. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Neosync, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

funds); NeuroSigma. F. Consulting Fees (e.g., advisory boards); Artica Health, Cereve, NeuroDetect, HeartCloud. **L.L. Carpenter:** A. Employment/Salary (full or part-time):; Butler Hospital. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI (site) Janssen global clinical esketamine trial, PI (site) Neosync trial. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Neuronetics (equipment). F. Consulting Fees (e.g., advisory boards); Magstim.

Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.24/ZZ2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Different patterns of functional connectivity between sensorimotor network, thalamus, and neurotransmitter-related nuclei in psychomotor excitation and inhibition: A resting state fMRI study in manic and depressive phases of bipolar disorder

Authors: *M. MARTINO[1], P. MAGIONCALDA[1], B. CONIO[1], M. AMORE[1], M. INGLESE[2], G. NORTHOFF[3]
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Abstract: *Background*: Manic and depressive phases of bipolar disorder (BD) show opposite core psychomotor symptoms. At a neural level, these may be related to functional disorganization of the sensorimotor system. Thus, the aim of the study was to investigate the functional relationships between sensorimotor network (SMN), subcortical loops, dopamine-related substantia nigra (SN) and serotonin-related raphe nuclei (RN), in healthy controls (HC), as well as in mania and inhibited depression, as characterized by psychomotor excitation and inhibition respectively. *Methods*: This is a resting state functional magnetic resonance imaging (fMRI) study, conducted with 67 HC and 100 BD patients - 34 in manic, 37 in depressive (subdivided in 21 inhibited depressed and 16 agitated depressed), and 29 in euthymic phases (age between 18 and 60). A functional connectivity (FC) analysis was performed using a region of interest (ROI)-to-ROI approach. Firstly, in HC, we calculated: the FC between thalamus and SMN and its modulus (i.e. the absolute value of this parameter without regard to sign); the FC of SN or RN with basal ganglia (BG) and thalamic regions. A partial correlation analysis was then performed between the thalamus-SMN FC and SN-BG/thalamus FC, as well as between the

thalamus-SMN FC and RN-BG/thalamus FC (with age, gender, and motion as covariates). Secondly, in BD, the same measures of thalamus-SMN FC (and its modulus), SN-BG/thalamus FC and RN-BG/thalamus FC were calculated and compared (with age, gender, and motion as covariates) between manic patients, inhibited depressed patients, and HC. Agitated depressed and euthymic patients were also included as control. Finally, a replication study was performed. *Results*: In HC, the thalamus-SMN FC showed a quadric correlation with SN-BG/thalamus FC (confirmed by its positive linear correlation with the modulus |thalamus-SMN FC|) and a linear negative correlation with RN-BG/thalamus FC. In BD, mania showed an increase in thalamus-SMN FC toward positive values with a concomitant reduction of RN-BG/thalamus FC. By contrast, inhibited depression showed a decrease in the modulus |thalamus-SMN FC| toward around-zero values with a concomitant reduction of SN-BG/thalamus FC and RN-BG/thalamus FC. The results were replicated in an independent HC dataset (n=108), and in an independent BD dataset (n=40). *Conclusions*: These findings suggest a functional link between networks, subcortical-cortical loops and neurotransmitter-related areas within the sensorimotor system, which may be disrupted in mania and inhibited depression, finally resulting in opposing psychomotor alterations.

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Poster

320. Depression and Bipolar Disorders: Depression: Human Imaging and Behavioral Studies

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 320.25/ZZ3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Bipolar disorder can be predicted by neural network and logistic regression analyses of facial principal components derived from images of self-declared bipolar and control individuals

Authors: *J. CANNON[1,2], T. M. BIELINSKI[2], C. ANZULEWICZ[2], A. LAU[1]
[1]Dept. of Psychology, [2]Neurosci. Program, Univ. of Scranton, Scranton, PA

Abstract: Embryological development of the face and anterior brain occur in synchrony, can be influenced by common genes, and have the potential to be dramatically and characteristically altered by genetic abnormalities and environmental insults. Bipolar disorder is thought to be caused by genetic and environmental factors that have the potential to affect the development of the brain and face. Previous studies have identified bipolar disorder-related abnormalities in striatum, amygdala, prefrontal cortex, and lateral ventricles (Strakowski, DelBello, & Adler, 2005). Decreased brain-derived neurotrophic factor has also been connected to manic and depressive episodes of bipolar disorder (Angelo et al., 2005). Both the face and bipolar disorder

have been shown to be highly heritable (McGuffin et al., 2003, Claes et al., 2018). The face has been found to potentially contain useful biomarkers differentiating bipolar and non-bipolar individuals (Hennessy et al., 2010).
Photographs were obtained from publicly available resources such as Google Image, IMDb, etc. Using ImageJ, x-y coordinates of 75 landmarks were measured blind. Using MorpoJ, coordinates were subjected to a full Procrustes transformation and reduced to seven principal components (PCs) accounting for 78% of the total variance in the dataset. There were significant Pearson correlations between bipolar disorder and PC2 ($p = 0.049$) as well as PC7 ($p = 0.003$). While PC4 did not reach statistical significance, it was the next most related ($p = 0.143$); the remaining PCs had probabilities greater than 0.32. All seven PCs were then analyzed using a logistic regression to assess their predictive value with regards to bipolar disorder. Null prediction rate was 51% correct. Percent correct using the PCs increased to 82.1. Receiver operating characteristic (ROC) curves gave area under the curve (AUC) values of 0.705 for PC2, 0.611 for PC4, and 0.776 for PC7; the remaining PCs had AUCs no greater than 0.566. To further assess predictive value, the PCs were used to train ($n = 22$) and test ($n = 17$) a neural network that, when tested, predicted bipolar disorder with 82.4% overall accuracy (bipolar = 100%, non-bipolar = 62.5%). An ROC curve for the neural network data gave an AUC of 0.968. These results are congruent with previous literature and further support that facial landmarks have potential as biomarkers for bipolar disorder.

Disclosures: J. Cannon: None. **T.M. Bielinski:** None. **C. Anzulewicz:** None. **A. Lau:** None.

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.01/ZZ4

Topic: B.04. Ion Channels

Support: National Key R&D Program of China (2016YFA0501000),
National Natural Science Foundation of China 91432108
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Strategic Priority Research Program (B) of the Chinese Academy of Sciences
XDB02030004

Title: Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression

Authors: *Y. CUI[1], Y. YANG[1], Z. NI[1], Y. DONG[1], G. CAI[2], A. FONCELLE[3], S. MA[1], K. SANG[1], S. TANG[1], Y. LI[1], Y. SHEN[1], H. BERRY[3], S. WU[2], H. HU[1]

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Abstract: It is now well understood that astrocytes intimately interact with neurons to support and regulate their functions in many aspects. One of most discussed functions of astrocytes concerns their role in extracellular potassium spatial buffering. A wealth of investigations has focused on the astroglial-neural interactions at the tripartite synapses, where astrocyte processes tightly wrap around pre- and post-synaptic sites. In contrast, not as much attention has been placed on astroglial-neural interaction in proximity to neuronal soma. Particularly, how astrocytes regulate intrinsic firing patterns of neurons, and what structural basis may underlie this regulation, are much less explored.

The interest of lateral habenular (LHb) in negative emotion is surging, but only limited attention has been given to astrocytes and their potential roles in LHb hyperfunction in depression. In the accompanying poster, we demonstrate that bursting activity of LHb neurons are greatly enhanced in animal models of depression. LHb burst drives depressive-like behaviors and is a prominent target of the rapid antidepressant ketamine. However, the cause of this enhanced burst of LHb neurons remains unsolved.

Here using high-throughput quantitative proteomic screen, we identified an astroglial potassium channel, Kir4.1, to be upregulated in the LHb of animal models of depression. Kir4.1 shows exquisite expression pattern on the astrocytic membrane processes tightly wrapping around the neuronal soma. Electrophysiology and modeling data demonstrate that the level of Kir4.1 on astrocytes tightly regulates the degree of membrane hyperpolarization and the amount of burst activity of LHb neurons. Astrocyte-specific overexpression of Kir4.1 in LHb drives more neuronal bursting and causes depressive-like symptoms. Conversely, knocking down Kir4.1 or overexpression of its dominant negative form in LHb reduces neuronal bursting and ameliorates behavioral despair and anhedonia. Together, these results reveal a new form of glial-neural interaction in setting neuronal firing mode in a devastating psychiatric disease, and discover the therapeutic potential of targeting LHb Kir4.1 for treating major depression. We also expect that the perisomatic K+ buffering mechanism described here may have a more widespread function.

Disclosures: Y. Cui: None. **Y. Yang:** None. **Z. Ni:** None. **Y. Dong:** None. **G. Cai:** None. **A. Foncelle:** None. **S. Ma:** None. **K. Sang:** None. **S. Tang:** None. **Y. Li:** None. **Y. Shen:** None. **H. Berry:** None. **S. Wu:** None. **H. Hu:** None.

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.02/ZZ5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Academy of Finland Grants: 276333, 284596, 305195, 312664
Finnish Funding Agency for Innovation Grant
Doctoral School Position: Doctoral Programme Brain & Mind

Title: Rapid-acting antidepressants evoke rebound slow EEG oscillations which coincide with TrkB signaling

Authors: *S. KOHTALA[1], W. THEILMANN[1], M. ROSENHOLM[1], L. PENNA[1], G. KARABULUT[3,4], S. UUSITALO[1], K. JÄRVENTAUSTA[5], A. YLI-HANKALA[6,7], I. YALCIN[3], N. MATSUI[8], H.-K. WIGREN[2], T. RANTAMÄKI[1]
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Abstract: Introduction The neurobiological basis underlying rapid antidepressant responses remains incomplete despite extensive research investments. In this study we have recorded EEG (electroencephalogram) signatures of acute drug treatments in adult mice with the aim of identifying shared EEG features that correlate with the activation of BDNF (brain-derived neurotrophic factor) receptor TrkB and inhibition of GSK3β (glycogen synthase kinase β) - proposed key molecular effectors of ketamine's action. **Methods** Medetomidine, an α_2 agonist used in animal anesthesia, and three putative rapid-acting antidepressants (ketamine, nitrous oxide, flurothyl) were administered for acute EEG recordings and the investigation of molecular markers implicated in antidepressant responses (pTrkB, pGSK3β, immediate early genes). All experiments were conducted with adult C57BL6 mice using standard experimental techniques (e.g. western blot, qPCR). Antidepressant-like behavioral phenotypes were assessed with the learned helplessness model. **Results** Rapid-acting antidepressants evoked rebound slow EEG oscillations after the peak of pharmacological effects had subsided, and TrkB and GSK3β signaling also became altered during these rebound periods. Medetomidine facilitated slow EEG oscillations and TrkB signaling directly without preceding cortical excitability, but these effects were not translated into antidepressant-like behavioral changes in the learned helplessness paradigm. **Conclusions** Our findings indicate that rapid-acting antidepressants produce a transient period of cortical excitability followed by homeostatic slow EEG oscillations which coincide with the activation of TrkB and GSK3β signaling. Taken together, these observations provide important conceptual advance in the field and promote new ways to approach the development of novel therapeutics against major depressive disorder.

Disclosures: S. Kohtala: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Helsinki has filed a patent application wherein part of the data presented have been disclosed (S.K., W.T. and T.R. as inventors). **W. Theilmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Helsinki has filed a patent application wherein part of the data presented in this

manuscript have been disclosed (S.K., W.T. and T.R. as inventors).. **M. Rosenholm:** None. **L. Penna:** None. **G. Karabulut:** None. **S. Uusitalo:** None. **K. Järventausta:** None. **A. Yli-Hankala:** None. **I. Yalcin:** None. **N. Matsui:** None. **H. Wigren:** None. **T. Rantamäki:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Helsinki has filed a patent application wherein part of the data presented in this manuscript have been disclosed (S.K., W.T. and T.R. as inventors).

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.03/ZZ6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: IRP-NIMH-NIH

Title: Ketamine and attentional bias to threat: MEG correlates of stimulus-evoked neural response

Authors: *J. R. GILBERT, C. GALIANO, A. NUGENT, C. ZARATE
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Abstract: The glutamatergic modulator ketamine elicits rapid antidepressant response in many patients with treatment-resistant major depressive disorder (MDD). Thus, modulation of glutamatergic transmission must be a critical feature of treatment efficacy, although the mechanisms of ketamine's antidepressant response are not fully understood. Recent work has suggested that AMPA-mediated glutamatergic neurotransmission following synaptic potentiation leads to increased stimulus-evoked gamma responses, providing an account for how ketamine might influence mood. Our study sought to extend these findings by probing magnetoencephalographic (MEG) stimulus-evoked neural responses in theta, alpha, beta, and gamma frequencies to an attentional bias to threat task. Nineteen drug-free patients with MDD participated in a double-blind, crossover, placebo-controlled experiment where an intravenous subanesthetic dose of ketamine hydrochloride was compared to a placebo infusion. The Montgomery-Asberg Depression Rating Scale (MADRS) was administered 230 minutes post-infusion to measure change in depression scores. MEG recordings were collected ~6.5 hours following both infusions using a 275-channel CTF system. During scanning, the neural correlates underlying facial processing and attentional bias were examined using a dot probe task with emotional faces. The multiple sparse priors routine in SPM12 was used to localize theta, alpha, beta, and gamma frequency activity from -100-1000 msec peristimulus time. A linear mixed effects model in AFNI was used to assess significant source-localized differences in each frequency of interest. Behaviorally, there were no significant differences in reaction time or

accuracy. Group-level source analyses identified a network of regions showing enhanced stimulus-evoked gamma-band responses during our task following ketamine. In addition, left inferior frontal gyrus showed significant source-level interactions in beta for infusion by emotion. Right lingual gyrus showed significant source-level interactions in gamma for infusion by congruency and in alpha for infusion by emotion by congruency. Finally, bilateral amygdala showed robust theta and gamma source-level interactions for infusion by MADRS. These findings add to a growing literature showing that processing of emotional faces with attentional bias recruits a network of brain regions. It also adds to a growing literature on stimulus-evoked neural responses following ketamine administration, particularly in gamma. Ongoing work will model ketamine-mediated connectivity between early visual cortex, higher order brain areas, and the amygdala.

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Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.04/ZZ7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01 DA039533

Title: Ketamine normalizes lateral habenula excitability and reduces depressive-like behavior following maternal deprivation

Authors: *R. D. SHEPARD[1], L. D. LANGLOIS[3], C. A. BROWNE[2], M. E. AUTHEMENT[1], A. BERENJI[5], I. LUCKI[4], F. S. NUGENT[1]
[1]Pharmacol., [2]Pharmacol. & Mol. Therapeut., Uniformed Services Univ., Bethesda, MD; [3]Pharmacol., [4]Dept. of Pharmacol. and Mol. Therapeut., Uniformed Services Univ. of the Hlth. Scienc, Bethesda, MD; [5]Old Dominion Univ., Norfolk, VA

Abstract: Depression is a current concern in mental healthcare due to the lack of fast and long-lasting treatments available to patients. Ketamine has emerged as a novel fast- and long-acting anti-depressant; however, the mechanism by which ketamine exerts this effect is still unknown. Recent attention has been called to the importance of the lateral habenula (LHb), a critical hub for the regulation of dopamine (DA) and serotonin (SERT) within the context of aversion and motivated behaviors. Thus, LHb dysfuction could contribute to changes in DA or SERT

signaling that are a component in the development and pathophysiology of psychiatric disorders. Using whole cell patch clamp recordings from LHb neurons in rat brain slices, we previously showed that maternal deprivation (MD), a severe early life stressor that is known to predict psychiatric illnesses later in development, induces hyperexcitability of LHb neurons in juvenile rats (P21-P28). Now, we show that this neuroadaptation persists into young adulthood (P42-50). Furthermore, we show that when subjected to the Forced Swim Test, MD induces significant immobility in comparison to control rats. We found that in response to a single i.p. injection of ketamine (20 mg/kg), LHb neuronal excitability is normalized up to 72hrs post-injection and corresponding MD-induced immobility is decreased 24hrs post-injection. This suggests that one of the sites of action for ketamine's anti-depressant effects could be through modulation of LHb neuronal firing in this stress model, thus influencing other monoamergic signaling pathways. In addition, we also identified that mature BDNF (mBDNF), an important neurotrophic factor that impacts synaptic plasticity and mediates part of ketamine's anti-depressant effects, might be dysregulated following MD and thus supports LHb dysfunction. We hypothesize that one of the ways in which ketamine exerts an anti-depressive mechanism of action is through changes in the expression of mBDNF in the LHb that involves epigenetic mechanisms.

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Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

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Program #/Poster #: 321.05/ZZ8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Academy of Finland grants 276333, 284569, 305195, 312664 (T.R.)
Finnish Funding Agency for Innovation (T.R.)
Doctoral Programme Brain & Mind (S.K.)

Title: Signaling pathways connected to rapid antidepressant responses of ketamine are activated by hypnotic-sedative drugs but not hydroxynorketamine

Authors: *M. ROSENHOLM[1], S. KOHTALA[1], W. THEILMANN[1], L. PENNA[1], P. KIURU[1], J. YLI-KAUHALUOMA[1], A. B. KLEIN[2], N. MATSUI[3], T. RANTAMAKI[1]
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Abstract: Aims Dissociative anesthetic ketamine has been shown to rapidly alleviate depressive symptoms at subanesthetic doses. A recent study has proposed ketamine's metabolite hydroxynorketamine (HNK), a non-sedative AMPA receptor potentiator, to be responsible for

these antidepressant effects. Our recent data however suggests that a volatile anesthetic isoflurane regulates similar signaling pathways as ketamine, namely activation of BDNF receptor TrkB and inhibition of GSK3β (glycogen synthase kinase 3β). Here, we have examined the ability of ketamine (at subanesthetic and anesthetic doses), HNK, and various hypnotic-sedative, anesthetic and stimulant drugs to regulate TrkB and GSK3β signaling. **Methods** Adult male C57BL/6JRccHsd mice were subjected to the following treatments: 1) ketamine HCl (10-100 mg/kg i.p.) 2) cis-6-hydroxynorketamine HCl (20 mg/kg i.p.) 3) 6,6-dideuteroketamine (100 mg/kg i.p.) 4) gamma-hydroxybutyrate HCl (GHB, 275 mg/kg i.p.) 5) hydroxyzine HCl (50 mg/kg i.p.) 6) gaboxadol HCl (10 mg/kg i.p.) 7) atipamezole HCl (1 mg/kg i.p.) 8) dextroamphetamine HCl (10 mg/kg i.p.) 9) isoflurane (4% induction, 2% maintenance in O_2). Prefrontal cortex and hippocampi were collected after treatments and analyzed for $TrkB^{Y816}$ and $GSK3\beta^{S9}$ phosphorylation with western blotting. **Results** Ketamine, unlike cis-6-HNK, dose-dependently increases $TrkB^{Y816}$ and $GSK3\beta^{S9}$ phosphorylation. These signaling effects were also activated by 6,6-dideuteroketamine, a modification of ketamine with strongly reduced metabolism to HNK. Remarkably, anesthetic doses of ketamine produced most significant effects on TrkB and GSK3β signaling. Indeed, pharmacologically diverse hypnotic-sedative drugs readily regulate TrkB and GSK3β signaling, whereas stimulant drugs have no such effects. Instead, amphetamine partially blocks TrkB and GSK3β signaling alterations induced by hypnotic drug medetomidine. Our further studies using isoflurane suggest that TrkB and GSK3β signaling remains regulated as long as animals remain anesthetized. **Conclusions** Our findings imply that the ability of ketamine to regulate TrkB and GSK3β signaling is by no means restricted to subanesthetic doses shown to bring antidepressant-like behavioral changes in rodents and that HNK is not responsible for these signaling effects. These results rather present an intriguing correlation between pharmacologically induced state of sedation and TrkB signaling effects and suggest that mere activation of these signaling pathways is not sufficient to elicit rapid antidepressant effects.

Disclosures: M. Rosenholm: None. **S. Kohtala:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Helsinki has filed a patent application wherein part of the data presented in this abstract have been disclosed (S.K., W.T. and T.R. as inventors). **W. Theilmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Helsinki has filed a patent application wherein part of the data presented in this abstract have been disclosed (S.K., W.T. and T.R. as inventors).. **L. Penna:** None. **P. Kiuru:** None. **J. Yli-Kauhaluoma:** None. **A.B. Klein:** None. **N. Matsui:** None. **T. Rantamaki:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Helsinki has filed a patent application wherein part of the data presented in this abstract have been disclosed (S.K., W.T. and T.R. as inventors)..

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.06/ZZ9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH Grant MH045481
NIMH Grant MH093897
State of CT

Title: Ketamine and rapastinel alter synaptic components of inhibitory and excitatory circuits in the prefrontal cortex

Authors: *C. H. DUMAN[1], S. POTHULA[1], R.-J. LIU[1], R. TERWILLIGER[1], S. GHOSAL[2], R. S. DUMAN[1]
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Abstract: The personal and societal impact of major depressive disorder (MDD) is compounded by low efficacy rates and the time lag for efficacy of currently available monoaminergic antidepressants. In contrast, recently identified drugs such as ketamine, an NMDA receptor antagonist, exert rapid antidepressant actions within hours in humans and in animal models. Rapastinel is a novel NMDA receptor modulator that also exerts rapid and sustained antidepressant effects, but without the side effects of ketamine. We are interested in mechanistic similarities and differences between ketamine and Rapastinel that could point to critical antidepressant mechanisms, as well as different side effect profiles. Chronic stress exposure in animal models can produce core behavioral features of depression, as well as morphologic changes that are consistent with those observed in post-mortem MDD brains. Ketamine and Rapastinel, and other rapid-acting agents have been shown to reverse stress-induced depressive behavior and synaptic deficits in rodent models (Li et al., 2011; Burgdorf et al., 2015).
The aim of the present study was to examine GABA inhibitory synaptic elements, as well as excitatory synapses that are regulated by stress and by rapid acting antidepressants.The expression of synaptic proteins following a single acute administration of ketamine or Rapastinel in mice was examined by Western blot and immunohistochemistry. Synaptic responses related to GABA and glutamatergic neurotransmission were assessed in whole-cell recordings in PFC pyramidal neurons. Ketamine and Rapastinel both increased GABA-related synaptic proteins (i.e., GAD65, GAD67, vGAT, gephyrin) in PFC 24 hr after single acute administration and both drugs also increased glutamate-related synaptic proteins (GluR1, PSD95, synapsin 1, vGLUT1), although the profiles were not identical. Whole-cell patch recordings in pyramidal cells indicate that ketamine and Rapastinel similarly increase the frequency of spontaneous and induced

excitatory postsynaptic currents (EPSCs) and that this effect may be balanced by a similar effect on inhibitory postsynaptic currents (IPSCs) for Rapastinel and to a lesser extent for ketamine. Ketamine and Rapastinel both showed efficacy in reversing the deficits in excitatory and inhibitory synaptic function resulting from chronic stress. We hypothesize that the different primary actions of these two drugs may lead to recruitment of overlapping as well as unique circuitry that is important for the antidepressant behavioral consequences and the side effect profiles of these agents. Additional ongoing studies are required to test this hypothesis.

Disclosures: C.H. Duman: None. **S. Pothula:** None. **R. Liu:** None. **R. Terwilliger:** None. **S. Ghosal:** None. **R.S. Duman:** F. Consulting Fees (e.g., advisory boards); Naurex.

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

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Program #/Poster #: 321.07/ZZ10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH Grant MH045481
NIMH Grant MH093897
State of Connecticut

Title: Role of GABAergic interneuron GluN2B subunits on the antidepressant actions of ketamine in male and female mice

Authors: *D. M. GERHARD[1], R. S. DUMAN[2]
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Abstract: Recent studies highlight the rapid antidepressant actions of the NMDA receptor antagonist ketamine. Rodent studies show that ketamine rapidly increases glutamate release, activates mTORC1 signaling and increases translation of synaptic proteins in the medial prefrontal cortex (mPFC) shortly following acute treatment. Furthermore, additional studies show that selective GluN2B receptor antagonists produce similar behavioral and molecular signaling effects. However, the initial cellular trigger underlying the actions of ketamine has not been identified. Collectively, these studies suggest that blockade of GluN2B-containing NMDARs may be a critical mediator for the rapid antidepressant effects of ketamine. We used Camk2-, Gad1-, parvalbumin (Pvalb)-, and somatostatin (Sst)-Cre mice and AAV-GluN2B shRNA to produce Cre-dependent knockdown of GluN2B receptors in glutamate and GABA neurons, as well as subpopulations of GABA neurons. AVV-GluN2B shRNA was infused into the mPFC of the cre recombinase lines and after 3 weeks, the mice were tested before and after ketamine administration in the forced swim test (FST) and novelty suppressed feeding test (NSFT). Viral-mediated knockdown of GluN2B in the mPFC of Gad1-Cre mice produced a

significant antidepressant response in the FST and occluded the antidepressant effects of ketamine in this model; preliminary studies suggest similar effects in the NSFT. Knockdown of GluN2B on pyramidal neurons in Camk2a-Cre mice did not significantly block the antidepressant response to ketamine in the FST or NSFT. Preliminary results in Sst- and Pvalb-Cre mice suggest a role for both interneuron subtypes in the antidepressant effects of ketamine. Using mice with a global, conditional, cell specific deletion of GluN2B in Sst-Cre mice we find that adult male knockout mice, when compared to wild-type littermates, have baseline behavioral effects in the FST, comparable to findings from our region-specific viral knockdown experiments in male Sst-Cre adults. Furthermore, genetic knockdown of GluN2B subunits on Sst+ neurons decreases mPFC layer V pyramidal cell responses to monoamine evoked inhibition and increases baseline spontaneous excitatory post-synaptic currents (sEPSCs). Preliminary results in adult, female Sst-deletion mutant mice suggest no baseline behavioral or electrophysiology differences compared to wild-type littermates; however, further analysis is underway on the effects of estrous cycle on behavior and electrophysiology in females. Additional experiments are being conducted to explore the cellular and behavioral antidepressant efficacy of ketamine in both male and female mice.

Disclosures: D.M. Gerhard: None. **R.S. Duman:** None.

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

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Program #/Poster #: 321.08/ZZ11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Navitor Pharmaceuticals Inc.

Title: Sestrin2 Modulator NV-5138, shows ketamine-like rapid antidepressant effects via direct activation of mTORC1 and BDNF signaling

Authors: *R. S. DUMAN[1], S. POTHULA[1], T. KATO[1,2], R.-J. LIU[1], C. DUMAN[1], R. TERWILLIGER[1], G. P. VLASUK[3], E. SAIAH[3], S. HAHM[3]
[1]Dept. of Psychiatry, Yale Univ. Sch. Med., New Haven, CT; [2]Sumitomo Dainippon Pharma Co., Ltd, Osaka, Japan; [3]Navitor Pharmaceuticals, Inc., Cambridge, MA

Abstract: The NMDA receptor antagonist ketamine produces rapid antidepressant actions, even in patients considered treatment resistant, addressing a major limitation of currently available medications. In preclinical rodent models the antidepressant behavioral actions of ketamine are associated with increased number and function of synapses in the medial prefrontal cortex (mPFC) and these effects are dependent on mTORC1 and BDNF signaling. The mTORC1 pathway is a cellular regulator of protein synthesis and is modulated by neuronal activity,

endocrine and metabolic signals, including amino acids, notably leucine, which activates mTORC1 signaling via the binding to sestrin2. We have recently demonstrated that NV-5138, a novel, specific small molecule modulator of sestrin2 that penetrates the blood brain barrier, produces rapid antidepressant behavioral responses in the rat forced swim test (FST), female urine sniffing test (FUST), and novelty suppressed feeding test (NSFT), and reversed the anhedonia caused by chronic stress exposure. As expected, the antidepressant actions of NV-5138 were dependent on mTORC1 signaling. We also found that NV-5138 rapidly increased the number and function of spine synapses in mPFC layer V apical dendrites. Here we tested the requirement for BDNF signaling in the actions of NV-5138. The results demonstrate that the infusion of a function blocking BDNF neutralizing antibody into the mPFC blocks the antidepressant behavioral actions of NV-5138 in the FST and NSFT, but had no effect on locomotor activity or home cage feeding. In addition, in mice with a knockin of the BDNF Val/met polymorphism, which blocks the processing and activity dependent release of BDNF, the antidepressant actions of NV-5138 in the FST and NSFT were completely blocked. Taken together, the results demonstrate that NV-5138 produces rapid synaptic and antidepressant behavioral responses via the direct activation of the mTORC1, and these effects also require activity-dependent BDNF release and signaling in the mPFC, supporting the possibility that sestrin2 modulation is a novel target for development of rapid acting antidepressants.

Disclosures: R.S. Duman: None. **S. Pothula:** None. **T. Kato:** A. Employment/Salary (full or part-time):; Sumitomo Dainippon Pharma Co., Ltd. **R. Liu:** None. **C. Duman:** None. **R. Terwilliger:** None. **G.P. Vlasuk:** A. Employment/Salary (full or part-time):; Navitor Pharmaceuticals, Inc. **E. Saiah:** A. Employment/Salary (full or part-time):; Navitor Pharmaceuticals, Inc. **S. Hahm:** A. Employment/Salary (full or part-time):; Navitor Pharmaceuticals, Inc..

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.09/ZZ12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH Grant MH045481
NIMH Grant MH093897
State of CT

Title: Projection-specific optogenetic stimulation of medial prefrontal cortex neurons expressing dopamine D1 receptors produces rapid antidepressant effects

Authors: *R. SHINOHARA, B. D. HARE, S. POTHULA, R. S. DUMAN
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Abstract: Depression is a leading cause of disability throughout the world with more than 300 million of people suffering with major depression. A single, subanesthetic dose of ketamine, a non-competitive NMDA receptor antagonist, produces rapid and sustained antidepressant effects in patients with depression. Ketamine infusions into the mPFC or optogenetic activation of principal neurons in the mPFC are sufficient to produce rapid and long-lasting behavioral changes in rodent models, demonstrating the importance of mPFC in the antidepressant response to ketamine. mPFC layer 5 principal neurons can be divided into at least two subtypes, referred to as Type A and B, based on morphological complexity, physiological properties, and projection targets. These subtypes can be targeted by expressing Cre recombinase (Cre) under the control of dopamine D1 (Type B), or D2 (Type A) receptor promotor. We recently found that optogenetic stimulation of Type B cells, but not Type A cells, in the mPFC is sufficient to produce rapid and sustained antidepressant behavioral responses concomitantly with immediate early gene expression in the basolateral amygdala (BLA) and bed nucleus of the stria terminalis (BNST). However, circuit mechanisms underlying the antidepressant responses of ketamine and optogenetic stimulation of Type B cells remain to be elucidated. To address this question, we expressed channelrhodopsin-2 (ChR2) selectively in Type B cells of the mPFC and examined the effects of photostimulation of ChR2-expressing axon terminals in the BNST or BLA. Photostimulation at a frequency of 10 Hz for 60 minutes in respective brain regions was performed 24 hours before the forced swim test (FST) and novelty suppressed feeding test (NSFT). Selective terminal stimulation of mPFC Type B cells in the BLA produced an antidepressant response in the FST and an anxiolytic response in the NSFT; these effects were evident 24 hours after stimulation. Although selective terminal stimulation of mPFC Type B cells in the BNST produced no obvious antidepressant response in the FST, the anxiolytic response in the NSFT was observed at least 24 hours after stimulation. These results indicate that projection-specific optogenetic stimulation of mPFC Type B cells is sufficient to produce antidepressant and anxiolytic responses, with the mPFC-BLA projection implicated in both, whereas the mPFC-BNST projection only in the anxiolytic response. Experiments are currently being conducted to test whether these circuits are necessary for the antidepressant and anxiolytic effects of ketamine.

Disclosures: R. Shinohara: None. **B.D. Hare:** None. **S. Pothula:** None. **R.S. Duman:** None.

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.10/ZZ13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01MH107615
NIH NS065371

Title: NMDA receptor inhibition is not a determinant for the antidepressant effects of the ketamine metabolite (2R,6R)-hydroxynorketamine

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Abstract: Preclinical studies indicate that (*2R,6R*)-hydroxynorketamine (HNK) is a fast-acting antidepressant devoid of ketamine's untoward side effects. Although NMDA glutamate receptor (NMDAR) inhibition has been proposed to underlie ketamine's antidepressant effects, its contribution to (*2R,6R*)-HNK's antidepressant effects remains to be elucidated. This study systematically assessed the effects of (*2R,6R*)-HNK, compared to ketamine, on NMDAR activity. The forced-swim and novelty suppressed feeding tests established antidepressant effectiveness of (*2R,6R*)-HNK at 10 mg/kg, i.p., in male CD-1 mice. (*2R,6R*)-HNK concentrations were measured in hippocampal microdialysates obtained from awake mice as well as in whole brain tissue and in plasma of mice at various times after the i.p. injection of 10 mg/kg (*2R,6R*)-HNK. The effectiveness of ketamine or (*2R,6R*)-HNK to prevent NMDA (250 mg/kg, i.p.)-induced lethality in mice was also examined. The effects of ketamine and (*2R,6R*)-HNK were evaluated *in vitro* on: (i) NMDAR-mediated field excitatory postsynaptic potentials in the mouse hippocampus, (ii) NMDAR-mediated miniature excitatory postsynaptic currents in rat CA1 pyramidal neurons, (iii) NMDA-evoked currents in CA1 pyramidal neurons, and (iv) recombinant GluN1/2A, GluN1/2B, GluN1/2C, and GluN1/2D NMDARs expressed in *Xenopus* oocytes. The effects of the *S*-isomer of (*2R,6R*)-HNK, i.e. (*2S,6S*)-HNK, on NMDAR-mediated fEPSPs in the mouse hippocampus and on NMDA receptors ectopically expressed in oocytes were also analyzed. Concentrations necessary for 50% reduction of NMDAR responses (IC_{50}) *in vitro* were calculated for each compound. During data collection and analyses, researchers were blind to the treatments. The antidepressant dose of (*2R,6R*)-HNK generated maximal plasma, brain tissue, and extracellular hippocampal concentrations of approximately 10 µM, which had no effect on NMDAR-mediated responses *in vitro*. (*2R,6R*)-HNK IC_{50} values were at least six times higher than its maximal plasma concentration following therapeutic dosing. *In vivo* and *in vitro*, ketamine inhibited NMDAR-mediated responses with 10-20-fold greater potency than (*2R,6R*)-HNK. In addition, (*2S,6S*)-HNK was more potent than (*2R,6R*)-HNK, but less potent than ketamine in inhibiting NMDA-mediated responses. These data suggest that NMDAR inhibition is unlikely to contribute to the (*2R,6R*)-HNK's antidepressant behavioral effects. NMDAR inhibition is a major determinant of ketamine's undesirable side-effects, and thus (*2R,6R*)-HNK, and next generation drugs sharing similar pharmacodynamics, may be better tolerated antidepressants than ketamine.

Disclosures: E.W. Lumsden: None. **T.A. Troppoli:** None. **S.J. Myers:** None. **P. Zanos:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent

holder, excluding diversified mutual funds); Co-Investor Patent Application. **S. Kim:** None. **Y. Aracava:** None. **J. Kehr:** None. **F. Wang:** None. **S. Schmidt:** None. **C.E. Jenne:** None. **M. Lane:** None. **R. Moaddel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Investor Patent Application. **P.J. Morris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Investor Patent Application. **C. Thomas:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Investor Patent Application. **S. Traynelis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Founder: NeurOp, Inc.. F. Consulting Fees (e.g., advisory boards); Sage Therapeutics. **E.F.R. Pereira:** None. **S.M. Thompson:** None. **E.X. Albuquerque:** None. **T.D. Gould:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Investor Patent Application.

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.11/ZZ14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH grant R21MH105746
NIH grant K01AG054729
NIH grant P20GM113131

Title: Comparative phosphoproteomic analysis using frontal cortices from type 3 adenylyl cyclase knockout and wild-type mice

Authors: *Y. ZHOU, L. QIU, F. CHU, X. CHEN
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Abstract: The type 3 adenylyl cyclase (AC3) is predominantly expressed neuronal primary cilia throughout the brain. To date, how AC3 regulates neuronal signaling and function is unknown. We employed a mass spectrum(MS)-based phosphoproteomic approach to identify phosphoproteome differences between tamoxifen-inducible AC3 knockout (KO) and wild-type (WT) mice. Proteins of frontal cortex tissues from KO and WT mice (both genders) were extracted and digested with trypsin. Phosphopeptides were enriched using a TiO_2 enrichment method and then subjected to HPLC-MS/MS analysis. All target peptides spectra were reviewed and verified manually. Phosphopeptides were identified using their MS spectra to search against proteomic database. Here we report that 4188 phosphorylated modification sites were detected from 1767 proteins. Comparison of KO and WT female samples led to identification of 18

posttranslational phosphorylation modifications that had significant enrichment in female KO samples (e.g. Sh3gl1), whereas 4 modifications were found to be selectively present in female WT samples. Comparative analysis of KO and WT male samples revealed 10 modifications present only male KOs (e.g. Pde1b). We also identified 18 modifications having gender differences with 7 only identified in females and 11 in males (e.g. Ctnnd2, Ctnna2). We also examined the relative abundance of phospho-serine, phospho-threonine and phospho-tyrosine residues in each sample. On average, (p)Ser accounted for 85% of total phosphorylated residues, (p)Thr 13%, and (p)Tyr 1%, respectively. Interestingly, in phospho-serine residues, motifs matching proline-directed kinases had higher abundance ($P<0.05$, $n = 8$ pairs) in WT mice than KO mice, indicating that ablation of AC3 affects the overall activity of proline-directed kinases in the brain. This work provides useful clues to understand how AC3 modulates neuronal signal pathways and their function.

Disclosures: Y. Zhou: None. **L. Qiu:** None. **F. Chu:** None. **X. Chen:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Corresponding author.

Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.12/ZZ15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: CD1 and BALB/c mice did not differ in the additive influence of ZMA, & ketamine (1 mg/kg) on the anti-depressive index, "swimming time" produced during the forced swimming test

Authors: *V. J. MEDINA ARANDA[1], A. L. ROSADO PEREZ[2], S. A. VILLALOBOS CETINA, JR[1], M. A. VILLALOBOS CETINA, JR[1], J. PINEDA[4], J. HERRERA[3]
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Abstract: Depression is a disorder with a high rate of resistance to treatment. Ketamine, an antagonist of N-methyl-D-aspartate (NMDA) receptors, produces a rapid and sustained antidepressant effect in patients with treatment-resistant depression. But in therapeutic doses it produces psychomimetic symptoms which limits its use. We found that ZMA (11 mg of pyridoxine, 450 mg of magnesium and 30 mg of zinc) potentiates the antidepressant influence of ketamine in undeffective doses to reduce depressive indices in BALc mice expressing a depressive phenotype. However, its influence has not been proven in other strains with different sensitivity to antidepresant drugs such as the mice strain CD1. So in this work we compared the

influence of co-administration of sub-threshold doses of Ketamine with ZMA on the behavior of CD1 mice in the forced swimming test and compare such influence whith that produced in BALc mice. Methods: 32 CD1 mice and 32 BALB/c were divided into 8 groups of 8 mice each, received a dose of: Ketamine (1 mg / kg); Ketamine (1 mg / kg) + ZMA (0.028125mg / kg); Or ZMA in the same dose; 24 hrs. Later the mice were subjected to the open field test, (6 minutes). One week after the open field test the same treatment was repeated and 24 hrs. Later the mice were subjected to the forced swimming test for 6 minutes. When vehicle was applied to the mice, the immobility time in the last 4 min of the test was 42 ± 2, 43 ± 4 bins. After Ketamine, was: 33 ± 3 and 34 ± 3 bins. After Ketamine + ZMA: 23 ± 3, 22 ± 3 bins and after ZMA: 22 ± 2 and 18 ± 3 bins. Bonferroni´s posttest showed that only the influence of ketamine on the ST was different between both mice strains. No changes were detected in the CT ($p > 0.05$). The distance traveled by CD1 mice, was larger than in BALc mice in all the conditions tested ($p < 0.01$). Even though, there were no differences with any treatment. Conclusion: CD1 strain traveled distance in the open field test was significant larger than BALB/c homologous group and 1 mg/kg of ketamine increases antidepressant-like index in BAL/c, but not in CD1 mice. ZMA expressed the same antidepressan-like activity in both strains.

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Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 321.13/ZZ16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NSFC Grant 91432108, 31225010, 81527901,81600954

Title: Ketamine blocks bursting in the lateral habenula to rapidly relieve depression

Authors: *Y. YANG[1], Y. CUI[2], K. SANG[2], Y. DONG[2], Z. NI[2], S. MA[2], H. HU[2]
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Abstract: The discovery of the rapid antidepressant effects of the N-methyl-D-asparate receptor (NMDAR) antagonist ketamine is arguably the most significant advance in the field of psychiatry. But the mechanism of how ketamine elevates mood so quickly has remained elusive. A single administration of ketamine elicits fast and sustained antidepressant effects both in human clinical trials and animal models of depression. It also has a fast metabolic turnover rate, with a half life of 3hrs in humans. This rapid “hit-and-go” temporal profile suggests that ketamine is likely to act on a system that has ongoing activity with open NMDAR channels. The lateral habenula (LHb) has recently emerged in the coding of negative emotionand

pathophysiology of major depression. LHb hosts primarily glutamatergic neurons, but it inhibits brain's reward centers (including the dopaminergic ventral tegmental area (VTA) and the serotonergic dorsal raphe nucleus (DRN), whose hypoactivity has been implicated in depression) either through relay at the GABAergic rostromedial tegmental nucleus (RMTg) or local interneurons within VTA and DRN. Although accumulating evidence suggest that aberrantly overactive LHb is crucial to depression, it remains unknown how the spike patterns of LHb neurons are altered during depressive state and what role it may play in depression etiology and the fast antidepressant effects of ketamine. We recently found that a significant portion of LHb neurons are spontaneously active and intrinsically prone to burst firing. LHb neurons have significant increase in burst activity and theta-band synchronization in depression, which is reversed by ketamine. Our pharmacology and modeling experiments reveal that LHb bursting strongly requires both NMDAR and low-voltage-sensitive T-type calcium channels (T-VSCCs). Behaviorally, burst-evoking photostimulation of LHb drives despair and anhedonia. Furthermore, local blockade of NMDAR or T-VSCCs in the LHb is sufficient to be rapidly antidepressant. Our results suggest a simple model whereby ketamine quickly elevates mood by blocking NMDAR-dependent bursting activity of LHb neurons to disinhibit downstream reward centers, and provide a framework for developing new rapid-acting antidepressants.

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Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

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Program #/Poster #: 321.14/ZZ17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Discriminative stimulus properties of the ketamine metabolite (2R, 6R)-hydroxynorketamine (HNK) and ketamine enantiomers in C57BL/6 mice

Authors: *R. RICE, F. ZHANG, H. NANGUNURI, A. N. BALDWIN, J. H. PORTER
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Abstract: Major Depressive Disorder (MDD) afflicts an estimated 17% of US citizens during their lifetime (Kessler et al., 2005). For 50 years, the monoamine hypothesis of MDD has prevailed, but it doesn't fully explain the delay of therapeutic effects and the approximately 40% of treatment-resistant patients. Clearly, there is a critical need to develop better, alternative treatment targets for MDD. After the demonstration that a single, subanesthetic dose of ketamine (0.5 mg/kg i.v.) produced a rapid and relatively long lasting (3 days) improvement of symptoms in MDD patients (Berman et al 2000), there is increased focus on glutamatergic mechanisms for the treatment of MDD (Hillhouse and Porter 2015). Animal research also has reported

antidepressant-like effects with ketamine (Maeng et al., 2008; Zhou et al., 2014), but these promising findings are limited by ketamine's abuse liability and aversive psychomimetic side-effects.Ketamine is a noncompetitive antagonist at NMDA glutamate receptors, but the mechanisms responsible for its antidepressant effects are unclear. Zanos et al (2016) recently reported that the ketamine metabolite (2S,6S;2R,6R)-hydroxynorketamine (HNK) is important for its antidepressant effects. The antidepressant-like actions of HNK were independent of NMDAR inhibition and appeared to lack many of ketamine-related side effects (e.g. abuse liability). A preclinical assay that has proven to be very valuable for predicting the abuse liability of drugs is Drug Discrimination. The discriminative stimulus properties of drugs reflect their subjective (interoceptive) effects and are mediated by specific receptor actions. The present study trained adult male C57BL/6 mice to discriminate 5.0 mg/kg racemic ketamine from saline in a two-lever food reinforced operant task. After establishing ketamine discrimination, substitution testing was conducted with HNK (10 and 60 min injection times) with the (*R*) and (*S*) ketamine enantiomers. While both the (*R*) and (*S*) ketamine isomers shared discriminative stimulus properties with racemic ketamine, the HNK metabolite did not, producing only saline-lever appropriate responding. The lack of shared subjective effects with ketamine suggests that HNK lacks many of ketamine's side effects. In contrast, both the (*R*) and (*S*) isomers fully substituted for ketamine; (*S*)-ketamine isomer was more potent (ED_{50} = 1.067 mg/kg) than (*R*)-isomer (ED_{50} = 2.69 mg/kg) or racemic ketamine (ED_{50} = 2.032 mg/kg). While clinical trials are being conducted with racemic ketamine and (*S*)-ketamine for the treatment of MDD, current preclinical findings suggest that HNK and (*R*)-ketamine also should be tested in clinical trials.

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Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

Location: SDCC Halls B-H

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Program #/Poster #: 321.15/ZZ18

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Rapid antidepressant response to ketamine is mediated by Drd1 expressing principal neurons in the medial prefrontal cortex

Authors: *B. D. HARE, R. J. LIU, R. SHINOHARA, S. POTHULA, R. J. DILEONE, R. S. DUMAN
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Abstract: The rapid antidepressant actions produced by ketamine administration require medial prefrontal cortex (mPFC) activation. Consistent with this, optogenetic activation of mPFC pyramidal neurons results in rapid synaptic changes that are mechanistically linked to the

antidepressant behavioral responses to ketamine. mPFC pyramidal cell subtypes have been distinguished by morphological complexity, response to neurotransmitters, projection targets, and physiological properties. The role of pyramidal cell subtypes in the antidepressant response is unclear. The current study addresses this issue using transgenic mice that express Cre recombinase under the control of the promoters for dopamine *Drd1* or *Drd2*, which distinguish two major pyramidal neuron subtypes in the mPFC, for targeting optogenetic viral constructs. Studies utilized male and female mice (*Drd1*cre, *Drd2*cre, littermate controls). In initial studies placement of Cre-dependent optogenetic constructs in to the mPFC was followed by photostimulation/inhibition and behavioral testing. Testing included the forced swim test (FST), elevated plus maze (EPM), and novelty suppressed feeding test (NSF) and occurred 24 hours or more after optogenetic manipulations. We observed that photostimulation of the *Drd1* cell subtype resulted in a rapid (24hrs) and prolonged (7days) antidepressant response, as well as reduced anxiety like behavior. In contrast, photostimulation of the *Drd2* containing subtype failed to produce antidepressant or anxiolytic effects. Importantly, photoinhibition of mPFC *Drd1* containing cells immediately after ketamine administration blocked ketamine associated behavioral effects. In support of the optogenetic results, additional studies demonstrated that mPFC infusion of a D1 agonist (SKF81297) produced an antidepressant response 24 hours after administration, while mPFC infusion of a D1 antagonist (SCH39166) blocked the antidepressant response produced by ketamine. These results demonstrate a critical role for the mPFC *Drd1* containing cell population in the rapid antidepressant actions of ketamine. Experiments are underway to examine the necessity of the *Drd2* population to the rapid antidepressant response and to identify the key target projection regions for these effects.

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Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

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Program #/Poster #: 321.16/ZZ19

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

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Allergan Inc., NJ, USA

Title: Cellular target and downstream signaling mechanisms underlying the rapid antidepressant actions of rapastinel

Authors: *S. POTHULA[1], T. KATO[1], D. GERHARD[1], P. BANERJEE[2], R. S. DUMAN[1]
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Abstract: Rapastinel (Glyx-13) is a novel NMDA receptor (NMDAR) modulator that enhances NMDAR function. It exerts rapid antidepressant effects similar to ketamine but lacks the ketamine-like psychotomimetic effects. Recent studies revealed that the antidepressants actions of both rapastinel and ketamine are mediated by similar downstream mechanisms, including BDNF release, mTOR activation, synaptogenesis, and AMPAR and NMDAR-dependent synaptic plasticity. Dopamine D1 receptor (D1R), Src family kinases (SFKs) and STEP61 are all known to regulate the surface expression of NMDARs and NMDAR function but the initial cellular trigger and the role of these signaling molecules in rapastinel's rapid antidepressant actions and enhancement of NMDAR function remain unknown. Here, we use a combination of AAV2-viral mediated cell specific knockdown, behavioral, pharmacological and biochemical approaches to identify the cellular target and to examine the role of NMDAR subunits and downstream signaling in the actions of rapastinel. The results demonstrate that knockdown of GluN2B subunits on glutamatergic but not GABAergic neurons in the medial prefrontal cortex (mPFC) blocks the antidepressant effects of rapastinel. In contrast, the actions of ketamine were blocked by knockdown of GluN2B on GABAergic but not glutamatergic neurons. Also, rapastinel significantly increases the surface expression of GluN2B, phosphorylation of GluN2B and SFKs, and decreases the levels of STEP61 in the mPFC. Further, pharmacological inhibition of D1R and SFKs in the mPFC blocks the rapid antidepressant behavioral actions of rapastinel in the forced swim test and Novelty suppressed feeding test. Together, our findings suggest that the GluN2B subunit on glutamatergic neurons act as cellular target for rapastinel to trigger a downstream signaling cascade. The results also show that D1Rs and SFKs are required for the rapid antidepressant actions of rapastinel and these signaling molecules may underlie the enhanced surface expression and function of NMDARs. Ongoing experiments are evaluating the role of D1R, SFKs and STEP61 in the regulation of surface expression of NMDARs and antidepressant effects observed in response to rapastinel treatment.

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Poster

321. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants II

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MH105910

Title: Role of cortical somatostatin and parvalbumin interneurons in the rapid antidepressant actions of scopolamine

Authors: *M. FOGACA, R. DUMAN
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Abstract: Major depressive disorder (MDD) is a debilitating psychiatric illness that affects approximately 17% of the population, causing substantial health and socioeconomic burdens. This reflects in part the low efficacy, delayed response and low adherence of patients to present-day drug treatments. A single dose of scopolamine, a nonselective muscarinic acetylcholine receptor antagonist induces rapid antidepressant effects in patients. Previous evidence demonstrates that scopolamine acts through blockade of M1-type receptors on GABA interneurons, and here we are conducting additional studies to extend this work. Using Cre-dependent Design Receptors Exclusively Activated by Designer Drugs (DREADD), we tested the effects of stimulating GABA interneurons in the medial prefrontal cortex (mPFC) on the antidepressant actions of scopolamine. We also evaluated if scopolamine effects could be mediated by M1 receptors specifically located in somatostatin (SST) interneurons, as well as the cellular mechanisms underlying activity-dependent synaptic effects of scopolamine, such as vesicular transporters (VGLUT1, VGAT, VCHAT) and GABA synthetic enzyme (GAD1). Here we used mice that express Cre-recombinase in GABA interneurons (Gad1-Cre) or in specific subpopulations, including parvalbumin (Pv-Cre) and somatostatin (Sst-Cre). The viral vector (pAAV-hSyn-DIO-hM3D(Gq)-mCherry) was infused into mice mPFC to induce Cre-recombinase-dependent expression of Gq-coupled hM3Dq receptors, which are sensitive to clozapine-N-oxide (CNO). Two weeks later, mice received 3 injections (every 48 h) of CNO (1 mg/kg) followed, 20 min later, by saline or scopolamine (25 µg/kg). Moreover, we have generated mice with Sst-Cre conditional deletion of M1 that were also tested. Twenty-four hours after the last injection, the mice were subjected to the forced swim test (FST), and 48 hours later, to the novelty suppressed feeding test (NSFT). The efficiency of viral infusion was confirmed at the end by histology and electrophysiological recordings. Stimulation of Gad1-, Pv- and Sst-Cre interneurons by CNO injections prevented the antidepressant effects of scopolamine in the FST and NSFT. In addition, the actions of scopolamine in the FST and NSFT were blocked in the Sst-Cre M1 deletion mice. Scopolamine administration increased levels of the glutamatergic and GABAergic-related proteins in the mPFC. The results are consistent with the hypothesis that the initial trigger for the rapid antidepressant action of scopolamine is antagonism of M1 receptors on mPFC interneurons, which then promotes a more long-term balance between GABAergic and glutamatergic neurotransmission.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

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Program #/Poster #: 322.01/ZZ21

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CBN Pilot Project Grant
MH113899
BX000559

Title: Behavioral deficits caused by inescapable shock

Authors: *A. STEPHENS[1], D. A. MORILAK[1,2,3], D. J. LODGE[1,2], A. FRAZER[1,2,3], F. R. CARRENO[1,2]
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Abstract: Stress is a precipitating factor in the development of Major Depressive Disorders (MDD) as well as Post Traumatic Stress Disorder (PTSD). In order to develop a pre-clinical model sensitive to stress that is able to produce a variety of behavioral deficits that are relevant for depressive- and PTSD-like symptomatology, we used the inescapable shock (IS) paradigm. IS session of 60 x 15 sec shocks on two consecutive days produced significant escape deficits in about 70% of the rats that lasted up to 3 weeks when they are placed into the same box where they received shock when compared to control non-shocked rats (NS). The effect of IS on the performance of rats in the forced swim test (FST) and shock probe defensive burying (SPDB) test was measured as well. Rats received IS for 2 consecutive days and the FST was performed 24h later. They were tested in the SPDB test the next day. IS caused a significant increase in immobility in the FST and changed the coping behavior of rats in the SPDB test, i.e., it produced a significant increase in the time the animal spent immobile.
In subsequent experiments, NS controls were replaced with escapable shock (ES) controls, which received foot shocks in the same boxes as IS, but were allowed to escape to the other side to terminate the shock. In order to evaluate possible hedonic deficits of IS, the female urine sniffing test (FUST) was used. Baseline performance in the FUST was measured at least 24h before rats received IS or ES. Rats then received two consecutive days of IS or ES and 24h later were tested in the FUST. After IS, but not ES, rats showed a decrease in preference for female urine, which lasted for up to 3 days. In a small cohort of animals, we tested the effect of the α5-$GABA_A$ NAM, L-655,708 on the behavioral deficits in the FUST. I.P. injections of L-655,708, but not vehicle, partially restored the IS-induced reduction of time spent sniffing female urine.
Thus, we have developed a stress paradigm that produces robust behavioral deficits that are relevant to MDD- and PTSD-like symptomology and and we will continue to study the effects of novel compounds that have relevance for the treatment of MDD and/or PTSD, such as L-655,708.

Disclosures: A. Stephens: None. **D.A. Morilak:** None. **D.J. Lodge:** None. **A. Frazer:** None. **F.R. Carreno:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.02/ZZ22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Ontario Graduate Scholarship 2017-18
Campbell Family Mental Health Research Institute

Title: Chronic stress induces elevated levels of neuronal activity in the prefrontal cortex and ventral hippocampus that correlates with depressive- and anxiety-like behaviors in mice

Authors: *C. J. FEE[1,3], T. D. PREVOT[1], K. A. MISQUITTA[2,3], M. BANASR[5,3], E. SIBILLE[6,3,4]
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Abstract: Major depressive disorder (MDD) involves diverse symptomatology of low mood, anhedonia, cognitive deficits, and highly comorbid anxiety. Past neuroimaging studies found altered neuronal activity associated with MDD severity, suggesting a mechanism bridging cellular- and symptom-level deficits. Parallel imaging and postmortem studies further identified GABAergic deficits linked to reduced measures of inhibition across mood-related brain regions. These findings suggest that regional excitation-inhibition imbalances play a causal role in MDD. However, it is unclear how regional changes contribute to the emergence of specific symptoms. To address this, we assessed depressive-, anxiety-, anhedonia-like, and cognitive behavioral dimensions, and quantified c-fos expression via immunohistochemistry (IHC) across stress-/mood-related brain regions in mice exposed to unpredictable chronic mild stress (UCMS) or chronic restraint stress (CRS). 3 groups of adult C57BL/6J mice (n=12/group; 50%♀) underwent 5-week UCMS (random mild stressors, 2-4x/day), CRS (1h 2x/day), or handling (controls). Week 0-5 deficits were characterized with repeatable weekly phenotyper, sucrose consumption, and fur coat tests. In weeks 6-8, endpoint tests assessed depressive/anxiety-like behaviors (tests aforementioned plus open field, elevated plus maze, novelty-suppressed feeding, novelty-induced hypophagia), and cognition (object recognition, y-maze). At week 8, mice were sacrificed 90min after an acute stressor. Extracted brains were cryosectioned for IHC analysis. Density of c-fos+ cells was quantified in 23 brain regions (processing/segmentation with ZEN Blue). One-way ANCOVA (sex covariate) was used for between-group comparisons, Pearson's r assessed relationships between regional cell densities and behavior, and z-scoring compiled behavioral dimensions i.e. anxiety-, anhedonia-like behavior, and cognition. We found that

UCMS and CRS induced elevated anxiety-like behavior starting in W1. Across endpoint tests, both groups had elevated z-anxiety, CRS elevated z-anhedonia, whereas UCMS more consistently reduced z-cognition. Across both stress groups, c-fos+ cell density was elevated in cortical area 24b and ventral hippocampus CA1 and CA3. These changes each correlated with z-scores for depressive-/anxiety-like behaviors across several tests. Ongoing analyses will assess glutamate/GABA markers to investigate cellular underpinnings of increased neuronal activity. Together, this work supports a link between altered neuronal activity in limbic regions associated with chronic stress exposure and specific MDD symptom dimensions.

Disclosures: C.J. Fee: None. **T.D. Prevot:** None. **K.A. Misquitta:** None. **M. Banasr:** None. **E. Sibille:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.03/ZZ23

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Center for Undergraduate Research, Bowling Green State University

Title: The impact of binding on crayfish aggression

Authors: *S. GARRETT-RUFFIN, B. SIZEMORE
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Abstract: The aim of this study was to develop a new crayfish model of depression. Our model of depression involved binding the claws of crayfish and using aggressive behavior, as well as, exploratory behaviors as indexes of depression. Aggression was defined by the amount of time crayfish spent near a mirror reflection of themselves. Using a matched design based on weight, thirty crayfish of the species *procambarus clarkia* were randomly assigned to either a bound or unbound condition. Interestingly, the bound crayfish engaged in more exploratory behavior, as well as, spent more time in the area with the mirror reflection, which was interpreted as aggressive behavior. We found no differences in weight between bound and unbound crayfish which suggests similar feeding behaviors across groups. Our work also involved developing a model of crayfish depression based on the behavioral data from this study coupled with previous behavioral and neurochemical studies on crayfish aggression.

Disclosures: S. Garrett-Ruffin: None. **B. Sizemore:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.04/ZZ24

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: German Research Foundation (DFG) grant (SFB1280/ A18)

Title: Experimentally induced glioblastoma and its treatment with rapamycin alters neurobehavioral functioning in rats

Authors: *M. HADAMITZKY[1], A. HERRING[2], L. LÜCKEMANN[1], E. M. MARTINEZ-GOMEZ[1], I. BENDIX[3], U. SURE[4], M. SCHEDLOWSKI[1], M. UNTEROBERDÖRSTER[4]
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Abstract: Neurobehavioral symptoms are common and often multiple in patients with brain tumors such as glioblastoma (GBM). The causation can be multifactorial and greatly restrict patients` quality of life. Dysfunction of mTOR signaling is a key driver of GBM progression. Coincidently, mTOR signaling has been implicated in the modulation of neurobehavioral disorders. Against this background, effects of treatment with the mTOR inhibitor rapamycin on tumor growth, behavior, and brain protein expression were analyzed in a rat model of experimentally induced GBM. Male Fisher 344 rats were intracranially implanted with syngen RG2 cells and treated with rapamycin (3mg/kg) for 7 days following surgery. Subsequently, mood and anxiety-related behavior were assessed and brain and blood samples were taken for biochemical analyses. Systemic treatment with rapamycin inhibited GBM-cell proliferation in vitro and impacted tumor morphology in vivo. GBM-bearing rats displayed less stress-coping strategies assessed in the forced-swim test (FST) an effect that was prevented by treatment with rapamycin. Importantly, the rapamycin-treated GBM animals showed elevated levels of anxiety-related behavior in the elevated plus maze (EPM). Correspondingly, protein expression of glucocorticoid receptors (GR) protein expression in these animals was decreased in the hippocampus, but increased in the amygdala. These findings show for the first time that, as seen in humans, GBM disease progression in an experimental preclinical setting is associated with neurobehavioral alterations. Together, these findings provide novel insights in central effects of systemic rapamycin in subjects with a neurological disorder. The results of the present approach point towards a modulatory role of central mTOR-dependent mechanisms on RG2-induced GBM disease progression and behavior.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.05/ZZ25

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CAPES scholarship

Title: Antidepressant effect of pramipexole in a dexamethasone induced depressive-like behavior model

Authors: *L. C. SOUZA, M. M. MUNOZ, J. M. TURNES, E. L. MOURA, R. ANDREATINI, M. A. B. F. VITAL
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Abstract: Major depressive disorder is a common psychiatric disease characterized by diverse debilitating symptoms that include hopelessness and anhedonia. Systemic exposure to glucocorticoids like dexamethasone (DEX) has been shown to induce some of the behavioral features of depression in humans and thus has been used as an animal model of the disease. Pramipexole (PPX) is a non-ergot dopaminergic agonist with higher affinity for the D2/D3 dopamine receptors and several studies both in humans and animals have demonstrated that it has a antidepressive potential. The present study investigated the acute effects of pramipexole in the depressive-like behavior induced by prolonged exposure to dexamethasone. Wistar rats were first submitted to a dose-response curve (experiment I) to establish the PPX dose that would be used in experiment II. The modified forced swimming test (FST) were used for testing 3 different doses of PPX (1, 2 and 3mg/kg; i.p.). The rats were also submitted to the open field test (OFT) for evaluation of the locomotor activity. All three doses of PPX reduced the immobility time in the FST in comparison with the control group, however only the 1mg/kg dose did not reduce locomotor activity. Thus, the 1 mg/kg dose was chosen. After the dose definition, we started the prolonged dexamethasone treatment for the evaluation of the possible antidepressant-like effect of acute PPX (experiment II). The rats were treated for 21 days with dexamethasone (1mg/kg; i.p.) or its vehicle, weighted every two days, and the preference for sucrose and locomotor activity were evaluated weekly along the 21 days of treatment. The FST test was run on day 22, after the acute treatment with pramipexole (1mg/kg) 23, 5 and 1h before the test. The DEX group demonstrated a significant weight loss (anorexic effect) along the experiment. Also, the DEX treatment reduced the sucrose solution preference on day 21 and the locomotor frequency since day 7 until the end of the experiment. In the FST, the dexamethasone-treated group displayed a higher immobility time when compared to the control group, demonstrating a depressive-like behavior. The PPX acute treatment was capable of reducing the time of immobility in the DEX+PPX group in comparison with the control group, indicating an

antidepressant-like effect, without any effect in the locomotor activity. The present study demonstrated that the prolonged dexamethasone administration was able to induce a depressive-like behavior, and in agreement with our hypothesis, the acute treatment with pramipexole showed an antidepressant-like effect, reinforcing its potential as an antidepressant.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.06/ZZ26

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: FAPESP- 2017/06100-8
CNPq

Title: Purinergic receptors gene expression in the brain of male adolescent mice submitted to chronic social defeat stress

Authors: *S. CHIAVEGATTO[1], H. ULRICH[2], J. C. CORRÊA-VELLOSO[2]
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Abstract: Stressful early life experiences can induce several behavioral dysfunctions associated with mental illness, which may extend well into adulthood. Prolonged stress is one of the main factors involved in the etiology of depression. Accordingly, exposure to psychosocial stress during adolescence is implicated in the development of depression. The underlying mechanisms are poorly understood. Purinergic signaling and the activity of specific purinergic receptors have been shown to play a role in several psychiatric disorders, like depression. In this study, we used social defeat (SD) stress, a valuable animal model for depression to study expression patterns of P2X and P2Y purinergic receptors in the prefrontal cortex (PFC) and hippocampus (HC) of male adolescent mice. C57BL/6 (30 day-old) were subjected to daily bouts of SD with an aggressive adult male CD-1 mouse for 10 days. Twenty-four hours after the last defeat, mice were evaluated in the social approach-avoidance and sucrose preference (SP) tests. Approximately 50% of adolescents were susceptible, displaying social avoidance ($p<0.0001$) and reduced SP (anhedonia) ($p<0.001$). The remaining defeated mice were similar to controls ($p>0.05$) and were classified as resilient. Twenty-four hours after the last behavioral test, animals were sacrificed and brain areas of interest were collected. Reverse transcription followed by qPCR was conducted to evaluate the expression levels of purinergic receptors. In PFC, resilient and susceptible groups showed different patterns of purinergic receptors expression. Resilient mice

showed a decreasing trend of P2X7 receptor expression (p=0.06) whereas susceptible group displayed an increased P2Y1 receptor expression (p<0.01). On the other hand, in HC an overall increase of P2X4 receptor expression (p<0.05) and a decrease in P2X5 receptor expression (p<0.05) was observed for both defeated groups. This is the first description of purinergic receptor expression patterns in the social defeat model, as well as, during adolescence. Our results suggest a participation of specific purinergic receptors in depressive-like behavior of male adolescent mice submitted to social defeat. Additionally, purinergic signaling seems to be relevant on the molecular mechanisms involved in the resilience process.

Disclosures: S. Chiavegatto: None. **H. Ulrich:** None. **J.C. Corrêa-Velloso:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.07/AAA1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: GMU URSP OSCAR GRANT- Fall
GMU URSP OSCAR GRANT-Summer

Title: Behavioral and biochemical analyses of C57BL/6J mice with available voluntary exercise: Considerations for enrichment in laboratory rodents

Authors: *M. A. MARTINEZ, JR[1], J. M. FLINN[2], C. L. C. NEELY[2]
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Abstract: Behavioral and biochemical analyses of C57BL/6J mice with available voluntary exercise: Considerations for enrichment in laboratory rodents
Strong evidence has demonstrated the beneficial effects of exercise on both physical and mental health; indeed, not only is physical activity linked to better physical outcomes (i.e., weight reduction, cardiovascular health) but also to improved quality of life and longevity (CDC, 2017; Penedo & Dahn, 2005). In rodent studies, most research focuses on the beneficial effects of exercise and the improvement in learning and memory as assessed by the Morris Water Maze. We sought to explore the effects of availability of voluntary exercise on rodent wellbeing and affective measures not as commonly studied in this domain of research. Forty-four 3-week old C57BL/6J male (24) and female (20) mice were group-housed in homecages containing a functional running wheel (BioServ) or a non-functional, “locked” running wheel for approximately 30 days. Mice were run through the open field test (OFT), elevated zero maze (EZM), nesting, burrowing, and the forced swim test (FST). Mice with running wheels constructed better nests compared to mice with locked running wheels ($F[1, 40] = 4.28$, $p <$ 0.05), with female mice with locked wheels building the lowest-quality nests compared to the

other groups. Mice with running wheels also burrowed more rocks over a 12 hour period compared to their locked-wheel counterparts, $F(1, 40) = 3.86$, $p = 0.06$. These data suggest that enrichment in the form of running wheels improved general wellbeing. We did not see differences in anxiety and depression as measured by the OFT, EZM, or FST. This led to a focus on biochemical signatures within the brain related to social behavior and other measures indicative of general wellbeing. Western blotting and immunohistochemistry will examine oxytocin and vasopressin receptor expression in brains obtained from these mice. Findings from this study will elucidate the importance, or perhaps the need for, enrichment and how it may promote animal health and prosocial behavior in laboratory rodents.

Disclosures: M.A. Martinez: None. **J.M. Flinn:** None. **C.L.C. Neely:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

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Program #/Poster #: 322.08/AAA2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NRF-2016M3C7A1913845

Title: Elevation of O-GlcNAcylation induces antidepressant-like phenotype and synaptic deficit

Authors: *Y. CHO[1,2], H. HWANG[1], C. CHUNG[3], H. RHIM[1,2]
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Abstract: Depression is a devastating mental disorder affected by change of brain metabolism. Although several studies have reported the correlation between depression and dysregulated glucose metabolism, the molecular mechanism in the pathophysiology of depression is still unclear. A small percent of glucose is converted to uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) via the hexosamine biosynthetic pathway, which serves as a donor molecule for the transfer of β-N-acetyl-D glucosamine (GlcNAc) to protein. O-GlcNAcylation is a dynamic, reversible post-translational modification by attaching of GlcNAc to serine and threonine residues. O-GlcNAcylation of protein is catalyzed by O-GlcNAcase (OGA) and O-GlcNAc transferase (OGT) that is implicated in brain function including cell signaling, synaptic plasticity. In this study, we tested how increased levels of O-GlcNAcylation by Oga heterozygosity affect animal behavior and synaptic function. Interestingly, *Oga heterozygous* (*Oga* $^{+/-}$) mice showed decreased immobility in the forced swim test, suggesting that *Oga* $^{+/-}$ mice exhibit an antidepressant-like phenotype. Synaptic function in the medial prefrontal cortex (mPFC) is

known to be associated with the pathogenesis of depression, but molecular mechanisms are poorly understood. We recorded spontaneous excitatory postsynaptic current and spontaneous inhibitory postsynaptic current (sEPSC and sIPSC) in the layer II/III prelimbic cortex (PrL) of *Oga* $^{+/-}$ mice and found that *Oga* heterozygosity led to a significant decrease in sIPSC frequency, without affecting in sEPSC in layer II/III PrL.Therefore, our studies indicate that alternation of O-GlcNAcylation could be associated with an antidepressant-like phenotype and that impaired synaptic function in layer II/III PrL may underlie the phenotype. Also, importantly, OGT and OGA may serve as a novel target for the antidepressant.

Disclosures: Y. Cho: None. **H. Hwang:** None. **C. Chung:** None. **H. Rhim:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

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Program #/Poster #: 322.09/AAA3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Korea Food Research Institute E0164501-03/E0133116-05

Title: Chlorogenic acid from hawthorn berry (crataegus pinnatifida fruit) prevents stress hormone-induced depressive behavior, through monoamine oxidase B-reactive oxygen species signaling in hippocampal astrocytes of mice

Authors: *M. UM[1], J. LEE[2]
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Abstract: Oxidative stress has been implicated in mental disorders, including depression. Chlorogenic acid (CGA), a phenolic compound abundant in herbs and fruits, has been reported to have antioxidant and free-radical scavenging properties. In this study, we investigated the antidepressant-like effects and active mechanisms of CGA from the extract of Crataegus pinnatifida (CP) fruit. Depression-like phenotypes were induced in mice by daily injection of stress hormone for 1-2 weeks. The brains of these animals exhibited reduced brain-derived neurotrophic factor expression and increased astrocytic hypertrophy, which are typical markers of depression in animal models. Stress hormone injection 1) upregulated monoamine oxidase B (MAOB) expression and 2) reduced spine numbers along neuronal dendrites, which indicates synaptic depression. The oral administration of CGA (30 mg/kg) or CP (300 mg/kg) prevented MAOB activation following reactive oxygen species (ROS) production and had an ameliorative effect on depressive behavioral tests (e.g., tail suspension and forced swim tests). In vitro assays performed on cultured C8-D1A cells revealed that CGA and CP inhibited MAOB activity and ROS production.

Disclosures: M. Um: None. **J. Lee:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.10/AAA4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Changes in affective behaviors associated with a lack of creatine

Authors: *Z. I. ABDULLA[1], J. L. PENNINGTON[1], A. GUTIERREZ[2], M. R. SKELTON[1]
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Abstract: It is estimated that approximately 20% of adults in the U.S. will experience an affective disorder during their life. While it is well established that serotonin (5-HT) is a crucial factor in mood, it is important to note that impaired cellular bioenergetics are also implicated. The role of bioenergetics in affective disorders has gained substantial interest, with most of the work focused on energy production in neurons. Creatine (Cr), through the Creatine/Phospho-Cr shuttle, maintains high ATP concentrations in the neuron. This system may be implicated in the bioenergetic deficits seen in affective disorders, as reduced Cr and Phospho-Cr concentrations are found in the brains of those with major depressive and bipolar disorders. As an adjunct, clinical trials have shown that Cr supplementation can improve mood in treatment resistant depression and can improve mood in patients with neurological disorders. In rodents, Cr reduces forced swim and tail-suspension immobility times. We have shown that mice lacking Cr due to mutations in the Cr transporter (Crt) gene (*Slc6a8*; *Slc6a8*$^{-/y}$ mice) have increased levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in the striatum and hippocampus, suggesting that the lack of Cr disrupts 5-HT function. Given 5-HT's and Cr's role in mood, we have hypothesized that mice lacking Cr will develop an altered affective phenotype. To this end, we are testing *Slc6a8*$^{-/y}$ on behaviors assessing anxiety and depression. *Slc6a8*$^{-/y}$ mice display an anxiety-resistant phenotype, as suggested by results in the elevated zero maze, while the tail-suspension test indicated a potentially depressive phenotype. Interestingly, *Slc6a8*$^{-/y}$ produced faster escape latencies in learned helplessness results, potentially indicating an increased resilience to behavioral despair. Conversely, this data could be interpreted to indicate deficient fear learning in mice lacking Cr. Additionally, Crt deficient mice have an increased response to para-chloroamphetamine, a serotonergically mediated stimulant, suggesting a hypersensitivity of the 5-HT system. Given the increase in 5-HIAA it is interesting to note that western blots revealed no differences in tryptophan hydroxylase-2 or monoamine oxidase content in the hippocampus or striatum. Our results indicate that Cr plays a complex role in affective disorders, warranting

further investigation. Future studies will assess these behaviors in mice specifically lacking serotonergic Cr.

Disclosures: Z.I. Abdulla: None. **J.L. Pennington:** None. **A. Gutierrez:** None. **M.R. Skelton:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.11/AAA5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CIBM
Leenaards Foundation
Louis-Jeantet Foundation

Title: Deletion of CRTC1 is associated with strong neuroenergetic dysfunctions in a mouse model of mood disorders

Authors: *A. CHERIX[1], G. DONATI[1], C. POITRY-YAMATE[1], J.-R. CARDINAUX[2], R. GRUETTER[1,3,4]
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Abstract: CRTC1 (CREB-regulated transcription coactivator 1) is a coactivator of the transcription factor CREB, and is predominantly expressed in the brain. CRTC1 plays an important role in brain plasticity, and its dysfunction has been implicated in many neurological disorders, such as neurodegenerative and mood disorders. Mice lacking the *Crtc1* gene, show a depressive-like phenotype and have been proposed as a model for preclinical mood disorder studies. Using *in vivo* metabolic imaging tools (^{1}H-MRS, ^{13}C-MRS and PET), we have shown that these animals have a strong neuroenergetic alteration of the dorsal hippocampus. *Crtc1* KO animals show a reduced glucose entry in the brain as well as lower CMRglc (cerebral metabolic rate of glucose). The resulting drop in pyruvate production is compensated by a higher brain lactate entry allowing a normal mitochondrial energy production. Mitochondrial gene expression profile and ^{13}C-MRS-measured TCA cycle were comparable in both groups as well. ^{1}H and ^{31}P-NMR analysis of dorsal hippocampus metabolic extracts revealed no change in ATP or NADH/NAD^{+} suggesting normal energy homeostasis. A significant drop of phosphocreatine observed *in vivo* and *in vitro* together with higher creatine kinase expression (mtCK and CKB) suggest however that the reduced glycolytic ATP puts the mitochondria under allostatic load.

The altered metabolic profile linked to this mechanism correlated with the depressive-like behavior and followed the behavior change upon social isolation of mice. Together these results suggest that the depressive-like behavior of *Crtc1* KO mice is related to an altered neuroenergetic production efficiency putting the hippocampus under allostatic load.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.12/AAA6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Chronic social defeat stress induces social avoidance and changes the plasma cytokines levels in mice

Authors: *Y. NAKATAKE[1,2], M. YAMADA[2], H. FURUIE[2], H. KUNIISHI[2], M. UKEZONO[3], K. YOSHIZAWA[1], M. YAMADA[2]
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Abstract: Objectives
Chronic social defeat stress (CSDS) models in rodents are often used for researches on stress-related psychiatric disorders. CSDS includes emotional and physical aspects of stress and it is difficult to distinguish these two components. However, in many cases, patients are affected solely by emotional rather than physical distress. Recently, we have established a new stress model focusing on the emotional stress using witnessing the defeat of a conspecific. In this study, we examined the effect of emotional stress on the behavior and the plasma cytokine levels in mice.
Methods
We modified the social defeat witness model reported by the other group (Warren et al., 2013). Male C57BL/6J mice were placed into the home cages of male aggressive ICR mice and exposed to attack of ICR mice (PS mice), while the other cohort of mice could observed it (ES mice). To determine the effect of physical and emotional stress, mice were tested in the social interaction test, the elevated plus-maze, the forced swim test, and the sucrose preference test 24-hour and 1 month after the last stress session. We also measured plasma cytokines levels at the same time point in mice.
Results
PS mice showed decreased social interaction 24-hour after the stress and spent less time in the open arms of the elevated plus-maze 24-hour and 1 month after the stress. Similarly, ES mice

exhibited decreased social interaction 24-hour after the stress and slight decline of time spent in the open arms 1 month after the stress. PS mice, but not ES mice, showed changes in the levels of several cytokines in plasma 24-hour after the last stress session. After 1 month, both ES and PS mice showed decreased levels of plasma chemokine C-X-C ligand 16 (CXCL16), which is a small cytokine belonging to the CXC chemokine family.
Conclusions
In this study, witnessing the defeat of a conspecific induced social avoidance. It is suggested that witnessing the defeat of a conspecific is sufficient to cause stress-related behavioral changes in mice. On the other hand, this behavioral change was not associated with the changes in the level of plasma chemokine, which were found in PS mice. In conclusion, it is suggested that ES mice would be a useful animal model to study neurobiological mechanism of emotional stress and to develop new treatments for stress-related psychiatric disorders.

Disclosures: Y. Nakatake: None. **M. Yamada:** None. **H. Furuie:** None. **H. Kuniishi:** None. **M. Ukezono:** None. **K. Yoshizawa:** None. **M. Yamada:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.13/AAA7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Ankyrin-G heterozygous conditional knockout mice display increased sensitivity to social defeat stress

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Abstract: Genome wide association studies have repeatedly identified ANK3 (encode Ankyrin-G protein) as one of the major risk factors for bipolar disorder. Our previous work on forebrain specific Ankyrin-G homozygous knockout mice found behavioral features reminiscent of human mania, such as locomotor hyperactivity, decreased anxiety and decreased depression-like behavior. Lithium and Valproic acid ameliorated behavioral changes. Patients with Bipolar disorder experience both mania and depression. One trigger of the transition to depression is stress. We have now characterized behavioral phenotype of Ankyrin-G heterozygous knockout mice (Ank-G Het cKO). In behavioral tests, there were only subtle differences from control animals. The behavioral tests include open field (locomotor activity test), elevated plus maze and light/dark box test (test for anxiety) as well as forced swim test (for depression-like behavior). Upon 14 days of chronic social defeat stress, both control and Ank Het cKO mice displayed depression-like behavior: reduced locomotor activity in open field test, lower percent time in

open arm of the in elevated plus maze test, and increased immobile time in forced swim test. Treating both stressed control and stressed Ank-G Het cKO mice with a low dose of fluoxetine rescued the depression-like behavior. When the mice were exposed to only 4 days of social defeat stress, control animals show no deficits, while Ank-G Het cKO mice displayed lower percent time in open arm of the elevated plus maze test, and increased immobile time in forced swim test. These results indicate that Ank-G cKO mice are more vulnerable to sub-threshold stress. Future study will be to study the mechanism of stress vulnerability and effect of anti-depressant. These results indicate Ank-G Het cKO mice could be a valuable model to study mechanisms of depression-like behavior, and to test experimental therapeutics.

Disclosures: S. Zhu: None. **C.A. Zachary:** None. **S. Khambadkone:** None. **J. Xiong:** None. **C.A. Ross:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.14/AAA8

Topic: H.01. Animal Cognition and Behavior

Title: Behavioral phenotyping of a Wolfram syndrome transgenic mouse model showed cognitive alteration and anxiety disorder

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Abstract: Wolfram syndrome (WS) is a rare multisystem neurodegenerative disorder also known as DIDMOAD (diabetes insipidus, insulin-deficient diabetes mellitus, optic atrophy and deafness). WS is an autosomal recessive disease causing degeneration of β cells in the pancreas, ganglion cells in the retina and hair cells in the inner ear. The syndrome is due to mutations in *WFS1*, coding Wolframin, a mitochondria-associated ER membranes (MAM) protein involved in regulation of ER Ca^{2+} homeostasis. This pathology constitutes a genetic model of MAM dysfunction leading to neurodegeneration. MAM are functionalized domains of interaction between organelles, driving local Ca^{2+} transfer. MAM dysfunction contributes to neurodegeneration in numerous pathologies including Alzheimer, amyotrophic lateral sclerosis or Huntington. We characterized the behavioral phenotype of WFS1 KO mice in terms of general activity, learning and memory and anxiety response. Female and male 3-month old wild-type and WFS1 KO mice were compared, in the open-field, spontaneous alternation, passive avoidance, object recognition, water-maze, black-and-white box and elevated plus-maze tests. Results show an hypolocomotor response and short-term memory deficits for both male and female WFS1 KO mice and a deficit in recognition memory only in KO males. Both gender showed increased anxiety parameters but with significant differences measured mainly for WFS1

KO females. These data show that young WFSI KO mice present marked deficits in cognitive abilities and anxiety response in relation with the WS symptomatology. Therefore this model can be useful in the development of new therapeutics approaches targeting neurodegenerative processes due to MAM dysfunction.

Disclosures: B. Delprat: None. **L. Crouzier:** None. **C. Delettre:** None. **T. Maurice:** None.

Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.15/AAA9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH
HDRF

Title: Sex-specific role for long non-coding RNAs in stress susceptibility and resilience

Authors: *O. ISSLER[1], Y. Y. VAN DER ZEE[1], I. PURUSHOTHAMAN[1], Y.-H. E. LOH[1], A. RAMAKRISHNAN[1], W. JUNSHI[2], D. M. WALKER[1], Z. S. LORSCH[1], P. J. HAMILTON[1], C. C. PEÑA[1], B. J. HARTLEY[1], E. FLAHERTY[1], B. T. ANGÉLICA[1], E. M. PARISE[1], H. KRONMAN[1], A. N. START[1], E. S. CALIPARI[1], B. LABONTE[1], K. BRENNAND[1], Y. DONG[2], E. J. NESTLER[1]
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Abstract: Depression is a common, chronic and debilitating disorder. Women are twice as likely to suffer from depression as men, yet the molecular mechanisms contributing to this sex difference remain poorly understood. Long non-coding RNAs (lncRNAs) are a recently discovered class of regulatory transcripts which represent a substantial portion of the human genome. To explore the role of lncRNAs in depression we utilized a comprehensive genome-wide profile of RNAs in six brain regions from both male and female post-mortem depressed and control human subjects. Overall, lncRNAs represent about one-third of the differentially expressed genes in depressed subjects compared to controls, and displayed complex region- and sex-specific patterns of regulation. Next, we carried out bioinformatic genome-wide correlation analysis between lncRNAs and protein-coding genes in our dataset. Using this approach, we identified stronger correlations between lncRNAs and protein-coding genes in females than in males, and specific lncRNAs with potential sex-specific roles in depression. To explore the causal role for two of the identified lncRNAs in depression, each lncRNA was expressed in neurons of the mouse prefrontal cortex (PFC). Such viral-mediated expression mimicked the human sex-specific phenotype: expressing a female upregulated depression-related lncRNA increased depression- and anxiety-related behaviors in female but not male mice, while

expressing a female downregulated lncRNA induced stress resilience in females only. To analyze the molecular mechanism of action of these lncRNAs, we performed RNA sequencing on PFC infected with the target lncRNAs or control viruses. We found that expression of the female specific pro-depressant lncRNA promoted transcriptional changes that resemble the depressed female transcriptome only. In parallel, expressing the female-specific pro-resilient lncRNA blunted the normal transcriptional changes in response to stress that was observed in control mice. Furthermore, electrophysiological recording from PFC pyramidal neurons expressing the pro-resilient lncRNA compared to control indicated changes in synaptic properties in female mice only. Interestingly, the female pro-susceptibility lncRNA is expressed in oligodendrocytes in addition to neurons; therefore, we are utilizing a cell-type specific viral expression system to test the role of this lncRNA in mediating sex-specific effects on mouse behavior and myelin sheaths. These studies provide a fundamentally new view of molecular adaptations in brain that contribute to depression risk and may lead to the identification of novel targets for treatment.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.16/AAA10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

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Title: Glutamate-glutamine transfer and chronic stress-induced sex differences in cocaine responses

Authors: *A. SHIMAMOTO[1], T. FARRIS[1], H. MUNJAL[1], C. MOORE[2], C. DAVIS[1], A. WILSON[1], M. EDWARDS[1], C. REYNOLDS[1], V. RAPPENEAU[1], C. K. MESHUL[3,2]

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Abstract: Major depression (MD) is one of the common co-occurring mental illnesses in patients with substance use disorders (SUD). The comorbidity of SUD and MD (SUD/MD) is sex-dependent and therefore requires sex-tailored pharmacological intervention. Our previous findings indicate that the sex difference in glutamate (Glu) and glutamine (Gln) transfer between neurons and astrocytes in the nucleus accumbens (NAc) in animals that are chronically exposed to social defeat stress (CSDS), an animal model for MD. Thus, the current study first investigated the role of membrane-expressing transporters for Glu (glutamate transporter-1; GLT-1) and Gln (sodium-coupled neutral amino acid transporter subtype 1/2; SNAT 1/2) on sex differences in CSDS animals. CSDS took place for 21 days using a resident-intruder paradigm in Long-Evans male and female rats. Ten days after the last social defeat, brains from CSDS or non-CSDS animals were collected for western blot analysis. CSDS showed long-lasting behavioral effects on both males and females, as indicated by the prolonged attenuation in intake for sweet-tasting solution, reduced weight gain, and disruption in estrous cycle. Compared to their respective non-CSDS controls, CSDS increased membrane GLT-1 in the NAc and prefrontal cortex (PFC) in females but no change was observed in males. By contrast, CSDS decreased SNAT 1/2 in the NAc in males but not in females. An electron microscopic analysis showed that CSDS males had more Gln localized in outer membrane of mitochondria in glutamatergic neurons in the NAc projecting from PFC. Second, a subset of CSDS and non-CSDS animals were subjected to cocaine repeatedly. Compared to their non-CSDS controls, CSDS females showed a significant increase in locomotor activity while CSDS males showed an attenuated activity. The increased locomotor responses corresponded with a reduction in cytosol fraction of GLT-1 and an increase in membrane SNAT 1/2 in PFC. By contrast, the attenuated locomotor responses in males corresponded with an increase in membrane GLT-1 and SNAT 1/2 and neuronal phosphate-activated glutaminase (PAG) in PFC. Collectively, CSDS impairs both accumbal and prefrontal membrane-expressing transporters that may mediate the sex difference in cocaine-induced locomotor responses.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.17/AAA11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH
HDRF

Title: Sex specific role for slit1 in regulating susceptibility to chronic stress

Authors: *Y. VAN DER ZEE[1], O. ISSLER[1], E. M. PARISE[1], A. TORRES BERRÍO[1], C. J. PEÑA[1], B. LABONTÉ[2], B. P. RUTTEN[3], E. J. NESTLER[1]
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Abstract: Major depressive disorder (MDD) is a ubiquitous and disabling disorder that is characterized by mood disturbances, anhedonia, and alterations in cognitive functions. While it has been well-established that women are twice as likely to suffer from MDD than men, the molecular mechanisms of this sexual dimorphism in depression are poorly understood. To explore this, we utilized a recently published RNA-seq expression profile from postmortem tissue from both male and female MDD subjects and healthy controls across six brain regions. We identified the human transcript Slit Guidance Ligand 1 (*SLIT1*), which encodes a secreted molecule essential for axonal navigation and molecular guidance in cellular migration, as a hub gene that drives female-specific gene networks in MDD. Furthermore, we found that *Slit1* mRNA is down-regulated in the ventromedial prefrontal cortex (vmPFC) in postmortem tissue from depressed females, but not depressed males, as compared to healthy controls. We observed a similar sex-specific down-regulation of *Slit1* in the vmPFC of mice exposed to the chronic variable stress (CVS) paradigm. In parallel, we found that early life stress exposure using a maternal separation protocol led to down-regulation of *Slit1* in the vmPFC of female mice compared to controls. To test the potential sex-specific causal role of *Slit1* in depression-related behavioral abnormalities, we used modified Herpes Simplex Viruses (HSVs) to manipulate *Slit1* expression. Our results show that knockdown of *Slit1* in vmPFC neurons, in combination with exposure to CVS, induces an increase in anxiety- and depression-like behaviors in adult female but not male mice. Conversely, HSV-mediated overexpression of *Slit1* has a behavioral sex-specific stress-protective role. Ongoing studies are examining the effects of manipulating *Slit1* expression levels in early life to determine its role in life long sensitivity to stress. Our results propose important sex-specific roles of *Slit*1 in regulating depression- and anxiety-like behaviors selectively in female mice, in both adulthood and early life. Taken together, this is the first study that investigates the role of *SLIT1* in MDD, and provides further insight in understanding novel signaling pathways and molecular factors contributing to sex differences in depression susceptibility.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.18/AAA12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01MH111604

Title: Sex differences in hippocampal physiology: Circuit-specific mechanisms underlying stress susceptibility

Authors: *E. S. WILLIAMS[1], A. L. EAGLE[2], C. MANNING[3], A. ROBISON[4]
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Abstract: Depressive syndromes are a major cause of morbidity, and often arise in response to life stress. Aside from its social and financial burden, a striking characteristic of depression is that it affects women nearly twice as often as men. The impact of depression and the disparity in numbers of affected men and women have been recognized for some time, but the molecular underpinnings of the disease remain unknown. This knowledge gap is critical, as treatments remain ineffective in many patients and no sex-specific therapies are known. Glutamatergic pyramidal neurons that project from the ventral hippocampus (vHPC) to the nucleus accumbens (NAc) are mediators of stress responses, but little is known of the regulation of this circuit at the level of cell function or gene expression. This circuit has gained recent attention in mood disorder research as it has been shown that increased activity in these neurons promotes susceptibility to chronic social defeat stress (CSDS), a validated mouse model of depression. Using whole-cell slice electrophysiology, we show that vHPC-NAc neurons from female mice have heightened excitability compared to those from male mice. Additionally, we show that vHPC-NAc neurons from orchiectomized male mice have similar activity to those from wild-type female mice, suggesting a role for androgens in the regulation of excitability in this circuit. These findings may begin to explain the apparent differences in the number of males and females diagnosed with depression, as the increased activity observed in vHPC-NAc neurons of female mice may indicate increased susceptibility of females to stress. Our group has also shown that the transcription factor ΔFosB is required for hippocampal learning, and its expression is induced in the vHPC by stress or antidepressant treatment. Because of its clear role in resilience in other brain regions, ΔFosB is an exciting prospective target for the differential regulation of vHPC-NAc neuronal activity in male and female mice at baseline as well as in response to stress. To this end, we show that general inhibition of ΔFosB function throughout the vHPC (but not dHPC) promotes susceptibility to subchronic stress, that overexpression of ΔFosB in vHPC reduces cell excitability, and that reduction of *FosB* gene expression in vHPC-NAc neurons

increases cell excitability. We thus hypothesize that stress-induced ΔFosB in vHPC-NAc neurons mediates changes in the function of these neurons and regulates gene expression to promote stress resilience in male and female mice.

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Poster

322. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 322.19/AAA13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Human experimenter modulates mouse behavioral responses to stress and to the antidepressant ketamine

Authors: *P. GEORGIOU[1], P. ZANOS[2], D. GERHARD[3], C. JENNE[1], J. N. HIGHLAND[4], D. LOESCH[1], P. YUAN[7], S. M. CLARK[5], L. H. TONELLI[8], R. MOADDEL[9], C. A. ZARATE, JR[10], R. S. DUMAN[11], T. D. GOULD[6]
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Abstract: Rodent differentiation of the sex of human experimenters may influence physiological and behavioral responses. We show that mice manifest aversion to human male odors, and attraction to human female odors, while showing increased susceptibility to stress responses when handled by male experimenters. Administration of the antidepressant drug ketamine to mice by male experimenters reversed stress-mediated behavioral responses, while such responses were absent following injection of the drug by female experimenters. Similar experimenter sex-dependent effects were identified with the ketamine metabolite (*2R,6R*)-hydroxynorketamine, but not with other mechanistically distinct antidepressants. Non-antidepressant behavioral actions of ketamine where present regardless of the sex of the experimenter. We establish that male scent is necessary to induce ketamine's antidepressant effects in our mouse models; however female scent dominantly prevents such an effect in a manner dependent upon production of stress hormones. Moreover, blocking stress responses prior to ketamine administration by male experimenters inhibited ketamine's antidepressant effects. Ketamine administration increased GluA1 AMPA receptor subunit in the ventral hippocampus when injected by male but not female experimenters. Overall, these findings demonstrate that experimenter sex influences the outcome of behavioral and pharmacological assessments,

impacting replicability, and arguing that experimenter sex should be considered as a relevant experimental variable.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.01/AAA14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH Grant 5UH2MH109334-02

Title: A novel cross-species neurophysiological assay of cognitive control: Development of a touchscreen-based rodent Flanker task

Authors: *M. A. ROBBLE, S. NICKELS, B. D. KANGAS, L. WOOLDRIDGE, E. CÁRDENAS, S. PERLO, J. BERGMAN, W. A. CARLEZON, Jr, D. A. PIZZAGALLI
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Abstract: Deficits in cognitive function, such as reward sensitivity and cognitive control, are a common feature of virtually all neuropsychiatric disorders. While perturbations in cognitive control have been studied extensively in humans, it has been challenging to examine these complex processes in laboratory animals. In turn, stagnation in the development of animal-based tasks to assess these processes has impeded the identification and development of innovative treatments for neuropsychiatric disorders. As part of a larger effort to create reliable and valid cross-species assays of cognitive function, we are developing a rodent version of the Eriksen Flanker Task to assess cognitive control. Using fading and correction procedures combined with touch-sensitive response technology, we trained Sprague Dawley and Long Evans rats to discriminate between several distinct pairs of visual stimuli including arrows (</>) and letters (H/S) used in traditional (human) versions of the Flanker Task, as well as colored stripes, colored shapes, and more detailed photographic stimuli. Discrimination was deemed successful when the criterion of 80% response accuracy per stimulus-type during the session was observed on two consecutive days. The results of these studies indicated that detailed photographic stimuli (green leaf/violet flower) would be optimal stimuli for use in the Flanker Task and that stimulus control was more likely to be achieved when testing Long-Evans rather than Sprague-Dawley rats. Following training under these final conditions, rats were surgically implanted with skull surface and depth electrodes and neurophysiological data were collected during Flanker Task testing. In parallel, EEG data were collected from human subjects using the stimuli validated in the rodent

task. All human subjects showed the expected Flanker interference effects of reduced accuracy and increased response latency on incongruent trial types. In addition, we observed robust N200 and error-related negativity (ERN) components in humans, as well as increased theta power, when comparing incongruent and congruent trial types. These results indicate that the stimuli chosen for the rodent Flanker Task elicit the expected effects in humans. Preliminary electrophysiological recordings in rodents suggest ERP and spectral findings that have qualitative similarities to those observed in humans. Once behavioral and neurophysiological correspondence between species has been established, the rodent task may provide predictive power to screen potential therapeutics for neuropsychiatric conditions.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

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Program #/Poster #: 323.02/AAA15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: University of Connecticut Tier II
The Connecticut Institute for Brain and Cognitive Sciences

Title: Pharmacological and genetic studies of effort-related decision making using mouse touchscreen procedures: Effects of dopamine antagonism and humanized catechol-o-methyltransferase variants

Authors: *J.-H. YANG[1], R. E. PRESBY[1], A. A. JARVIE[1], R. A. ROTOLO[1], R. FITCH[1], M. CORREA[2,1], J. D. SALAMONE[1]
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Abstract: Effort-based decision making tasks offer animals choices between a more preferred reinforcer that requires high effort to obtain vs. a low effort/low reward option. The neural mechanisms of effort-based choice have been widely studied in rats, and evidence indicates that a distributed forebrain circuit that includes mesolimbic dopamine (DA) and related neural systems plays a key role. DA antagonism or depletion produces a low-effort bias in rats tested on effort-based choice tasks. However, fewer studies of effort-based choice have been performed in mice, and most of these have involved T-maze choice tasks. The present studies used touchscreen operant procedures (i.e., Bussey-Saksida boxes) to assess effort-based choice in mice. The high-effort component involved rearing up to press an elevated lit panel on the touchscreen in order to receive Ensure strawberry milkshake as the reinforcer. The low effort

choice was a dish of less preferred food pellets (Bio-serv) that was freely available in the box. CD1 mice were tested in a series of experiments in which the mice pressed the panel on a fixed ratio 1 (FR1) schedule. Injections of the DA antagonist haloperidol (0.05-0.15 mg/kg IP) produced a dose-related decrease in panel pressing. Intake of the concurrently available food pellets was not reduced by haloperidol, and in fact, there was a significant quadratic trend, showing that there was a tendency for pellet intake to increase at the low/moderate doses. In contrast, reinforcer devaluation by prefeeding substantially decreased both panel pressing and pellet intake. In free-feeding choice tests, mice strongly preferred the Ensure vs. the pellets, and haloperidol had no effect on food intake or preference. Additionally, humanized catechol-O-methyl transferase (COMT) transgenic mice with two genotypes (Val, and Met variants) as well as wild-type (WT) mice from the S129 background were tested using touchscreen choice procedures. Mice were trained in a FR/choice task with FR requirements varied (FR1, 2, 4, 8, to 16) in an ascending and descending sequence. Results show an inverse relationship between the number of reinforcers delivered by panel pressing and pellet intake across the different FR levels in all three groups. There was a significant group x FR level interaction, with panel presses in the Val group being significantly lower than WT group on FR1, 2, 4, and 8, and lower than Met group on FR4. These studies show that haloperidol did not reduce panel pressing due to decreases in primary food motivation or preference, and illustrate the possible relation between COMT polymorphisms and negative symptoms such as motivational dysfunctions in human psychopathologies.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

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Program #/Poster #: 323.03/AAA16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The novel atypical dopamine uptake inhibitor S-CE-123 partially reverses the effort-related effects of the dopamine depleting agent tetrabenazine

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Abstract: Animal studies of effort-related choice behavior are being used to model effort-related motivational dysfunctions in humans. With these procedures, animals are offered a choice between high effort instrumental actions leading to highly valued reinforcers vs. low effort/low reward options. Several previous studies have shown that dopamine (DA) transport inhibitors, including GBR12909, lisdexamfetamine, methylphenidate, and PRX-14040, can reverse the effort-related effects of the vesicular monoamine transport inhibitor tetrabenazine, which blocks DA storage. Because many drugs that block DA transport (DAT) act as major stimulants that also release DA, and produce a number of undesirable side effects, there is a need to develop and characterize novel atypical DAT inhibitors with unique and selective binding profiles. Recent studies have shown that the atypical DAT inhibitor modafinil, which elevates extracellular DA but is not a major psychomotor stimulant, can also reverse the effects of tetrabenazine. Modafinil also has been reported to improve motivational function in depressed patients and non-pathological control subjects, albeit without a strong abuse liability. S-CE-123 is a recently developed analog of modafinil, (S)-5-((benzhydrylsulfinyl)methyl)thiazole, with the biochemical characteristics of an atypical DAT blocker. A recently synthesized and chromatographically separated analog of modafinil, S-CE-123 is highly selective for DAT vs. the norepinephrine and 5-HT transporters. S-CE-123 has been shown to enhance cognitive flexibility and reduce impulsivity in rats. For the present studies, S-CE-123 was assessed for its ability to reverse the effort-related motivational effects of tetrabenazine. Rats were assessed using the fixed ratio 5/chow feeding choice test. Tetrabenazine (1.0 mg/kg) shifted choice behavior, decreasing lever pressing and increasing chow intake. S-CE-123 was co-administered at doses ranging from 6.0-24.0 mg/kg, and the highest dose partially but significantly reversed the effects of tetrabenazine. In summary, S-CE-123 was able to reverse the effort-related effects of tetrabenazine, which suggests that that S-CE-123 or a similar compound could be useful as a treatment for effort-related motivational dysfunction in humans. Future studies should determine the abuse liability of S-CE-123 and other modafinil analogs.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.04/AAA17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Chronos Therapeutics

Title: The novel atypical dopamine transport inhibitors CT-005094 and CT-005404 reverse the effort-related motivational effects of the dopamine depleting agent tetrabenazine

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Abstract: Motivational symptoms such as fatigue, anergia, and amotivation are seen in depression, multiple sclerosis, Parkinson's disease, schizophrenia, chronic fatigue syndrome, and other disorders. Considerable evidence from basic research and clinical studies implicates brain dopamine (DA) in the regulation of behavioral activation and effort-related aspects of motivation. Animal studies of effort-based choice behavior are being used to provide formal models of effort-related motivational dysfunctions in humans. For assessment of effort-based choice, animals are offered the option of a high effort instrumental action leading to highly valued reinforcer (preferred, or higher magnitude) vs. a low effort/low reward choice. Drugs that block DA transport, such as GBR12909, lisdexamfetamine, methylphenidate, and PRX-14040, are able to reverse the effort-related effects of the vesicular monoamine transport inhibitor tetrabenazine, a drug that blocks DA storage and depletes DA. Many of the existing drugs that are labeled as DA transport (DAT) inhibitors are either classic DA blockers such as cocaine, or drugs that also stimulate release of DA. These drug can produce a number of undesirable side effects, including psychotic symptoms and abuse liability. Thus, there is a need to develop and characterize novel atypical DAT inhibitors that are highly selective and have unique binding profiles. The present studies focused on recently synthesized atypical DAT inhibitors, CT-005094 and CT-005404. These compounds bind to DAT with high selectivity relative to the serotonin and norepinephrine transporters, and can elevate extracellular levels of DA as measured by microdialysis without stimulating DA release. In the present studies, CT-005094 and CT-005404 were assessed for their ability to reverse the effort-related motivational effects of tetrabenazine. Rats were tested using the fixed ratio 5/chow feeding choice test. Tetrabenazine (1.0 mg/kg) shifted choice behavior, decreasing lever pressing and increasing chow intake. CT-005094 was co-administered at doses ranging from 2.0-16.0 mg/kg IP, and the 8.0 mg/kg dose partially but significantly reversed the effects of tetrabenazine. CT-005404 was orally active, and reversed the effects of tetrabenazine in the dose range of 15.0-30.0 mg/kg PO. Atypical DAT inhibitors such as CT-005094 and CT-005404 offer potential as a new avenue for drug treatment of motivational dysfunctions in humans.

Disclosures: J.D. Salamone: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Chronos Therapeutics. **R.A. Rotolo:** None. **F. Murray:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Chronos Therapeutics. **B. McNamara:** None. **R.E. Presby:** None. **J. Yang:** None. **M. Correa:** None.

Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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CREST of Japan Science and Technology Agency to A.N.

Title: Dopamine D1 receptor activation in the dentate gyrus enhances antidepressant effects of an SSRI, fluoxetine in a mouse model of depression

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Abstract: Major depression is a psychiatric disorder with high lifetime prevalence. Selective serotonin reuptake inhibitors (SSRIs) are commonly used for treatment of depression. However, current pharmacological treatment of depression is insufficient, and development of improved treatments especially for treatment-resistant depression is desired. Recently, chronic administration of SSRI is reported to increase the expression of dopamine D1 receptors in mature granule cells of the hippocampal dentate gyrus, but the mechanisms underlying involvement of D1 receptors of SSRIs to improve symptoms of depression are not fully understood. In this study, we investigated the role of D1 receptors in the dentate gyrus in antidepressant actions of SSRIs. Mice were treated with fluoxetine, an SSRI, chronically by subcutaneous implantation of matrix-driven delivery pellets (15 mg/kg/day, 14 days). The fluoxetine-induced changes in gene and protein expression were analyzed by quantitative real-time PCR and Western blot analysis, respectively. In addition, depression-like behaviors were evaluated with the novelty-suppressed feeding test (NSFT) and tail suspension test (TST) in mice subjected to chronic restraint stress. Chronic treatment with fluoxetine induced the expression of D1 receptor mRNA and protein in the dentate gyrus, but not other subtypes of dopamine receptor mRNA. Regular restraint stress (2 hr/day, 14 days) increased the feeding latency in the NSFT, and chronic treatment with fluoxetine reduced the increased feeding latency. However, in mice subjected to severe restraint stress (4 hr/day, 28 days), chronic treatment with fluoxetine failed to reduce the stress-induced increase in feeding latency in the NSFT and immobility time in the TST. Chronic co-administration of a dopamine D1 receptor agonist, R(+)-SKF81297 (1.5 mg/kg/day, i.p. for 5 days), with fluoxetine resulted in the reversal of the depression-like behaviors. These results suggest that the increase in D1 receptor signaling in the dentate gyrus is essential for the

antidepressant actions, and activation of dopamine D1 receptors in the dentate gyrus enhances therapeutic actions of SSRI under SSRI-resistant stress conditions.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: JSPS KAKEN Grant Number 25861006
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JSPS KAKEN Grant Number 17K10273

Title: Intracerebral infusion of beta-hydroxybutyrate, an endogenic NLRP3 inflammasome inhibitor, produces antidepressant like effects in a rodent model of depression

Authors: *N. KAJITANI[1], M. IWATA[1], T. YAMANASHI[1], K. TSUNETOMI[1], A. MIURA[1], T. NISHIGUCHI[1], R. S. DUMAN[2], K. KANEKO[1]
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Abstract: Although the pathology of psychiatric disorders such as depression is unclear, recent studies demonstrate a role for the involvement of intracerebral inflammation, including evidence that the inflammatory cytokine interleukin-1β (IL-1β) causes depressive behavior. Previously we reported that stress increases ATP, which activates the Nucleotide-binding protein, Leucine-rich repeat, Pyrin domain containing 3 (NLRP3) inflammasome, which in turn promotes the formation of mature IL-1β in the rat brain. Thus, we propose a hypothesis that the inhibition of the NLRP3 inflammasome will produce an antidepressant effect by preventing IL-1β production caused by stress. Recently it has been reported that beta hydroxybutyrate (BHB), a ketone body that supports mammalian cell metabolism during states of energy deficiency, such as fasting or exercise, reduces NLRP3 inflammasome-mediated production of IL-1β. We have found that peripheral BHB administration suppressed NLRP3 activation and reduced inflammatory cytokines such as IL-1β and tumor necrosis factor α, and improved anxiety and depressive behaviors in a rodent chronic unpredictable stress (CUS) model of depression. However, whether BHB acts directly on the brain or on peripheral inflammatory NLRP3 responses remains unknown. The brain imaging studies demonstrate altered morphology and blood flow of the prefrontal cortex (PFC) and hippocampus in depressed patients, rodent studies show that chronic stress increase NLRP3 inflammasome and pro-inflammatory cytokines in the these brain regions.

Here, we evaluate the influence of direct infusions of BHB into the PFC and hippocampus. The results show that intracerebral infusion of BHB into medial PFC produces antidepressant like effects in the forced swim test with no effects on locomotor activity. Similar tendencies were observed in the sucrose preference test and the elevated plus maze test. In contrast, infusions of BHB into the hippocampus had no effect on these behaviors. Together, these studies indicate that BHB is capable of producing antidepressant effects by direct actions on the central nervous system and that these effects are specific to the medial PFC. Further studies will be needed to test the contribution of peripheral blockade of NLRP3 on stress-induced antidepressant responses. Nevertheless, these findings are consistent with the hypothesis that inhibiting the NLRP3 inflammasome in brain is a novel effective approach for the treatment of depression.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: JSPS KAKEN Grant Number 25861006
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JSPS KAKEN Grant Number 17K10273

Title: Beta-hydroxybutyrate ameliorates depressive like behavior induced by social defeat stress

Authors: *K. TSUNETOMI[1], M. IWATA[1], T. YAMANASHI[1], N. KAJITANI[1], A. MIURA[1], M. NAGATA[1], R. MATSUO[1], T. NISHIGUCHI[1], R. S. DUMAN[2], K. KANEKO[1]
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Abstract: Stress is known to decrease neurogenesis and synaptogenesis inhippocampus and induces depressive-like behavior in rodent models, but the mechanisms by which stress causes these neuroplasticity deficits is still unclear. Previously, we had reported that a proinflammatory cytokine such as interleukin-1β (IL-1β) is an essential mediator of the anti-neurogenic effects of stress. Recently we have focused on the Nucleotide-binding protein, Leucine-rich repeat, Pyrin domain containing 3 (NLRP3), a cytosolic pattern recognition receptor (PRR), which is considered a key molecule for the stress inflammatory response. NLRP3 recognizes various molecules such as Damage Associated Molecular Patterns (DAMPs) and Pathogen Associated Molecular Patterns (PAMPs), and the activated NLRP3 inflammasome cleaves immature IL-1β to the active form. Thus, we hypothesized that NLRP3 is a novel target for inhibiting stress-related neuroinflammation, which promotes antidepressant actions in rodent models. To inhibit

NLRP3, we applied beta-hydroxybutyrate (BHB), which has recently been reported to reduce NLRP3 inflammasome-mediated production of IL-1β. We have demonstrated that peripheral BHB administration suppresses the activation of the NLRP3 inflammasome, and reduces inflammatory cytokines such as IL-1β and tumor necrosis factor α (TNFα), and improves anxiety and depressive behaviors in a rodent chronic unpredictable stress (CUS) model of depression. In this study, we found that peripheral BHB administration completely prevents depressive like behavior in the forced swim test (FST) induced by the social defeat model of mice. Further studies will be needed to test the contribution of the blockade of NLRP3 on stress-induced antidepressant responses. Nevertheless, these findings are consistent with the hypothesis that inhibiting the NLRP3 inflammasome is a novel effective approach for the treatment of depression.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Program #/Poster #: 323.08/AAA21

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grants to K.S. MH102445 and MH105567

Title: Age-dependency of effects of enriched environment treatment on depression-like behavior and BDNF expression in normal and promoter IV-BDNF deficient mice

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Abstract: Enriched environment treatment (EET), a potential intervention for depression, induces expression of brain-derived neurotrophic factor (BDNF), while BDNF deficiency via inactive promoter IV is implicated in the pathophysiology of depression. We previously reported that EET was more effective than antidepressant drug treatment in reversing the depression-like behavior caused by promoter IV-BDNF deficiency in young adult mice (Jha et al., Transl. Psychiatry e40, 2011; Sakata et al., Eur J. Neurosci. 37(11)1863-1874, 2013). However, its age-dependency, i.e., whether EET effects on antidepressive behavior and BDNF expression differ across life stages, remains unclear. Here, we addressed this question by determining EET effects across three life stages—early-life development (ED: 0-2 months), young adult (YA: 2-4 months), and old adult (OA: 12-14 months) in wild-type (WT) and promoter IV-BDNF-deficient

(KIV) mice. KIV mice, at all life stages, displayed reduced exploratory activity in the open field test, stress-induced despair in the tail suspension test, and anhedonia in the sucrose preference test, when compared to WT mice. Two months of EET increased exploratory activity and reduced despair-like behavior in ED and YA, but not OA mice, with the largest effect seen in ED KIV mice. EET normalized anhedonia in KIV age groups. The largest EET-induced increases in BDNF protein levels were observed in ED in the KIV hippocampus and frontal cortex. EET-induced increases in BDNF mRNA levels were similar for all ages in the hippocampus, but were observed only in ED KIV and OA WT mice in the frontal cortex. EET-induced BDNF transcription by promoters I and IV were age dependent in the WT hippocampus with a larger induction of exon IV or I during ED or OA, respectively. EET-induced BDNF transcription by most of the 9 promoters was age dependent in the frontal cortex, mostly observed in ED KIV mice. When mice were housed in standard cages for one month after EET, the EET effects persisted for anti-depressive behavior, BDNF protein expression in the hippocampus, and BDNF transcription in both hippocampus and frontal cortex, but only when EET was provided at ED and particularly in KIV mice. These results suggest that BDNF deficiency causes depression-like behavior regardless of age, but EET during ED can be a potent and lasting intervention against depression caused by BDNF deficiency. Conversely, older adults may require additional treatment.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.09/AAA22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Seizures as a side effect of deep brain stimulation of the dorsal peduncular subregion of the prefrontal cortex in a rat model of experimental depression

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Abstract: Deep brain stimulation (DBS) of the ventromedial prefrontal cortex (vmPFC) in a chronic mild stress (CUS) model in rats has shown anti-depressant effects. Mostly the infralimbic (IL) and prelimbic (PreL) subregions of the vmPFC have been investigated. The dorsal peduncular (DP) subregion however, has not yet been widely researched. This DP subregion, like the IL and PreL subregions, has direct connections to the dorsal raphe nucleus

(DRN) which indicate a potential role of this DP subregion in mood. Further investigation into this region might therefor be of great value. In our experiments we have stimulated the DP subregion to see if DBS could alleviate 'depressive-like' behavior in an CUS model in rats. To our surprise, 40% (n = 7/18) of our stimulated animals showed severe involuntary movements when applying DBS repetitively. These involuntary movements were not seen in our control groups indicating a direct stimulation effect. To classify these involuntary movements, we acquired EEG and video recordings upon stimulation, showing Racine stage IV-V seizures with typical spike and wave discharges between the implanted electrodes. Both biphasic and monophasic bipolar DBS showed these findings. A trend towards neophobia when conducting the home cage emergence test and a trend towards less sucrose intake when conducting the sucrose intake test was seen in the animals developing seizures later on, considering our CUS sham (n = 4) and non-CUS control group (n = 4) were very small. Due to the severity of the induced seizures upon further stimulation we were unable to continue behavioral testing. Our findings indicate that the DP subregion of the vmPFC in the rat is not a safe brain structure to conduct DBS experiments. A relatively novel finding is that this region is involved in seizure induction and may be an experimental model of frontal epilepsy.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

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Program #/Poster #: 323.10/AAA23

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Evaluation of antidepressant-like activity of kiwifruit (actinidia deliciosa) extract in mice

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Abstract: Antidepressant pharmacotherapies have a slow onset of clinical efficacy which is critical for therapeutic outcome and patient compliance. In recent years, an increasing number of studies suggest that phytochemical compounds activity on mood might be a clinically relevant co-adjuvant to current medications.
Many studies suggest a positive association between fruits and vegetables-rich diet and prevention of depression, therefore the consumption of a whole phytocomplex may increase serotonin bioavailability both at CNS and systemic levels. The aim of this study is to evaluate the activity of kiwifruit (*Actinidia deliciosa*) extracts on mood in murine model of depressive behavior. Indeed, kiwifruit is rich in polyphenols (e.g. ferulic acid, kaempferol, catechin, etc.)

with a known inhibitory effect on both monoamine oxidases A and B.
Naïve male C57BL/6J mice were administered with three increasing concentrations of kiwifruit extracts under chronic or acute regimes. Immobility time was then assessed in forced swimming test (FST) and tail suspension test (TST); additionally, the efficacy of kiwifruit compared to vehicles and selective serotonin reuptake inhibitor fluoxetine (20 mg/kg, i.p.) were investigated. The highest kiwifruit concentration produced a reduction of 40% and 45% in immobility time in FST and TST respectively, without causing hyperlocomotion in the open-field test.
Taken together, these data suggest that kiwifruit may have a mood-improving effect through modulation of the serotonergic system. To support these findings, pharmacokinetic profiles and monoamines detection through chromatographic and mass-spectrometric analyses are in progress on both whole brain homogenate and serum samples.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Program #/Poster #: 323.11/AAA24

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NSERC DG to LEK
NSERC DG to HJC

Title: Peripheral reelin administration rescues neurochemical alterations and depression-like behavior in a preclinical model of depression

Authors: J. ALLEN[1], R. ROMAY-TALLON[1], K. BRYMER[2], M. MITCHELL[2], L. E. KALYNCHUK[1], *H. J. CARUNCHO[1]
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Abstract: Chronic stress is a significant risk factor for the onset of depression. This can be studied preclinically using a corticosterone (CORT)-administration paradigm, in which rodents receive daily injections of CORT for several week followed by behavioral testing and post-mortem analyses of biological tissues. We have shown that 21 days of CORT treatment produces a behavioral phenotype of depression that is associated with deficient hippocampal neurogenesis, decreased hippocampal reelin levels, and larger serotonin transporter (SERT) protein clusters in peripheral lymphocytes, all of which parallel changes seen in these parameters in human depression patients. Our most recent data revealed that intrahippocampal infusions of reelin can normalize the behavioral and neurobiological alterations produced by CORT. Here we examined

whether peripheral intravenous administration of reelin may have a similar antidepressant-like effect.
Rats received 21 days of daily CORT or vehicle injections along with either 3µg or 5µg of reelin every 5 or 10 days. Thereafter, they were subjected to the forced swim test to measure depression-like behavior and then sacrificed to permit immunohistochemical analyses of the number of reelin+ cells in the subgranular zone (SGZ) and paraventricular nucleus (PVN) as well as the number and complexity of immature newborn neurons in the granule cell layer. We also analysed the pattern of SERT protein clustering in peripheral lymphocytes. Our results revealed that reelin reversed the CORT-induced increases in FST-immobility, the downregulation of reelin in the SGZ, and the increase in size of SERT clusters. However, only 3µg every 10 days reversed the decreases in reelin expression in the PVN, and all doses failed to reverse the CORT-induced decrease in the number and complexity of dendritic processes of developing newborn neurons.
These novel findings show for the first time that peripheral reelin administration can normalize CORT-induced increases in depression-like behavior and the size of SERT protein clusters in peripheral lymphocytes and the decreases in hippocampal plasticity. Although additional mechanistic and pharmacokinetic studies are necessary, our data also open the possibility of developing reelin peptides with antidepressant activity.

Disclosures: J. Allen: None. **R. Romay-Tallon:** None. **K. Brymer:** None. **M. Mitchell:** None. **L.E. Kalynchuk:** None. **H.J. Caruncho:** None.

Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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RGC is a pre-doctoral fellow (Consejería de Innovación, Investigación y Turismo del Gobierno de las Islas Baleares y del Fondo Social Europeo)

Title: Methamphetamine administration impedes the expected antidepressant-like effect induced by repeated electroconvulsive shock in adult rats

Authors: *R. GARCIA-CABRERIZO, C. BIS-HUMBERT, J. GARCIA-FUSTER
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Abstract: Recent data from our laboratory demonstrated that: (1) binge methamphetamine administration induced hippocampal cell damage (i.e., impaired cell genesis and BDNF regulation) in rats when administered specifically during a window of late adolescence (postnatal day, PND 54-57) and evaluated 24 h later (PND 58), (2) these negative effects persisted in time as measured by a decrease rate in cell survival (41-43 days old cells) observed at PND 91 following prolonged withdrawal, and (3) binge methamphetamine administration enhanced negative affect (i.e., behavioral despair and anhedonia) following prolonged withdrawal. This subsequent study evaluated whether rats with a history of methamphetamine administration in late adolescence (PND 54-57) would benefit from an antidepressant treatment, such as repeated electroconvulsive shock (ECS), in adulthood while being re-exposed to the drug. Rats were treated with BrdU (2 x 50 mg/kg/day, 3 days, i.p., PND 48-50) followed by administration of binge methamphetamine (M group: 5 mg/kg, n=20) or saline (C group: 0.9% NaCl, 1 ml/kg, n=20) (3 pulses/day, i.p., PND 54-57). Rats were exposed to the forced-swim test (FST:15 min pre-test, PND 58, 5 min test, PND 59) to evaluate possible immediate negative effects of drug treatment. Following prolonged withdrawal, rats were re-exposed to daily methamphetamine (5 mg/kg) or saline – accordingly to what they received in late adolescence – and 3 h after injection, treated with a single ECS session (95 mA, 0.6 sec, 100 Hz, via earclip electrodes: C-ECS, n=10 vs. M-ECS, n=10) or connected to earclips eletrodes with no electrical current (C-SHAM, n=10 vs. M-SHAM, n=10) for 5 days (PND 91-95). Rats were then re-exposed to the FST on PND 96 and sacrificed on PND 97. The main result demonstrated that methamphetamine administration (PND 54-57) did not induce changes in behavioral despair (i.e., immobility time in the FST) in adolescence (PND 59) or later on during adulthood following re-exposure to the drug (PND 96). Interestingly, ECS induced the expected antidepressant-like response in C-treated rats (i.e., decreased time spent immobile: -66±17 sec, C-ECS vs. C-SHAM, $p<0.01$) but had no benefitial effect on rats with a prior history of methamphetamine use (+3±19 sec, M-ECS vs. M-SHAM, $p>0.05$). Therefore, these results indicate that methamphetamine exposure during late adolescence and its later re-exposure in adulthood prevents the expected antidepressant-like effects induced by ECS. Current studies are evaluating possible neural correlates (i.e., hippocampal neurogenesis on PND 96) that could help explain this maladaptive behavioral response.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH GM109098

NIH GM104942

Title: B cell deficiency is associated with depressive-like behavior in mice

Authors: *E. B. ENGLER-CHIURAZZI, J. M. POVROZNIK, X. REN, D. DOLL, H. HU, J. W. SIMPKINS
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Abstract: Major depressive disorder (MDD) is a debilitating mood disorder afflicting 20% of the population. That available pharmacotherapies exert delayed and often insufficient symptom alleviation suggests that the pathology of MDD is more complex than previously appreciated. Neurotransmitters thought to underlie MDD-associated brain pathology may not be the sole contributors to its presentation; as such, monoamine-based therapeutic interventions targeting these systems will remain inadequate at relieving symptoms or treating the underlying dysfunction, thus novel treatments that modulate innovative targets are critically needed. As mounting evidence supports the complex interaction of the brain, endocrine, and immune system (IS), a plethora of findings implicate a pro-inflammatory state and T cell over-activation in MDD. Yet the impact of the B cell on affect is uncertain. Without a clear understanding of the role of the B cell in mood, not only is the IS theory of MDD incomplete, but also potential therapeutic targets are likely being overlooked. Recently, B cell subtype-specific changes were noted in circulation of MDD patients such that while levels of total B cells were not significantly altered, there were reduced levels of IS-regulating B cells. Here, we evaluated the impact of B cell deficiency on depressive-like behavior using male B6.129S2-Ighm^{tm1Cgn}/J homozygous mice (aka muMT$^{-/-}$) that lack mature B cells and have no membrane-bound IgM expression. Depressive-like behavior was assayed using the forced swim and sucrose preference tests. As compared to wild type mice, muMT$^{-/-}$ mice displayed an age-dependent depressive-like phenotype that could not be alleviated with typical antidepressant therapy (20mg/kg desipramine given i.p. 30 min prior to test) but was reversed via immune modulation (adoptive transfer of splenic CD19^{+} B cells). This effect was not explained by locomotor or motivational group differences. These data implicate humoral IS deficiency in MDD, an observation that could contribute to the body of knowledge regarding the IS role in brain disease, inform clinical practice with a paradigm-shifting therapeutic approach, and ease the global mental health burden of MDD.
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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

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Title: TMS to LPFC initiates electrophysiological changes in sgACC

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Abstract: Transcranial magnetic stimulation (TMS) is a therapeutic modality for the treatment of depression and other mood disorders. At present, no a priori detailed mechanism of therapeutic TMS has been validated; such a model would allow researchers and clinicians to predict which patients are likely to respond well, and what stimulation parameters will be most effective. However, previous research has identified some of these factors on the basis of statistical outcomes, and produced a post hoc working model according to which repetitive TMS to lateral prefrontal cortex (LPFC) acts indirectly upon subgenual anterior cingulate cortex (sgACC) via circuit-level effects, working somewhat analogously to deep brain stimulation. This provides a framework for guiding further research into the mechanisms underlying TMS.
To address the need for a mechanistic model, we performed TMS on nonhuman primates in conjunction with awake intracranial electrophysiology. We targeted LPFC (approximately area 9/46) for stimulation, using the theta-burst stimulation (TBS) protocol. To test our working model, we recorded the local field potential (LFP) activity in sgACC (area 24a) before and after LPFC-TBS, to ascertain whether and how sgACC function is affected by LPFC-TBS.
Spectral analysis of sgACC-LFP following LPFC-TBS revealed a transient decrease in power in the >350 Hz band lasting less than one hour, probably reflecting an overall decrease in multiunit spiking activity. By contrast, a narrow band centered at ~80 Hz ("high gamma" frequencies) was elevated, and continued to increase in magnitude over the course of 1 hour after stimulation. Additionally, we observed more modest narrow-band effects in the traditional EEG range. Infraslow (<1 Hz) power also showed a strong decrease in power following LPFC-TBS, recovering nearly to baseline by 1 hour after stimulation.

LPFC-TBS induces dramatic changes in sgACC-LFP, and the dynamics of these effects continue to unfold on the timescale of minutes to hours following stimulation. This effect is consistent with our working model of therapeutic TMS, and further work will explore whether sgACC does indeed play a causal role in alleviating symptoms.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Program #/Poster #: 323.15/BBB2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The effects of the antidepressant drugs on matrix metalleoprteinases release and the proteolysis of the perineuronal nets

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Abstract: Overall, the underlying pathology of depression is extremely heterogeneous and complex, which makes it difficult to find a treatment that is effective for all depressed individuals. Though a full understanding of the mechanisms that underlie antidepressant efficacy in responsive individuals is not yet fully appreciated, responsiveness correlates with increased volume of select brain regions, particularly the hippocampus. Antidepressant drugs that target monoamines induce structural remodeling in the adult brain, including increasing the volume of selected brain regions, and enhancing excitatory neuronal transmission. Emerging evidence suggests that neuroplasticity and neuronal transmission can be enhanced through modulation of the perineuronal nets (PNN), a lattice like structure that surrounds the parvalbumin (PV) positive interneurons, and by enhancing dendritic arborization and spine formation. Preclinical studies suggest that monoamine modulating antidepressants can reduce the integrity of PNN to potentially facilitate neuroplasticity. However, the specific mechanism of the effects of these medications on the brain plasticity has yet to be determined. Matrix metalloproteinase (MMPs) including MMP-2 and MMP-9, are expressed in neurons, glia and endothelial cells and are involved in the remodeling of the extracellular matrix, PNNs and dendritic plasticity. MMP-9 has been implicated in synaptic plasticity, learning and memory and tissue remodeling in response to enhanced neuronal activity. Herein we show that the monoamine and beta-adrenergic

receptor agonist can significantly increase the release of MMP-3 and -9 from cultured murine hippocampal neurons and astrocytes. We also, demonstrate that mice treated with the antidepressant venlafaxine have increased levels of Pro MMP9 and PSD-95. Golgi staining of pyramidal neurons in cortex showed an increase in the dendritic number of branches at the level of the second order in the Cortex of wild type mice treated with venlafaxine but not in MMP9-KO mice. Evaluation of PNN in venlafaxine treated mice showed reduced PNN intensity and an increase in cleavage fragment of aggrecan, one of the main PNN structural protein. Ongoing studies are evaluating the effect of venlafaxine on the neuronal dynamics by examining sharp wave ripples (SWR), which are population events in the hippocampus that can be increased by disinhibition of pyramidal cell excitability.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

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Title: Differential effects of monoamine uptake inhibitors on effort-related choice behavior and DARPP-32 phosphorilation patterns

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Abstract: Vigor, persistence, and work output are fundamental features of normal motivation. Nucleus Accumbens (Nacb) dopamine (DA) regulates behavioral activation and effort-related decision-making in motivated behavior, and DA depletion has been shown to induce anergia and fatigue in effort-based decision tasks in humans and animals. These motivational symptoms are seen in pathologies such as depression and are highly resistant to treatment. In the present work, we evaluate the impact of DA depletion by the administration of Tetrabenazine (TBZ), a VMAT2 blocker that has been reported to induce depression in humans. We also assessed the effect of Bupropion (BUP) that blocks DA uptake and Fluoxetine (FLUOX) that blocks

serotonin (5-HT) uptake. CD1 male mice received TBZ (0, 4, 6 or 8 mg/kg, IP), BUP (0, 5, 10 or 15 mg/kg, IP) or FLUOX (0, 10, 15 and 20 mg/kg, IP). Anergia was evaluated in a mouse T-maze task developed for the assessment of preference between physical activities (running in a RW) in one arm vs. sedentary reinforcers (freely available sucrose pellets) in another arm, as well as, a non-social odor in the third arm. In addition, DA receptor-activity-related markers (pDARPP32-Thr75 and Thr34) in Nacb were assessed using immunoblotting. In the T-maze, control mice spent more time running and less consuming sucrose or sniffing. TBZ produced a shift in the relative preference, reducing selection of the reinforcer that involved vigorous activity, but increasing consumption of a reinforcer that required little effort (sucrose). Although BUP did not have an effect on its own, it was able to reverse the shift in preferences induced by TBZ, restoring normal levels of performance. FLUOX produced a similar shift to TBZ, reducing time running in the RW but increasing time consuming sucrose pellets, moreover, FLUOX was not be able to reverse the effect of TBZ and, in fact, exacerbated it. BUP behavioral effects were parallel to phosphorylation changes in DARPP32, but not FLUOX. These results indicate that drugs acting on DA transmission are effective at reversing the anergia-inducing effects of TBZ, and are consistent with the hypothesis that drugs that enhance DA transmission may be effective to improve depressive symptoms related to reduced behavioral activation.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

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Title: Pharmacological inhibition of cell proliferation prevents the antidepressant and increased neurogenic effects induced by repeated electroconvulsive shock treatment in rats

Authors: *J. GARCIA-FUSTER, R. GARCIA-CABRERIZO
IUNICS. Univ. of the Balearic Islands, Palma, Spain

Abstract: Electroconvulsive shock (ECS) is an alternative treatment used in psychiatry that offers a safe, rapid and potent therapeutic effect in major depressive disorders. The basis for its

therapeutic effect is still unknown, although a special attention has been given to the role of neuroplasticity markers in the hippocampus, such as hippocampal neurogenesis. Previous data from our research group demonstrated a temporal and parallel course regulation for the antidepressant and increased neurogenetic effects induced by repeated ECS in rats suggesting hippocampal neurogenesis may play a role on the antidepressant-like effect induced by repeated ECS. To corroborate this idea, the present study evaluated whether the pharmacological inhibition of basal cell proliferation with temozolamide (TMZ) would prevent the benefitial effects exerted by ECS on behavior (i.e., antidepressant-like response) and brain function (i.e., increased hippocampal cell genesis). To address this, adult male Sprague-Dawley rats were treated with 2 cycles of TMZ (each cycle: 25 mg/kg, i.p., 5 days, two days rest in between cycles, n=21) or vehicle (V: 1 ml/kg DMSO, i.p., n=19). Every day during the second cycle, 3 hours after the daily injections, rats from each group received a single ECS session (95 mA, 0.6 sec, 100 Hz, via earclip electrodes, 1 session/day, 5 sessions) (TMZ-ECS, n=11 vs. V-ECS, n=11) or were connected to earclips eletrodes but without electrical current (TMZ-SHAM, n=10 vs. V-SHAM, n=8). The possible effect of TMZ on preventing the antidepressant-like effect induced by repeated ECS was evaluated in the forced-swim test in a time-course manner (1, 3 and 7 days after the last ECS session). Repeated ECS induced a temporal antidepressant-like effect by reducing immobility time up to 3 days after the last ECS session (Day 1: -68±23 sec, $p<0.05$; Day 3: -80±23 sec, $p<0.01$; Day 7: -27±23 sec, $p>0.05$; V-ECS vs. V-SHAM). Interestingly, these effects were prevented in animals treated with TMZ (Day 1: -25±20 sec, $p>0.05$; Day 3: -19±20 sec, $p>0.05$; Day 7: -15±20 sec, $p>0.05$; TMZ-ECS vs. TMZ-SHAM). In addition, the expected increase in hippocampal cell proliferation induced by ECS was also reduced in rats treated with TMZ (Day 1: -365±101 Ki-67+ cells, $p<0.05$; V-ECS vs. TMZ-ECS). Current studies are evaluating the regulation of other cell genesis markers (i.e., neuronal survival) in TMZ treated rats and its interaction with the course of ECS antidepressant-like response. So far, these results demonstrate that inhibiting cell proliferation in rats prevents ECS treatment to exert its expected antidepressant and neurogenic effects.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Program #/Poster #: 323.18/BBB5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Heising-Simons Foundation Science Program Grant 2017-0496

Title: Effects of chronic lithium exposure in a ketamine-induced hyperactivity model of mania

Authors: J. KRUG[1], A. KLEIN[1], E. M. PURVIS[1], K. AYALA[1], M. MAYES[1], L. COLLINS[1], M. P. A. FISHER[2], *A. ETTENBERG[3,1]
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Abstract: Bipolar illness is a psychiatric disease characterized by acute periods of "mania" -- high energy, irritability, and increased psychomotor activation. Unfortunately, there is a paucity of animal models of mania, which are needed for investigations of the underlying neurobiological basis of the disease and to screen for prospective pharmacotherapies. One recent rodent model has been proposed in which motoric hyperactivity is induced over days by repeated administration of sub-anesthetic doses of ketamine – an effect reversed by co-administration of lithium (the primary treatment for bipolar illness). Current applications of this model have, however, employed limited exposure to lithium (typically 15 days), and extremely brief (i.e., 5-min) tests of locomotor behavior. To increase the face validity and translational utility of the test, the current study examined the impact on ketamine-induced hyperlocomotion during extended 30-min test sessions after 80 days of lithium exposure. Male albino rats consumed 2.0mEq/kg of lithium chloride presented daily in a high incentive food source (8 gm of sweetened peanut butter). Control animals ingested peanut butter infused with an equimolar concentration of sodium chloride to control for the salty taste of the food. During the final 11 days of treatment, animals were injected daily with a single dose of 25 mg/kg IP ketamine (in a volume of 1.0 ml/kg). A subset of animals received a comparable volume of IP 0.9% physiological saline and served as vehicle controls. Locomotor testing was conducted during test sessions both before ketamine injections were initiated and on the final day of treatment. The test apparatus consisted of a bank of 10 activity chambers each equipped with infrared sensors interfaced with a desk-top computer running custom software that measured the subjects' movement within the apparatus. Results confirmed that repeated ketamine administration produced a profound increase in locomotor activity relative to non-ketamine controls. Additionally, while lithium did not in and of itself alter locomotor activity, lithium-treated rats exhibited a highly reliable reduction in ketamine-induced locomotion compared to animals on the control diet. Blood samples obtained at the conclusion of testing, confirmed lithium plasma levels of 0.6mEq/L, comparable to low-moderate therapeutic levels in human patients. These data strongly confirm the viability and utility of ketamine-induced hyperlocomotion as a rodent model of mania.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH Grant MH077159

Title: Characterization of corticotropin-releasing hormone expressing cells in the anterior cingulate cortex of human subjects

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Abstract: *Introduction.* Corticotropin-releasing hormone (CRH) is implicated in a wide range of psychiatric illness. Our recent meta-analysis of 8 transcriptome studies revealed significant downregulation of CRH across 3 corticolimbic brain regions of major depressive disorder (MDD) subjects, suggesting that CRH-expressing cells are affected by disease. It is known that CRH is expressed in subgroups of neurons, mostly GABAergic interneurons in mouse cortex, however, CRH (+) cells are less characterized in human brains. The aim of this study is to investigate the cellular identity of CRH (+) neurons in human cortex. *Methods.* Using fluorescent in situ hybridization, we labeled cells in the human anterior cingulate cortex (ACC, Brodmann area 25) with probes targeting CRH and markers of excitatory (SLC17A7), inhibitory (GAD1) neurons, as well as three major subtypes of inhibitory interneurons (PVALB, SST, VIP). Coexpression patterns of CRH and cellular markers were analyzed. In parallel, CRH expression level was quantified using qPCR in the ACC of MDD subjects and matched controls (n=6/group). *Results.* CRH labeled 27% of GAD1-expressing GABA neurons. 80% of CRH (+) cells were GABAergic and 10% was glutamatergic. CRH (+) GABA neurons coexpressed markers of subpopulation of interneurons: VIP (52%), SST (7%), PVALB (7%). Notably 34% of CRH (+) cells expressed GAD1, but none of three GABA interneuron markers. CRH expression was significantly reduced in the brains of MDD patients compared to control (-24.4%, p=0.018). *Conclusions.* CRH is mainly expressed in GABAergic interneurons with 52% of CRH (+) neurons overlapping with VIP (+) interneurons and 34% expressed in a separate subgroups of interneurons which do not belong to three major interneuron populations. We confirm that CRH expression is significantly reduced in the brains of MDD patients, raising the question as to which CRH (+) GABAergic interneuron population is affected in MDD.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: W81XWH-14-0130

W81XWH-14-0390

Title: Distinct roles for 5-ht1b and 5-ht2a in antidepressant response

Authors: *Y. SAGI[1], L. MEDRIHAN[2], Z. INDE[2], O. KRUPA[2], C. DANIELS[2], A. PEYRACHE[4], P. GREENGARD[3]
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Abstract: Selective serotonin reuptake inhibitors are the most commonly used class of antidepressant drugs, but the cellular and molecular mechanisms by which their therapeutic action is initiated are poorly understood. Here we used a Translating Ribosome Affinity Purification (TRAP) strategy to determine the expression level of serotonin receptors in hippocampal neurons in mice, and found that 5-HT1B and 5-HT2A receptors are highly expressed in cholecystokinin (CCK) inhibitory interneurons of the dentate gyrus. Using conditional knockout strategy, it was found that 5-HT1B receptors in these cells mediate the initiation of the therapeutic response to antidepressants, whereas 5-HT2A receptors in these cells mediate their chronic effects. We describe the mechanisms by which these two receptors regulate CCK cells function and explain how p11, a protein associated with depression and antidepressant response, differentially regulate the function of these two 5-HTR pathways.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

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Campbell Foundation of CAMH

Title: Combined therapeutics: Anxiolytic, antidepressant and pro-cognitive properties of novel positive allosteric modulators at α5-containing GABAA receptors

Authors: *T. D. PREVOT[1], G. LI[2], A. VIDOJEVIC[3], K. A. MISQUITTA[4], A. SANTRAC[3], D. KNUTSON[2], M. R. STEPHEN[2], R. KODALI[2], N. M. ZAHN[2], L. A. ARNOLD[2], P. SCHOLZE[5], J. L. FISHER[6], M. BANASR[7], J. M. COOK[8], M. SAVIC[3], E. SIBILLE[9]
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Abstract: Altered γ-aminobutyric acid (**GABA**) function is frequently reported in psychiatric disorders, normal aging and neurodegenerative disorders. Reduced function of somatostatin (SST)-expressing GABA interneurons is associated with both mood and cognitive symptoms. SST/GABA-neurons signal in part through α5-subunit containing GABAA receptors (α5-GABAA-Rs) which are localized in brain regions involved in the regulation of emotion and cognition. We hypothesize that enhancing α5-GABAA-R activity has therapeutic potential for both mood and cognitive symptoms in stress-based and aging rodent models. Our group synthesized novel imidazobenzodiazepine (IBZD) amide ligands, tested them for positive allosteric modulation at α5-GABAA-R (α5-PAM), pharmacokinetic properties, and for potential anxiolytic and antidepressant activities in adult mice using escalading doses. Pro-cognitive activity was tested in adult mice submitted to chronic stress and in old mice using a spontaneous alternation task, assessing working memory performances. Diazepam (DZP), with broad PAM activity at GABAA-Rs, was used as a control. Three novel IBZD amide ligands (namely GL-II-73, GL-II-74 and GL-II-76) demonstrated adequate brain penetration, affinity and PAM activity at α5-GABAA-Rs, and metabolic stability for in vivo studies. GL-II-73/74/75 showed significant anxiolytic and antidepressant efficacies in adult mice. Moreover, GL-II-73 and GL-II-75 significantly reversed cognitive deficits induced by stress or occurring during normal aging. This activity was maintained after sub-chronic administration for GL-II-73. In contrast DZP displayed anxiolytic but no antidepressant or pro-cognitive activities. For the first time, our group demonstrated the potential for combined efficacies of newly designed IBDZ amide ligands mediated by efficacy at α5-GABAA-Rs, reducing anxiety and depression and enhancing cognitive performances. These results suggest a novel therapeutic approach targeting both mood and cognitive symptoms in depression and/or aging.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

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Title: Characterization of high-fat-diet-induced treatment-resistant depressive-like brain state: Neural hyperexcitability and responsiveness to the anticonvulsant retigabine

Authors: *M. FENG, N. A. CROWLEY[1], A. PATEL[1], Y. GUO[1], S. E. BUGNI[1], F. K. MALDONADO[2], B. LUSCHER[3]
[1]Biol., [2]Biochem & Mol, [3]Dept Biol, Dept Biochem & Mol, Penn State Univ., University Park, PA

Abstract: Excessive consumption of fat-rich diet and obesity are associated with neuroinflammation and increased vulnerability to psychiatric disorders including Major Depressive Disorder (MDD), a heterogeneous syndrome caused by both genetic vulnerabilities and environmental factors. Of particular interest are treatment resistant forms of MDD that fail to respond to current antidepressants and may or may not be responding to experimental treatment with subanesthetic ketamine. Increasing clinical evidence suggests that treatment resistance is associated with neuroinflammation and obesity, while obesity is independently linked to neuroinflammation. To start to elucidate possible mechanisms underlying treatment resistant MDD, we here established a High Fat Diet (HFD)-induced mouse model of a depressive like brain state. We exposed C57BL/6J mice to HFD for 18 weeks followed by analyses of glucose tolerance and markers of inflammation. HFD exposure of male mice resulted in glucose intolerance, increased microglial activation and elevated expression of the inflammatory cytokines interleukin-1β, tumor necrosis factor-αand interleukin-6. Similar but insignificant trends were observed in female mice. Behaviorally, the HFD induced inflammation of male mice was associated with anxious-depressive-like phenotypes in the novelty suppressed feeding test, female urine sniffing test, sucrose splash test and Y-maze. Slice recordings of HFD-treated animals revealed increased intrinsic excitability of pyramidal neurons in the medial prefrontal cortex, along with increased hyperpolarization-activated cation currents (I_h). Curiously, HFD-induced behavioral defects were resistant to chronic treatment with the conventional antidepressants, desipramine (40 mg/kg/d) and fluoxetine (18 mg/kg/d) except for the novelty suppressed feeding test, where both drugs elicited anxiolytic effects. Additionally, HFD induced depressive-like phenotypes were largely insensitive to acute treatment with the experimental

antidepressant ketamine (6 mg/kg), except for antidepressant-like effects in the forced swim test. Interestingly, systemic chronic treatment of mice with the anticonvulsant retigabine (1mg/kg/d, 8 d), a voltage-gated K+ channel opener that reduces neural excitability, normalized the $I_h$currents and partially reversed the HFD-induced behavioral defects. Our data suggests that HFD-induced inflammation leads to increased intrinsic excitability that underlies a treatment-resistant depressive-like brain state that can be ameliorated pharmacologically by agents that reduce neural hyperexcitability.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

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Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R03-MH112984

Title: Effects of the serotonin transport inhibitor fluoxetine on effort-related decision making in male and female rats

Authors: *E. HURLEY[1], R. ROTOLO[1], R. PRESBY[1], H. MCMULLEN[1], B. YE[1], M. FLYNN[1], J.-H. YANG[1], M. CORREA[3], J. D. SALAMONE[2]
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Abstract: Major depressive disorder (MDD) is characterized by behavioral, cognitive, and mood-related symptoms. In addition, motivational symptoms such as anergia and fatigue are common facets of MDD. Depressed individuals show signs of anergia/fatigue that correlate with overall severity of symptoms, as well as effort-related dysfunctions and amotivation. Inhibitors of 5-HT uptake, known as serotonin transport (SERT) inhibitors, are the most commonly prescribed antidepressants, but treatment with SERT inhibitors is often accompanied by residual motivational symptoms that are resistant to treatment. Moreover, when compared to other antidepressants such as bupropion (Wellbutrin), SERT blockers are more likely to induce symptoms of sleepiness and fatigue. Due to the limitations and adverse effects of SERT blockers, there is a need to establish models for exploring the mechanisms underlying the motivational problems associated with these drugs. Our laboratory has developed behavioral tasks that allow rats to choose between high-effort alternatives that lead to more highly valued rewards vs. low-effort options that lead to less valued rewards. Depressed people show a low-effort bias in human tests of effort-related decision making, and rat studies report that conditions associated with

depression can induce changes in effort-based choice. Importantly, research from our laboratory shows that the SERT inhibitors fluoxetine (FLX; Prozac) and citalopram fail to reverse the effort-related effects of the dopamine depleting agent, tetrabenazine, and in fact tend to exacerbate them. The present studies were undertaken to characterize the effects of FLX on effort-related decision making in male and female rats. FLX (5.0-15.0 mg/kg IP) significantly reduced selection of running wheel activity, and also suppressed lever pressing but not chow intake in males and females tested on a concurrent choice task. Currently, several receptor subtypes are being studied as targets for psychiatric disorders. However, highly selective 5-HT2A and 5-HT2C receptor antagonists were not able to reverse the motivational impairments associated with FLX administration. This indicates the need to study non-selective 5-HT receptor antagonists such as mianserin, or antagonists at other receptors such as 5-HT1B, 3, 6, or 7, for reversing FLX-induced deficits. Elucidating the roles of specific 5-HT receptors could lead to a greater understanding of the neurochemical mechanisms that regulate effort-related aspects of motivation, and ultimately, could foster the development of possible treatments that augment the therapeutic efficacy of serotonin uptake inhibitors.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.24/BBB11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH 1R21AG049237
NIH 1R01NS092610-01A1
NIH 1R01AG032441

Title: Sex differences in duloxetine efficacy for depression: Estrogen dependency study in transgenic mouse models

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Abstract: Clinical evidences show sex differences in risk of developing depressive disorders as well as effect of antidepressants in depression treatment. However, whether such a sex-dependent risk of depression and efficacy of antidepressants is dependent on endogenous estrogen level remain elusive. The aim of this study is to explore the molecular mechanisms of

sex differences in antidepressant duloxetine. In the present study, we used genetic knockout or overexpression estrogen-synthesizing enzyme aromatase (Ar) gene as models for endogenous estrogen deficiency and elevation endogenous estrogen, respectively, to examine the antidepressive efficacy of duloxetine in males and females by force swimming test (FST). We also measured the sex-specific effect of duloxetine on dopamine and serotonin metabolisms in frontal cortex and hippocampus. Elevation of brain endogenous estrogen in male and female mice showed a reduction of immobility time in FST compared to control mice. Estrogen deficiency in females showed poor response to duloxetine treatment compared to sex-matched wildtype or aromatase transgenic mice. In contrast, male mice with estrogen deficiency showed same anti-depressive response to duloxetine treatments as aromatase transgenic mice. Our data showed that the sex different effect of endogenous estrogen on duloxetine-induced anti-depressive behavioral change is associated with brain region-specific changes of DA and 5-HT system. Endogenous estrogen exerts antidepressant effects in both males and females. Lacking of endogenous estrogen is responsible for poor response to duloxetine in females only. The endogenous estrogen level alters 5-HT system in female mainly, while both DA and 5-HT metabolisms were regulated by endogenous estrogen levels after duloxetine administration.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

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Program #/Poster #: 323.25/BBB12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant GM-123852
NARSAD
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HHMI

Title: Escitalopram in the endoplasmic reticulum

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Abstract: Serotonin selective uptake inhibitors (SSRIs) are commonly used and partially effective for major depressive disorder. After SSRIs bind the serotonin transporter (SERT) on the plasma membrane (PM), an incompletely known set of processes generate the anti-depressant

effect. SSRIs also permeate into the endoplasmic reticulum (ER) and *cis*-Golgi, and bind to nascent SERT. Downstream effects, such as pharmacological chaperoning of SERT by SSRIs, may partially underly therapeutic effects of SSRIs. Investigation of this and / or similar actions requires direct proof, quantification, and time resolution of these processes in live cells and brains. We are developing genetically encoded fluorescent biosensors to study the subcellular pharmacokinetics of SSRIs.
OpuBC, a monomeric bacterial periplasmic binding protein (PBP), has (a) a binding site for amines including a cation-π box, and (b) ligand-induced "Venus flytrap" conformational change involving relative motions of two domains. We insert circularly permuted "superfolder" GFP (cpGFP), flanked by several-residue linkers, within inter-domain hinge regions. We apply directed evolution, including X-ray crystallography, to optimize the sensing of drugs, and have achieved the goal of $\Delta F/F0 > 1$ at 1 μM for several drug-biosensor pairs.
Our most detailed studies for SSRIs thus far use "**i**ntensity-based **escitalopram**-**s**e**n**sing **f**luorescent **r**eporters" (iEscitalopramSnFRs). We insert targeting and retention sequences to direct the constructs to the ER or to the PM of clonal mammalian lines and cultured neurons. Live-cell video imaging shows that, after we jump [escitalopram] (increase or decrease) near cells, the drug appears in the ER within < 10 s and leaves within <20 s, reaching a plateau within 20 and 30 s, respectively. Responses are robust, even at the sub-μM steady-state [escitalopram] in the cerebrospinal fluid of human subjects.
We are developing other iDrugSnFRs for other SSRIs including fluoxetine and paroxetine. Further application of these tools will show the initial steps in the pathway of SSRI intracellular pharmacokinetics, allowing study of the role "inside-out" neuropharmacology plays in major depressive disorder.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.26/BBB13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NCN grant 2014/13/B/NZ7/02293

Title: Effects of selective depletion of CREB in serotonergic neurons on neurotrophin expression after fluoxetine treatment

Authors: *K. RAFA-ZABLOCKA, G. KREINER, M. BAGINSKA, I. NALEPA
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Abstract: Neurotrophins are a family of growth factors consisting of brain derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophin-3 (NTF-3). They play crucial role in maintaining survival, development and plasticity of neurons. Moreover, according to neurotrophic hypothesis of depression they are thought to be involved in the pathogenesis of illness itself as in the mechanisms of action of antidepressant treatment. In particular, it has been shown that after long-term administration of common antidepressants level of BDNF protein or mRNA expression increases. One of the promoter site of BDNF gene is regulated by cyclic AMP response element binding protein (CREB), so BDNF upregulation can be induced by this transcription factor. On the other hand, BDNF itself can trigger CREB phosphorylation thus creating a positive feedback loop.
In our studies we investigated the role of CREB in the mechanism of antidepressant treatment using novel, inducible transgenic mouse model lacking CREB selectively in serotonergic neurons ($Creb1^{TPH2CreERT2}$). Moreover, animals were depleted of CREM factor to exclude the compensatory effects of its upregulation upon CREB deletion. Our previous research showed no differences in basic behavior between mutant and wild type animals, while their responsiveness to acute fluoxetine was abolished in tail suspension test. In current study we assessed the mRNA synthesis and protein levels of three neurotrophic factors: BDNF, NGF, NTF3 as well as CREB in hippocampus and prefrontal cortex of mutant animals chronically treated with fluoxetine (10mg/kg ip., 1x daily for 21 days).
Our main findings confirmed the observed in other studies fluoxetine-induced upregulation of BDNF in hippocampus (males and females) and prefrontal cortex (only females) in wild type mice. However, in animals deficient in CREB in serotonergic neurons we observed no such changes in BDNF protein after drug. What is more, male mutants show increase in NGF and NTF3 levels in prefrontal cortex after fluoxetine administration, which effect is absent in wild type animals.
In conclusion, we have shown for the first time that BDNF upregulation in hippocampus or prefrontal cortex observed after fluoxetine administration might be dependent on the transcription factor CREB resident not within these particular structures targeted by serotonergic projections, but exclusively in serotonergic neurons. These results may shed a new light on neurotrophic hypothesis of depression linking CREB activity and BDNF level within distinct brain areas.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.27/BBB14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R03MH094966-01A1

Title: Comparison between male and female mice in behavioral activation and effort-related decision-making: Involvement of dopamine related markers

Authors: *M. CORREA[1], C. CARRATALA-ROS[1], A. MARTÍNEZ-VERDÚ[1], P. IBÁÑEZ-MARÍN[1], R. OLIVARES-GARCÍA[1], S. PORRU[1], J. D. SALAMONE[2]
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Abstract: Impairments in behavioral activation and effort-related symptoms are commonly seen in people with depression. These motivational symptoms, such as psychomotor retardation and anergia, are highly resistant to treatment. Nucleus Accumbens dopamine (DA) regulates behavioral activation and effort-related decision-making. In the present work, we study, in female and male CD1 adult mice, the impact of DA depletion with Tetrabenazine (TBZ), a vesicular monoamine transporter type 2 blocker, that has shown to induce depression in humans, on preference for activity-based reinforcers in a T-maze-RW-sucrose-task, developed for the assessment of preference between physical activities that require vigor (running in a RW) in one arm vs. sedentary reinforcers (freely available sucrose pellets) in another arm, as well as, a non-social neutral odor in the third arm. In addition, we also evaluated the impact of TBZ in the Forced-Swim-Test (FST). Under vehicle conditions, female and male mice spent the same time in the RW. TBZ reduced RW preference, but increased preference for sucrose in both sexes. In the FST, TBZ increased passive behaviors (immobility) in both sexes, but had a bigger impact on active behaviors (climbing) in male mice. TBZ had a similar impact in both sexes in terms of DARPP-32 phosphorilation patterns. These results indicate that DA is involved in vigorous and sustained behavioral activation, and DA depletion alters effort-related preferences and behavioral activation. Studies in animal models of both sexes are important in order to address potential sex differences in vulnerability to anergia in depression.
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Keywords: Dopamine, Nucleus Accumbens, behavioral activation, decision making, depression.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.28/CCC1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Transcriptional coregulators LIM domain-binding protein 1(Ldb1) and LIM-domain-only protein 1(LMO1) modulate Lmx1b-mediated activation of the human tryptophan hydroxylase-2 promoter

Authors: H. KANEKO[1], Y. NAWA[1], M. TSUBONOYA[1], T. HIROI[1], R. TAKAHASHI[2], *H. MATSUI[3]
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Abstract: Tryptophan hydroxylase-2(TPH2) plays an essential role in the regulation of 5-HT neurotransmission and is thus a promising therapeutic target for the treatment of neuropsychiatric disorders. The mechanism by which TPH2 gene expression is regulated still remains an open question. Lmx1b, a member of LIM-homeodomain (LIM-HD) family of transcription factors, contains two N-terminal LIM domains, a central DNA-binding homeodomain, and a C-terminal transactivation domain. Lmx1b is required for regulation and maintenance of normal functions of 5-HT neurons including transcriptional regulation of the TPH2 gene. LIM domain-binding proteins (Ldb1 and Ldb2) were discovered because of their ability to bind to LIM-HD proteins and LIM-domain-only (LMO) proteins (LMO1 to 4). It is conceivable that Ldbs bind to LIM domains of Lmx1b, thereby modulating Lmx1b-mediated regulation of the TPH2 gene expression. Moreover, it is postulated that LMOs modulate the transcriptional activity of Ldb-Lmx1b complexes by competing with Lmx1b for binding to Ldbs. In this study, to address these questions more directly, we examined how the human TPH2 (hTPH2) promoter activity changes by Lmx1b, Ldbs and LMOs. A 2-kb promoter region of the hTPH2 gene (-1850/+141) was cloned into pGL4-Basic (TPH2-55) and a mutant having deletion of its 5'-untranslated region (+10/+121; a region containing potential repression elements) was constructed (TPH2-100). Promoter activities were assessed by transient transfections into RN46A cells, a cell line derived from rat raphe neurons. Sequence analysis revealed two potential Lmx1b binding sites (-1418/-1409 and -950/-945) in the hTPH2 promoter. To facilitate analysis of the transactivation function of Lmx1b, an expression vector for the VP64 (promiscuous activator domain derived from HSV)-Lmx1b fusion protein was prepared. Overexpression of VP64-Lmx1b fusion protein increased promoter activity of TPH2-100. Mutation analysis revealed that both Lmx1b binding sites were critical for Lmx1b-mediated activation of the hTPH2 promoter. Quantitative real-time RT-PCR analysis revealed the expression of Ldb1, Ldb2, LMO1, LMO2 and LMO4 genes in RN46A cells. Co-expression study demonstrated that Ldb1 was more potent than Ldb2 in enhancing Lmx1b-mediated activation of the hTPH2 promoter. In turn, Ldb1-mediated enhancement was remarkably attenuated by co-expression of LMO1, LMO2 or LMO4. Among tested, LMO1 was the most potent. Altogether, these results imply that Ldb1 and LMO1 modulate Lmx1b-mediated activation of the hTPH2 promoter and ultimately regulate 5-HT synthesis in the brain.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.29/CCC2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Campbell Family Mental Health Research Institute

Title: Repeated assessment of anxiety-like behavior in mice: A new tool with increased reliability and consistency

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Abstract: Anxiety is a debilitating disorder with high prevalence and co-morbidity across multiple psychiatric diseases. Evidence from both clinical and preclinical studies suggest that the biological bases of anxiety and depression are associated with chronic exposure to stress. To identify the biological bases of anxiety-like behavior, rodent models have either studied the acute response to stress or acutely measured the effect chronic stress exposure. Little is known about the longitudinal progression of anxiety-like behavior. Most commonly used tests such as the open field test (OFT), elevated plus maze (EPM), novelty suppressed feeding (NSF) require a novelty component that undermines their ability to be used repetitively. Additionally, they measure behavior over a short duration, rely highly on housing and testing conditions and are subject to experimenter bias. Here, we have designed and validated a novel behavioral assay to measures anxiety-like behavior devoid of these limitations. Using a home cage-like apparatus (Noldus Phenotypers) we monitored baseline behavior by measuring time spent in designated zones (food and shelter zones) for a 12h period overnight. To assess anxiety-like behavior a 1h light challenge was applied over the food zone, 4h into the night. In this study, C57Bl/6 and Balb/c (n=12/group 50%♀) mice were subjected to chronic restraint stress (CRS) or unpredictable chronic mild stress (UCMS) for 5 weeks. Weekly assessments using the phenotyper plus a series of classical tests (OFT, EPM, and NSF) were performed at the end of the 5 weeks of stress exposure. Both literature and work in our lab have found that animal performances in classical behavioral tests show high heterogeneity not only across stress paradigm, strain and stress but also across test. Across experimental conditions and experiments (UCMS vs CRS, Balb/c vs C57Bl/6, male vs female) it was evident every week during the stress exposure that the phenotyper test could detect anxiety-like behavior (avoid the food zone, favor

the shelter during/after challenge). We also confirm baseline and anxiogenic response. Ongoing experiments will identify whether this assay can detect the potential reversal of induced anxiety-like behavior in control and stress conditions with treatment of diazepam. Altogether this new assay provides consistent and robust results as exhibited across different stress models, sexes and strains and can potentially be used to measure anxiety-like behavior repetitively. This novel tool should be instrumental in the design of longitudinal studies aiming to better understand the biological bases of chronic anxiety disorders and others stress-related illnesses.

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Poster

323. Depression and Bipolar Disorders: Animal Models of Therapeutics

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 323.30/CCC3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01MH104261
ONR N00014-12-1-0366
Hope for Depression Research Foundation
U01DA043098

Title: Investigating the neurobiological correlates of antidepressant treatment response: Findings from a novel rat model of treatment resistant depression

Authors: *C. AYDIN, P. BLANDINO, E. HEBDA-BAUER, H. AKIL
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Abstract: According the World Health Organization (2017) depression is the leading cause of disability worldwide affecting over 300 million people. Despite the availability of multiple modalities of antidepressant (AD) medications, fewer than half of depressed patients achieve full remission with a first line of treatment. Moreover, a significant percentage of patients are resistant to all available AD treatments. In an effort to understand the neurobiological mechanisms of antidepressant response versus resistance, we created an animal model of treatment-resistant depression using the bred High Responder-Low Responder (bHR, bLR) rats. These animals are selectively-bred in our laboratory, and differ in their emotional reactivity to environmental manipulations. In order to induce a depressed-like state in these rats, we employed a multiple-hit (MH) regimen starting in adolescence. Our data showed that this stress regimen induced affective resilience in bLRs, but vulnerability in bHRs to a stress challenge in adulthood, suggesting that environmental challenges encountered in adolescence interact with genetic background to alter affective behavior later in life. Interestingly, our data showed that

genetic background determined antidepressant response as well; a 2-wk treatment with a selective serotonin reuptake inhibitor, fluoxetine (FLX), following the MH regimen was effective in control bLRs, but ineffective in control bHRs. Moreover, FLX failed to reverse the depressed-like state observed in bHRs following multiple hits, whereas treatment with a tricyclic AD, desipramine (DMI), was successful in this measure. Using hippocampi from the FLX-resistant, and DMI-responsive bHRs we performed an RNA sequencing (RNAseq) experiment to identify the molecular correlates of AD treatment response versus resistance. Key findings from our analyses of the RNAseq data will be presented.

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Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.01/CCC4

Topic: H.01. Animal Cognition and Behavior

Support: ÚNKP-17-3-III-SE-9

Title: Brainstem nucleus incertus controls contextual memory formation

Authors: *A. SZONYI[1], K. E. SOS[1], R. NYILAS[2], D. SCHLINGLOFF[1], A. DOMONKOS[1], V. T. TAKACS[1], J. PRIESTLEY[2], B. POSFAI[1], P. HEGEDUS[1], Z. BARDÓCZI[1], A. L. GUNDLACH[3], V. VARGA[1], A. I. GULYAS[1], A. LOSONCZY[2], T. F. FREUND[1], G. NYIRI[1]
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Abstract: The hippocampal CA1 pyramidal cells (CA1PCs) play an important role in fear memory formation. These cells associate aversive stimuli conveyed by the entorhinal cortex to their distal dendrites, with the multisensory environmental contextual information conveyed by CA3 pyramidal cells to their proximal dendrites. However, the direct entorhinal input has to be excluded from most of the CA1PCs at the moment of fear conditioning to ensure precise contextual memory encoding. Oriens-lacunosum molecure (OLM) interneurons can exclude those direct entorhinal inputs, by inhibiting the distal dendrites of CA1PCs and they are activated by salient sensory information via glutamatergic and cholinergic inputs from the basal forebrain. However, for certain events, memory encoding is unnecessary, and OLM cells may need to be inhibited. It was unknown whether OLM cells receive any extrahippocampal inhibitory input that could fulfill this role. Using vesicular GABA transporter (vGAT)-Cre mice, here, we show that the GABAergic cells of the pontine nucleus incertus (NI) selectively inhibit OLM cells directly

and also indirectly via the inhibition of basal forebrain cholinergic and glutamatergic cells. Contextual fear conditioning experiments showed that optogenetic activation of NI GABAergic cells during aversive inputs can effectively disrupt, while their optogenetic inhibition can excessively enhance contextual fear memory formation. Using Cre-dependent monosynaptic rabies tracing, we also show that NI GABAergic cells receive inputs from forebrain areas related to the processing of salient environmental information. Two-photon calcium-imaging in head-restraint behaving mice showed that in vivo, NI GABAergic fibers are preferentially activated by salient sensory stimuli. Furthermore, in vivo optogenetic stimulation of NI changed the properties of the hippocampal theta-rhythm in freely moving mice. Finally, in vitro optogenetic stimulation of NI fibers decreased the frequency of sharp-wave ripple events in hippocampal slices suggesting a role of NI in the regulation of memory consolidation. These results suggest that by specifically controlling the activity of OLM cells, NI GABAergic cells can heavily influence the right balance between hippocampal contextual memories that needs to be formed and kept and those that are unnecessary.

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Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.02/CCC5

Topic: H.01. Animal Cognition and Behavior

Support: RSCF 14-15-00685
RFBR 17-04-02054

Title: New mouse object-in-place recognition task for *in vivo* two-photon calcium imaging in themobile home cage

Authors: *O. I. IVASHKINA[1], K. TOROPOVA[1,2], A. GRUZDEVA[1,2], E. KULIKOVA[3], K. ANOKHIN[1,2,4]
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Abstract: The goal of our study was to investigate neuronal specializations in the retrosplenial cortex to a new environment and objects in it. To this end, we used in vivo two-photon calcium

imaging in mice during object-in-place recognition task. As two-photon imaging requires head fixation of animals, we used the Mobile Home Cage (MHC, Neurotar Ltd) setup - an air-lifted mobile cage, where a head-fixed animal can move around and explore the environment. First, we developed the object-in-place recognition task in the MHC on C57 Bl/6 mice with implanted headposts (Neurotar Ltd). Mice were habituated to the MHC conditions during 14 days with session time increasing from 10 to 50 min. The object-in-place task consisted of 7 sessions. During sessions mice explored empty MHC, MHC with new proximal cues, MHC with two novel objects, MHC with one of the familiar objects displaced (place recognition task), and MHC with a familiar and a novel object (object recognition task). We showed that mice actively explored MHC with cues and objects. In the place recognition task, mice spent more time exploring and sniffing the familiar object in the new location, demonstrating place recognition memory. In the object recognition task, animals preferentially explored and sniffed the novel object, demonstrating object recognition memory. After we successfully developed the MHC-based object-in-place task, we performed two-photon calcium imaging using GCaMP6 in the retrosplenial cortex during task sessions. We showed the responses of the retrosplenial neurons to different objects and locations through the imaging sessions.

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Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.03/CCC6

Topic: H.01. Animal Cognition and Behavior

Title: Permanent damage or chemogenetic inactivation of the postrhinal cortex impairs two forms of higher order conditioning

Authors: *T. L. CHAKOMA, E. K. DONAHUE, A. E. DENNEY, S. ROBINSON
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Abstract: The postrhinal cortex (POR) provides a major source of visuospatial information to the hippocampal memory system and, similar to the retrosplenial cortex, is involved in a number of cognitive processes that require the formation of associations among environmental stimuli. To investigate the role of the POR in learning situations that require the formation of stimulus-stimulus associations, the effect of permanent electrolytic lesions or transient chemogenetic inactivation of the POR was evaluated in higher order sensory preconditioning studies that included either appetitive or aversive unconditioned stimuli. In Experiment 1, POR-lesioned or sham rats were exposed to two contexts that contained distinct visual, olfactory and auditory stimuli. In a subsequent classical conditioning phase, the salience of one of the auditory stimuli

was paired to an aversive footshock in a novel context while the other was not. Freezing behavior was analyzed upon re-exposure to the contexts and to the auditory stimuli in the absence of footshock. In separate cohorts of rats, higher order conditioning was evaluated following either permanent (Experiment 2) or transient (Experiment 3) inactivation of the POR. Specifically, during an initial learning phase, presentation of one auditory stimulus was paired with presentation of a visual stimulus whereas a second auditory stimulus was presented alone. Next, during a classical conditioning phase, the visual stimulus was paired with food. During a subsequent probe test, both auditory stimuli from the initial phase were presented individually and the amount of time spent in the food cup was assessed. The results from Experiment 1 and 2 revealed that the POR is necessary for rats to higher-order condition successfully, whereas the ability to form Pavlovian associations remained intact in the absence of POR signaling. Employment of a chemogenetic approach extended these findings by revealing that POR function is required for acquisition of stimulus-stimulus associations, but not for expression of higher order conditioning.

Disclosures: T.L. Chakoma: None. **E.K. Donahue:** None. **A.E. Denney:** None. **S. Robinson:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.04/CCC7

Topic: H.01. Animal Cognition and Behavior

Title: The social context is a cognitive enhancer for episodic-like memory in Wistar rats

Authors: *P. E. MARINHO[1], M. A. S. FRANÇA[2], R. V. C. B. MOURÃO[2], F. F. BARBOSA[2]
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Abstract: Episodic memory is our capacity to recall when and where a specific event occurred, initially addressed as a unique human cognitive ability. However, some studies have provided evidence that other species, such as birds and mammals, are capable of some sort of encoding, consolidation and retrieval of episodic information. Nevertheless, the social nature of the non-human species investigated has been often under-emphasized or ignored in the design and interpretation of experiments. Thus, considering that the laboratory rat strains are domesticated forms of the species *Rattus norvegicus* – a highly social species –, we aimed to investigate the effect of the social environment on the performance of Wistar rats in an episodic-like memory task. We used a three-trial "what", "when" and "where" object exploration task, based on the novelty preference paradigm. Our protocol comprised 2 samples and 1 test. In the first sample, 4 equal objects (A) were arranged in the experimental apparatus. The second sample was carried out 1 hour later, in which 4 equal objects (B), different from those already presented to the

animals, were provided. Of these, 2 remained at spatial coordinates already occupied by A objects. After a delay of 24 hours, the subjects performed a test session containing 4 objects, all of which were already presented in the previous sessions. In this session, 2 objects maintained stationary positions in the apparatus (A1 and B1) and 2 were displaced (A2 and B2). Episodic-like memory integration can be inferred when the subjects explore “A1” more than “A2". We analyzed the behavior of 26 male individuals, allocated into 3 groups: the control group (GC), the co-habituated dyad group (HD), and the co-tested dyad group (TD). The GC group went through the processes of habituation to the experimental apparatus individually and carried out the episodic-like memory task individually. The HD group was subjected to habituation to the apparatus in dyads, but performed the task individually. As for the TD group, the rats went through all the experimental procedures in dyads. The results showed that only the TD group presented episodic-like memory. Also, the co-tested dyad rats explored for a longer period the objects used in the task. In addition, the behavioral analysis applied showed that the rats in dyads spent a long time together, expressed social behaviors and exhibited fewer anxiety-like responses. Putting together, these results stand out the importance of investigating the cognitive processes in a more naturalistic setting, as well as to explore ethologically-relevant parameters related to information processing and allocation of attention.

Disclosures: P.E. Marinho: None. **M.A.S. França:** None. **R.V.C.B. Mourão:** None. **F.F. Barbosa:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

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Program #/Poster #: 324.05/CCC8

Topic: H.01. Animal Cognition and Behavior

Support: MH108837
MH078064

Title: VGlut1-expressing hippocampal neurons mediate stress-induced generalization of context memories

Authors: *L. Y. REN[1], J. M. RADULOVIC[2]
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Abstract: Episodic memories must be encoded and maintained with specificity so that information about different environments is not generalized to unrelated novel environments. Stress promotes inappropriate generalization of memories, and mechanistic study of this may provide insight into the generalization of negative memories commonly seen in major depressive

and anxiety disorders and PTSD. While it is well established that excitatory transmission in the dorsal hippocampus is crucial for associating aversive events with the environmental contexts in which they occur, the role of hippocampal excitatory neurotransmission in stress-induced generalization of memories is less understood. As dorsal hippocampus excitatory efferents contain either vesicular glutamate transporter 1 (VGlut1) or 2 (Vglut2), we used Vglut1- and Vglut2-Cre mice to investigate their roles in stress-induced generalization of context memories. After training mice to associate a context with a fear-provoking stimulus, we exposed mice to social defeat stress. Under these conditions, mice that normally acquired fear responses begun to show generalization during testing in a novel context. We found that chemogenetic inhibition of vGlut1-expressing neurons in the dorsal hippocampus before memory tests prevented generalization of context fear. These results suggest that fear generalization is enhanced by social defeat stress, and this effect is mediated through vGlut1-positive hippocampal neurons. These results suggest that fear generalization is enhanced by social defeat stress, and this effect is mediated through vGlut1-positive hippocampal neurons.

Disclosures: L.Y. Ren: None. **J.M. Radulovic:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.06/CCC9

Topic: H.01. Animal Cognition and Behavior

Title: SUVN-502: A pure and selective 5-HT_6 antagonist alleviates phenytoin and topiramate induced cognitive impairments

Authors: *R. ABRAHAM, J. FERNANDES, V. REBALLI, R. NIROGI
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Abstract: Anti-epileptics such as topiramate and phenytoin are known to induce memory deficits in epileptic patients. These anti-epileptics affect acquisition more adversely than retention. This is further worsened in aged population. In the current investigation we examined the effect of SUVN-502, a pure, potent and selective 5-HT_6 antagonist in conditions of cognitive deficits induced by topiramate and phenytoin. Doses of topiramate or phenytoin which disrupts acquisition was determined. The effect of SUVN-502 on cognitive deficits induced by topiramate or phenytoin was investigated. SUVN-502 was administered 60 minutes prior to trial and topiramate or phenytoin was administered 30 minutes before the trial. It was observed that SUVN-502 alleviated topiramate and phenytoin induced memory deficits in adult rats. A similar effect was observed in aged rats as well. Doses of SUVN-502 which reversed memory deficit did not affect the anti-convulsant properties of phenytoin or topiramate. Hence SUVN-502 can

alleviate learning deficits induced by anti-epileptics without adversely affecting their anti-epileptic property

Disclosures: R. Abraham: A. Employment/Salary (full or part-time):; Suven Life Sciences. **J. Fernandes:** A. Employment/Salary (full or part-time):; suven life sciences. **V. Reballi:** A. Employment/Salary (full or part-time):; suven life sciences. **R. Nirogi:** A. Employment/Salary (full or part-time):; suven life sciences.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.07/CCC10

Topic: H.01. Animal Cognition and Behavior

Title: SUVN-D4010 (5-HT_4 receptor partial agonist) shows promising therapeutic potential for aged post-menopause state associated dementia and Alzheimer's disease

Authors: G. VENKATA RAMALINGAYYA, J. TADIPARTHI, N. GANUGA, H. TALAKANTI, P. JAYARAJAN, S. PANDRINKI, N. PATIBANDLA, *N. MUDDANA, A. RASHEED MOHAMMED, R. NIROGI
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Abstract: Evidence shows that post-menopausal women are highly susceptible to dementia and Alzheimer’s disease (AD) which will have great negative impact on quality of life (QOL). Although acetylcholine esterase (AChE) inhibitors, viz. donepezil or hormonal replacement therapy (HRT) were tried clinically, the outcome was not satisfactory. Moreover there could be potential risk of ovarian and breast cancers with HRT. No effective intervention is available or approved till date for cognitive deficits associated with post-menopause population. In our continued efforts in discovering new medications for the treatment of cognitive related ailments, the 5-HT_4 receptor partial agonist SUVN-D4010 was evaluated for its potential to alleviate the cognitive deficits associated with post-menopause state. Menopause state was induced in 7-8 weeks old female Wistar rats by surgical removal of ovaries (bilateral ovariectomy). At the age of 12 months, overiectomized rats were subjected to novel object recognition task (NORT) and social recognition task (SRT) for evaluation of episodic and social memories respectively. SUVN-D4010 was administered for 6-9 days prior to testing. Exploration towards object or juvenile rats and also discriminative indices were assessed. Following the cognitive evaluation, exposures of SUVN-D4010 in plasma, brain and CSF were assessed. Sub-acute treatment (6-days) with SUVN-D4010 reversed surgical menopause induced object memory deficits. Sub-acute treatment (9-days) of overiectomized rats with SUVN-D4010 reversed social memory deficits in a dose dependent manner. Significant improvement in discriminative index was observed. Efficacy was correlated with SUVN-D4010 exposures. SUVN-D4010 could be a

potential future promising therapeutic medication in post-menopause women associated dementia and AD so as to improve their health related QOL

Disclosures: G. Venkata Ramalingayya: A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **J. Tadiparthi:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **N. Ganuga:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **H. Talakanti:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **P. Jayarajan:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **S. Pandrinki:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **N. Patibandla:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **N. Muddana:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Rasheed Mohammed:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **R. Nirogi:** A. Employment/Salary (full or part-time):; nvsrk@suven.com.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.08/CCC11

Topic: H.01. Animal Cognition and Behavior

Support: Fondation de France Grant 00070721
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Title: Resting-state functional connectivity is correlated to memory performance in the developing brain

Authors: A. BOUYEURE[1], D. BEKHA[1], R. CHAUVIN[2], D. GERMANAUD[1], V. DELATTRE[1], G. VAROQUAUX[3], C. CHIRON[4], L. HERTZ-PANNIER[1], *M. NOULHIANE[5]
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Abstract: Introduction The medial temporal lobe (MTL) plays a pivotal role in memory. In adults, resting-state functional connectivity (FC) predicts memory performance [1] but little is known about this relationship in children and adolescents [2]. Here, we propose to fill this gap by examining if FC is correlated to memory performance in the developing brain. We focused our analyses on intra-MTL FC as the functional maturation of the MTL network is yet to be fully described. **Methods** Functional images of 30 subjects aged 7-17yo were acquired on a Siemens 3T. On a separate day, subjects underwent a battery of 11 memory tests covering episodic, working and semantic memory. After preprocessing of functional data, we built FC connectomes

using an atlas of manually-defined ROIs of MTL regions. Dimensionality of raw memory scores was reduced using PCA. Subjects' coordinates on each component were correlated to the edges between each nodes of the connectome using linear regression. Multiple comparisons were corrected with FDR at p=0.05. **Results** We retained 3 PCA components explaining 70.48% of the variance. Each component was mainly representative of a specific type of memory (Fig. 1a,b). Correlations between FC and age showed several significant age-dependent FC diminutions. Correlations between FC and PCA components evidenced negative correlations for the two first components. Adding age as a covariate of non-interest, no major changes were observed for the episodic memory component while there were no more significant correlations for the working memory component (Fig. 1c-e). **Discussion** We described age-dependent diminution of FC between MTL regions and showed that FC was negatively correlated to episodic memory at constant age as well as for age-related improvements. Hence, diminution of FC in the MTL could be linked to memory development. The extent of this diminution may explain episodic memory efficiency in children and adolescents at a given age. Future work will have to pinpoint the role of FC on memory development. 1. Wang et al. (2010), *Hippocampus*. 2.. Riggins et al. (2016). Dev. Cog. Neurosci.

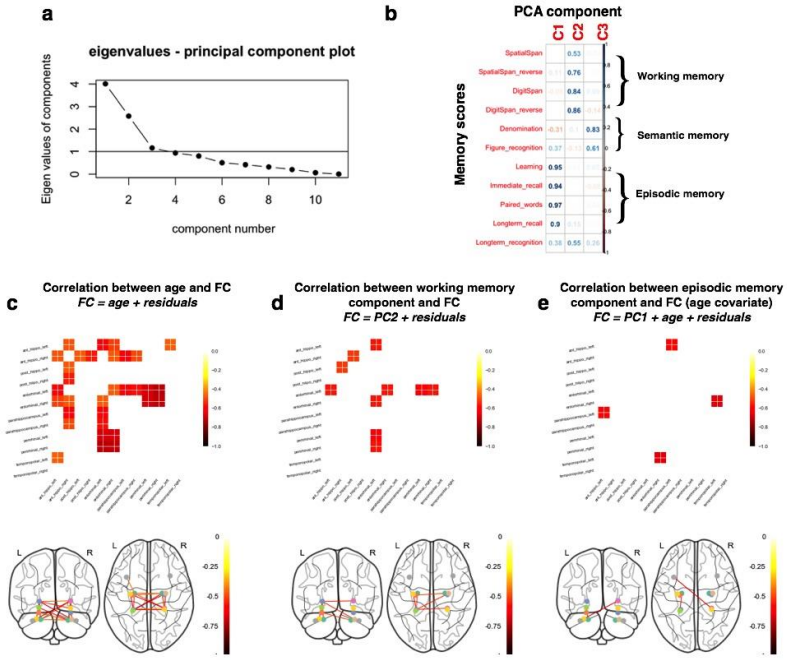

Figure 1: PCA and Regression results. a. Kaiser rule on the eigenvalues of PCA components retains 3 components. **b.** Loadings of memory scores on PCA components : component 1 is mainly representative of episodic memory variables, C2 of working memory variables and C2 of semantic memory variables. **c.** Significant correlations between age and FC of MTL ROIs after FDR correction. The correlations are represented as a matrix (top) or plotted on a glass brain (bottom). In both cases, the values of the significant correlations are plotted after conversion of the t-values to r-values. Only negative correlations were observed. **d.** Correlations between MTL FC and the second component of PCA (accounting for working memory), without age as a covariate. Only negative correlations were observed. **e.** Correlations between FC and the first component of PCA (accounting for episodic memory), with age as a covariate (results without age as a covariate are similar for this component). Only negative correlations were observed.

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Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIH R01NS085709
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Title: Identification of hippocampal subfields responsible for components of episodic memory

Authors: *B. M. COX[1], A. A. LE[1], B. G. GUNN[1], C. D. COX[1], N. R. HADIDI[1], J. QUINTANILLA[1], G. LYNCH[2], C. M. GALL[1]
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Abstract: Failure to properly encode episodes is a common feature of numerous neuropsychiatric and congenital intellectual disability disorders and is likely related to other cognitive problems. The hippocampus plays a central role in episodic memory formation by building codes needed for organizing sequences into a narrative about what happened, where particular features occurred, and the order in which they appeared ('what', 'where', and 'when'). Human and animal research indicates that the dentate gyrus, the first stage of hippocampal circuitry, receives semantic information ('what') via the lateral perforant path (LPP) projections from lateral entorhinal cortex, and spatial cues ('where') from the medial perforant path (MPP), which arises in the medial entorhinal cortex. However, it remains unclear how temporal information is processed or how the diverse information is integrated within the subfield(s) of hippocampus. To examine these questions, we used novel sequential olfactory tasks for mice that, as with human episodic memory, do not include explicit rewards or past training. Chemogenetic technology (i.e., DREADDs) was used to transiently silence discrete regions and pathways in hippocampal circuitry. The results point to a larger than expected role for the lateral entorhinal cortex and its LPP efferents to the dentate gyrus, and indicate that other subsystems have more specific involvement in encoding spatial information and temporal ordering.

Disclosures: B.M. Cox: None. **A.A. Le:** None. **B.G. Gunn:** None. **C.D. Cox:** None. **N.R. Hadidi:** None. **J. Quintanilla:** None. **G. Lynch:** None. **C.M. Gall:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Program #/Poster #: 324.10/CCC13

Topic: H.01. Animal Cognition and Behavior

Support: HHMI Janelia Research Campus

Title: Hippocampal replay of distinct contextual versions of the same sensory experience

Authors: *B. R. LUSTIG[1,2], Y. WANG[1], A. K. LEE[1], E. PASTALKOVA[1], S. ROMANI[1]
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Abstract: The same experience can result in very different memories depending on the context the experience was embedded in. For instance, the experience of driving home on the same road after a concert versus after a meeting at work is an example where internal states, shaped by the recent past, can color similar sensory experiences as very distinct episodic memories. Previously, most demonstrations of replay during sharp wave ripples (SWRs) in hippocampus have been replays of different sensory experiences, such as replay of the inbound or outbound traversal of a maze arm. Here we leverage a task design in which rats, undergoing the same sensory experience in a delay period, internally generate different sequential activity determined by the context shaped by recent arm choice. Analysis of population activity during SWRs found replay of the distinct contextually specific delay period sequences. These data provide a clear demonstration for replay of specific contextually differentiated experiences in rat hippocampus, a signature of episodic memory.

Disclosures: B.R. Lustig: None. **Y. Wang:** None. **A.K. Lee:** None. **E. Pastalkova:** None. **S. Romani:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Title: Replay of episodic memories in the rat

Authors: *D. PANOZ-BROWN, V. IYER, L. M. CAREY, IV, A. G. HOHMANN, J. D. CRYSTAL
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Abstract: Vivid episodic memories in people have been characterized as the replay of multiple unique events in sequential order. The hippocampus plays a critical role in episodic memories in both people and rodents. Although rats remember multiple unique episodes, it is currently unknown if animals *replay* episodic memories. Therefore, we developed an animal model of episodic memory replay. Here we show that rats can remember a trial-unique stream of multiple episodes and the order in which these events occurred by engaging episodic memory replay. We document that rats rely on episodic memory replay to remember the order of events rather than relying on non-episodic memories. Replay of episodic memories survives a long retention-interval challenge and interference from the memory of other events, which documents that replay is part of long-term episodic memory. Elsewhere, we show that episodic memory replay in rats is hippocampal dependent. Our approach provides an animal model of episodic memory replay, a process by which the rat searches its representations in episodic memory in sequential order to find information. Our findings support the view that rats can be used to model fundamental aspects of human episodic memory to both explore the biological mechanisms of memory disorders (e.g., Alzheimer's disease) and validate therapeutic approaches.

Disclosures: D. Panoz-Brown: None. **V. Iyer:** None. **L.M. Carey:** None. **A.G. Hohmann:** None. **J.D. Crystal:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Topic: H.01. Animal Cognition and Behavior

Support: DBTO/BCN/BJ/0402
DSTO/BCN/BJ/1102
DSTO/BCN/BJ/1297

JTT/MUM/INST/IIOS/201314/0033
CSIR-09/079(2590)/2012-EMR-I

Title: Hippocampus-dependent acquisition and rapid systems consolidation of new learning through elemental second-order conditioning during remote retrieval of contextual memories

Authors: *A. SINGH, S. KUNDU, V. SINGH, S. SAUMITRA, J. BALAJI
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Abstract: Second-order conditioning (SOC) plays a vital role in developing indirect associations between unconditional stimulus (US) and novel stimuli (conditioned stimulus, CS) encountered afterwards even in the absence of US. Sometimes a similar CS may be encountered long after the occurrence of primary conditioning between original CS and US and such delay could range from hours to weeks. In such cases when SOC occurs through remote retrieval of generalized primary conditioning memories while animals are exposed to a similar CS, it is not yet clear how does SOC take effect. To understand more about remote SOC, we perform experiments with C57/B6 mice (young adult males) in contextual fear conditioning paradigm. We find that SOC that occurs during remote configural retrieval of contextual memories has elemental nature and requires hippocampus for its manifestation. We also find that retrieval-based new learning resulting from SOC undergoes rapid systems consolidation even in absence of hippocampus. In our study, we incorporate three contexts A, B and C with more common elements between context A-B and B-C while there are less elements common between context A-C. Using discrimination paradigm, we establish the extents of feature overlap across the three contexts A, B and C. Further, using generalization paradigm with different orders of context exposure for testing remote retrieval, we demonstrate that ability to retrieve specific details and discriminate similar context could be intact post systems consolidation even after a month of training. Such remote retrieval with discrimination between training context A and similar context B is observed only when context A is tested before B. Notably, when animals are tested in a third context C, they show higher freezing in C for ABC testing order as compared to BAC testing order (control). We hypothesize that our observation of retrieval-associated new learning occurs in ABC testing order due to second order conditioning. We further explore the properties of such retrieval-associated new learning using hippocampal lesions at different time points along its acquisition. Based on our observations, we propose a theory to explain the occurrence of retrieval-associated new learning for specific testing orders during remote retrieval and identify neural correlates of such learning using immunohistochemistry. We also perform longitudinal in vivo imaging of dendritic spines in retrosplenial cortex to provide evidence for structural correlates of SOC based new learning in neocortex.

Disclosures: A. Singh: None. **S. Kundu:** None. **V. Singh:** None. **S. Saumitra:** None. **J. Balaji:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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DBTO/BCN/BJ/1102
DBTO/BCN/BJ/0402
DSTO/BCN/BJ/1297
JTT/MUM/INST/IIOS/201314/0033

Title: Structural correlates of NMDAR independent learning in retrosplenial cortex

Authors: *S. KUMAR[1], M. PRABOD KUMAR[2], S. SAUMITRA[3], B. JAYAPRAKASH[4]
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Abstract: It is currently thought that acquisition of related contextual memory does not require NMDAR activation. This phenomenon has been demonstrated in the water maze and contextual fear conditioning behavioural paradigms in mice. It has been shown that contextual learning induces spine clustering in the retrosplenial cortex (RSC).We used in vivo longitudinal imaging to visualize spine dynamics in RSC as the mice undergo contextual and related contextual learning across multiple days. Here, we contrast the spine clustering parameters between the novel and related contextual learning within individual mice.

Disclosures: S. Kumar: None. **M. Prabod Kumar:** None. **S. Saumitra:** None. **B. Jayaprakash:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Program #/Poster #: 324.14/DDD3

Topic: H.01. Animal Cognition and Behavior

Support: DBTO/BCN/BJ/0402
DSTO/BCN/BJ/1102
DSTO/BCN/BJ/1297
JTT/MUM/INST/IIOS/201314/0033

Title: Prior schema assists in acquiring complex multitude of information and acts as a substrate for emergence of novel solution through schema completion

Authors: *V. SINGH[1], S. KUNDU[1], B. JAYAPRAKASH[1], R. BHATT[1], S. RAMANADHAN[2], S. SHRIDHAR[1]
[1]Ctr. for Neurosci., [2]Dept. of Electrical Communication Engin., Indian Inst. of Sci., Bangalore, India

Abstract: Consistent related memories are stored in memory associative networks also known as “mental schema”. Neocortical structures have been shown to be involved in such cognitive processes, but no mathematical/statistical model has been tested to explain evolution of mental schema and its role in memory acquisition. In order to address this, we trained mice to learn same sets of flavour place associations (paired associates) in two different ways viz., i) Solitary Learning: Two sets of association are presented independently one after the other ii) Relational Learning: Second set is presented in relation to first set and. We discovered that only the animals that underwent relational learning were able to acquire both set of flavors. We have shown that older memories help in acquisition of new memories only if presented in a relational manner. Further we tested Bayesian based modelling approach on our acquired data and have gathered evidence that the memory acquisition in mice for our task follows Bayesian inference. We have also conducted additional experiments and found that only large sets of memories act as mental schema at remote time point while small sets of memories face interference and make animals performance worse.

Disclosures: V. Singh: None. **S. Kundu:** None. **B. Jayaprakash:** None. **R. Bhatt:** None. **S. Ramanadhan:** None. **S. Shridhar:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Program #/Poster #: 324.15/DDD4

Topic: H.01. Animal Cognition and Behavior

Support: MHRD fellowship

Title: Demonstration of high dynamic range two photon microscopy using single detector

Authors: *S. NA, SR[1], N. GURUSHANKAR[2], S. KUMAR[2], J. BALAJI[2]
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Abstract: Two-photon microscopy is an experimental tool to investigate neural correlates of brain function. Recently high dynamic range laser scanning microscopy using multiple detector channels has been demonstrated. However, such a setup is limited by shot noise and will not utilize the entire photon flux because of several emission optical elements in the path. Here, we report high dynamic range two-photon microscopy in-vivo using single detector by utilizing the entire photon flux. Two amplifier channels with low and high sensitivity were employed to obtain the scaling factor under a non-saturated regime. This improvement in image quality will be useful in depth imaging of neurons in-vivo.

Disclosures: S. Na: None. **N. Gurushankar:** None. **S. Kumar:** None. **J. Balaji:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.16/DDD5

Topic: H.01. Animal Cognition and Behavior

Support: Council of Scientific & Industrial Research (CSIR) India
DBTO/BCN/BJ/0402
DSTO/BCN/BJ/1102
DSTO/BCN/BJ/1297
JTT/MUM/INST/IIOS/201314/0033

Title: Generalization of temporal memory

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Abstract: Systems Consolidation is a process in which episodic memories which are dependent on the Hippocampus for acquisition and retrieval, gradually gain the ability to be retrieved independent of it. In this process, memories might lose richness of detail, and generalize the stimuli and contextual information. However, little is known about the nature of the temporal aspects of episodic memories and to what extent they are preserved or generalized during systems consolidation.Our current research aims to understand the consolidation of temporal memory, specifically that of temporal order memory. To this end, we have designed novel tasks where we can probe for temporal memory in mice. These paradigms include an Order-Place

association task, performed in an event arena and a compound tone fear conditioning task involving Tone-Order discrimination. These paradigms are designed such that they can be contrasted with comparable, established paradigms that lack an explicit temporal component. Further, these comparisons are important, since in the non-temporal version of these tasks, the precise time scales of consolidation are known. Using these tasks we have been able to quantitatively establish order learning in male C57BL/6 mice, by measuring their performance during probe trials. By probing for temporal-order memory at various time-points during the training/learning phase and after, where we attempt to quantify how much of the memory persists, we have been able to observe how this temporal-order memory evolves with time. Since the mice have been taught a sequence containing 4 events, and later, a 5-event sequence in a subsequent iteration, we are able to quantify, using their errors, how the well they discriminate events closer together in time and how their strategies evolve with subsequent training sessions. Further tests, with and without 'reminder' training sessions have also been performed to observe the effects of minimal re-training and priming on order memory. We have been able to show that a 'reminder' session is able to rescue a significantly deteriorated remote temporal order memory.

Disclosures: S. Shridhar: None. **V.P. Singh:** None. **S. Kundu:** None. **R. Bhatt:** None. **J. Balaji:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

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Title: Chemogenetic inhibition of episodic memory replay in rats

Authors: *V. IYER, D. PANOZ-BROWN, L. M. CAREY, IV, A. G. HOHMANN, J. D. CRYSTAL
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Abstract: Episodic memories have been characterized as the replay of multiple unique events in a sequential order. Profound impairments in episodic memory are a significant disabling

complication of several neurological diseases and disorders. Currently, there is a great need for accurate pre-clinical models that mimic these memory deficits observed in humans. Most existing methods used to create such models use lesions, toxins and gene knockouts which lack the ability to inactivate specific neuronal populations both selectively and reversibly. Therefore, we used chemogenetic inhibition of the hippocampus to temporarily impair episodic memory replay in rats. Rats first underwent extensive training on an episodic memory task where they were presented with a list of trial-unique odors, and reported, via their behavior, items that occupied multiple positions within the list. Next, a recombinant viral vector containing an inhibitory chemogenetic actuator (AAV8-hSyn-hM4Di-mCherry) was injected bilaterally into the hippocampus in all rats. After recovery, memory assessments were repeatedly conducted in all rats after receiving a dose of the chemogenetic activating drug, clozapine N-oxide (CNO, 10mg/kg i.p.) or a vehicle that served as the within subject control. Chemogenetic silencing of the hippocampus reversibly impaired episodic memory replay ($p<0.05$) while sparing other non-hippocampal dependent measures of memory and general odor detection, showing selectivity of this hippocampal-dependent impairment. Immunohistochemical analysis of all rats confirmed the presence of hM4Di-mCherry positive neurons in the dorsal hippocampus. The distribution of anti-mCherry immunofluorescence showed prominent labeling of the dentate gyrus and the mossy fiber pathway. Major labeling appeared in the dentate gyrus granule cell layer, hilus, mossy fibers, and CA3 stratum lucidum, which is the site of dense termination of mossy fibers. This experimental approach demonstrates for the first time a reversible model of episodic memory replay. It represents a unique paradigm for manipulating episodic memory that is currently unavailable in the field and could help further explore the role of hippocampal dysfunction in memory disorders like Alzheimer's disease.

Disclosures: V. Iyer: None. **D. Panoz-Brown:** None. **L.M. Carey:** None. **A.G. Hohmann:** None. **J.D. Crystal:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 324.18/DDD7

Topic: H.01. Animal Cognition and Behavior

Support: JSPS KAKENHI 15K09363

Title: Patterns of axonal collateralization of single neurons in layer III of the rat presubiculum

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Abstract: Connections among the hippocampal formation (DG, CA, subiculum), presubiculum (PreS) and entorhinal cortex (EC) are crucial for memory formation. Layer III cells of PreS provide strong projections to the superficial layers of the medial entorhinal cortex (MEC) in the rat. We have investigated that presubicular projections terminated in a band-like zonal area of MEC. The transverse axis of these zones was disposed parallel to the rhinal fissure. In the present study, we visualized the entire axonal processes of single presubicular layer III neurons in the rat, using in vivo injection of a viral vector expressing membrane-targeted green fluorescent protein (GFP). Anesthesia was performed with ketamine and xylazine. All experimental procedures were conformed to the guidelines for the case and use of laboratory animals (NIH). To facilitate the analysis, the hippocampal formation with adjacent cortices were flattened which allowed sections to be cut perpendicular to the septotemporal axis of them. By 3D-reconstruction of the axonal structures of presubicular layer III neurons in MEC, we found that there were several types of axonal branching patterns with some morphological features of their terminal arborization. Several layer III neurons (including both pyramidal and nonpyramidal neurons) provided two major axonal branches to MEC and each of them formed elaborate terminal arbors that seemed to face each other within layer III of MEC. To find the positional relationship between the soma and axon terminals, we represented them on the unfolded map of the entire PreS and EC. The width and axis of the area of terminal distribution resembled that of the band-like terminal field seen with massive-scale observation. Our results suggest that inputs from a single presubicular layer III neuron can directly affect each band-like zone in MEC.

Disclosures: Y. Honda: None. **T. Furuta:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

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DBTO/BCN/BJ/1102
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JTT/MUM/INST/IIOS/201314/0033

Title: Identification and segregation of neuronal ensembles of multiple memories using temporal expression dynamics of a single immediate early gene shows related memories are encoded in overlapping population

Authors: *M. PRABOD KUMAR[1], S. KUMAR[2], J. BALAJI[3]
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Abstract: Immediate early genes (IEGs) are widely used as a marker for neuronal plasticity. Yet, techniques to identify the temporal coupling of IEG expression to different behaviours or events (e.g. cellular compartment analysis of temporal activity by fluorescence in situ hybridisation (catFISH), Fos-tTA Tet-tag transgenic mice) are limited to in vitro applications and provide a snapshot of the different neuronal populations that were activated during behaviour. However, if one were to follow these populations in vivo then it amounts to several imaging sessions that are interspersed between behavioural tasks. This leads to anesthetizing the mice several times for identifying these neurons. Further, if one were to investigate the synchronous IEG activation of the neurons in an ensemble, it is harder and in many instances, not viable. Here, we model the dynamics of an IEG expression in vivo and experimentally show that this approach can be used to identify distinct neuronal subsets. The rationale is to use the kinetics of expression to estimate when the activity of the neuron was induced. We present a generalised theoretical framework of such a dynamical system. We show that the fluorescence measurement of cFOS-shGFP protein in the transgenic mice over time, from the onset of stimulus, is well fit to an analytical expression derived to describe the above model. Using this approach we obtain the general method by which we are able to distinguish between neurons that took part in multiple events that are separated in time, by looking at the level of fluorescence of individual neurons.

Disclosures: M. Prabod Kumar: None. **S. Kumar:** None. **J. Balaji:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

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Program #/Poster #: 324.20/DDD9

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Fellowship 202805/Z/16/Z
European Research Council grant ERC-2015-AdG, 694779

Title: Negative emotion disrupts the coherence of episodic memories

Authors: *J. A. BISBY[1], N. BURGESS[2]
[1]UCL Inst. of Cognitive Neurosci., London, United Kingdom; [2]UCL, London, United Kingdom

Abstract: Events are thought to be stored in episodic memory as coherent representations, in which the constituent elements are bound together so that a cue can trigger re-experience of all elements via hippocampal pattern completion. Negative events can influence memory in

complex ways, strengthening memory for emotional content whilst impairing associations between the content and its surrounding context, and in some situations resulting in severe memory disturbances as seen in posttraumatic stress disorder (PTSD). Here we examined the neural structures supporting the disruptive effects of negative emotion on memory coherence. During fMRI, participants viewed a number of person-location-object events encoded as overlapping pairwise associates. Half of the events including a negative element (e.g., an injured person), and memory was tested across all within event associations (e.g. present person, recall location). We show that the presence of a negative element at encoding reduces memory for associations between event elements, a reduction also seen for associations between two neutral elements that formed part of a negative event. Whilst neutral events were remembered in a holistic way, the presence of a negative element at encoding was found to reduce the coherence with which the multimodal event is remembered. In fMRI, we saw greater hippocampal activity for neutral but not negative events on the final encoding trial when events would be bound together, consistent with pattern completion and its disruption by negative elements. Further, we found that amygdala activity at encoding negatively correlated with subsequent associative memory accuracy and predicted reduced memory coherence. Our results highlight how the experience of negative events can disrupt both memory formation and the holistic manner in which they are remembered via opposing effects on amygdalar and hippocampal systems. These findings support a dual representation model (see e.g. Bisby & Burgess, 2017) and have important implications for the development and maintenance of memory disruptions in PTSD.
Bisby JA, Burgess N (2017) Differential effects of negative emotion on memory for items and associations, and their relationship to intrusive imagery. Curr Opin Behav Sci, 17 124-32. doi: 10.1016/j.cobeha.2017.07.012

Disclosures: J.A. Bisby: None. **N. Burgess:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: ERC starter grant "DEVSPACE"
MR/N026012/1

Title: The ontogeny of spatial memory consolidation during sleep

Authors: L. MUESSIG, M. LASEK, F. CACUCCI, *T. WILLS
Univ. Col. London, London, United Kingdom

Abstract: The ability of humans to encode and retrieve long-term episodic memories for past events does not develop until late childhood. It remains unknown whether the neuronal basis for such early-life amnesia lies with deficits in encoding, consolidation or retrieval. In rats, hippocampus-dependent learning emerges late, being absent before 3 weeks of age, and emerging slowly thereafter. Importantly, hippocampal place cells develop spatially localised firing before 3 weeks of age, leaving open the question of which changes in hippocampal circuits underlie the emergence of memory.
In this study, we aim to understand how the consolidation of spatial memories develops, using the offline 'reactivation' of place cell activity of previous experiences in population events (sharp wave ripples, SWR) during slow wave sleep (SWS), which is thought to be a candidate mechanism for memory consolidation. Reactivation is the increased tendency of neurons which fire together during experience to also be co-active during SWRs in post-experience sleep: reactivation following learning has been shown to correlate with performance on spatial memory tasks.
We recorded the activity of place cells in CA1 during exploratory behaviour in familiar and novel environments and their subsequent reactivation during SWRs in post-experience sleep, in young rat pups (aged 2.5-4 weeks) as well as in adult controls. Even the youngest animals show reactivation of previous place cell activity during SWS. However, the extent of reactivation was equal in both familiar and novel contexts, in contrast to adults, where exposure to a novel environment causes a significant increase in reactivation.
Because memory requires the association of sequences of events, in a second experiment we sought to investigate the emergence of place cell 'replay', defined as an ordered activation of a place cells during an SWR, tracing out a trajectory through the environment. We find that up to 3 weeks of age, firing during single SWRs does represent locations on the track, though less frequently than in adults. Importantly, the speed of replay trajectories was also significantly lower in pups, with most events representing static locations rather than trajectories through the environment.
These results indicate that while the basic mechanisms of consolidation in the hippocampus might already be present in young animals (i.e. offline reactivation of a previously active cell ensemble), the enhancement of reactivation by novelty, and the organisation of offline firing into sequences representing trajectories, may emerge later in development.

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Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: Wellcome
European Research Council

Title: After watching traumatic videos, wakeful rest and hippocampal activity have opposing effects on subsequent intrusive thoughts vs deliberate memory

Authors: L. D. HORLYCK[1], J. A. BISBY[2], *N. BURGESS[3]
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Abstract: Immediately following an event, offline processing is thought to support its integration into memory. Changes to these processes in the aftermath of trauma might lead to the occurrence of intrusive imagery, as in posttraumatic stress disorder (PTSD). According to dual representation theories this reflects an imbalance between weak explicit contextual processing and strong sensory/affective processing (e.g. reviewed in 1). To test this, we investigated the effects of brief wakeful rest following encoding of traumatic material on subsequent intrusive and explicit memory. Participants watched negative video clips immediately followed by wakeful rest or a working memory task, recorded any intrusive memories for 1-week using a diary and then returned for a recognition test for the clips. Brief wakeful rest reduced intrusive memory frequency but did not alter explicit memory performance.
In a second experiment, participants watched short negative clips (~30sec) in an fMRI scanner, with each clip followed by a wakeful rest period of similar duration. Participants again kept a diary to record intrusions of the footage and returned for a surprise recognition memory test. Results showed that subsequent explicit memory was associated with greater activity in entorhinal cortex and hippocampus both when viewing the clips and immediately following clip offset. In contrast, subsequent intrusive memory frequency correlated with increased amygdala activity, again seen during both viewing and rest periods. Further analysis showed a clear post-encoding increase in hippocampal activity at clip offset, which was greater for explicitly remembered clips (see also 2) but lower for clips that later intruded.
Our findings highlight the importance of post-encoding activity in facilitating memory formation and the way in which negative events might attenuate this process. The results further support a dual representation account in which intrusions are supported by amygdala-dependent strengthening of sensory/ affective representations and weakening of hippocampal processing to disrupt associative and contextual binding. The use of wakeful rest to boost hippocampal contextual processing might complement strategies aimed at interfering with consolidation of sensory representations (e.g. 3).
1. Bisby & Burgess (2017) Curr Opinion Behav Sci 17:124-32.
2. Ben-Yakov & Dudai (2011) J Neuroscience 24:9032-42.
3. Holmes et al. (2010) PlosOne 5:11.

Disclosures: L.D. Horlyck: None. **J.A. Bisby:** None. **N. Burgess:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: Sussex Neuroscience RTSG

Title: Functional populations in the pyramidal cell layer of hippocampal area CA1

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[1]Univ. of Sussex, Brighton, United Kingdom; [2]Univ. Col. London, London, United Kingdom

Abstract: A wide range of functional and physiological diversity has been reported among pyramidal cells in region CA1 of the hippocampus. The most widely studied subtype of pyramidal cells are place cells, neurons that respond in discreet spatial locations[1]. In the absence of spatial cues, some pyramidal cells show sequential firing during periods of locomotion[2]. Other cells have been identified as responding specifically to reward[3] and different frequencies of sound[4]. Currently it is unclear how these distinct functional types relate to one another - are they encoded by a single plastic population of cells, or by distinct subpopulations? Recent advances in two-photon (2P) calcium imaging allow concurrent recording of neural activity in large cell populations, with the additional advantages of precise spatial localisation and long-term stability. We used 2P microscopy to examine the activity of CA1 pyramidal cells in awake, behaving mice navigating through distinct virtual reality (VR) environments. Based on their activity profiles we classified cell as place cells, sequence-encoding cells, and other cell types. Using traditional and machine learning approaches we then investigate the relationship between the different cell types. Specifically, examining the extent to which individual cells predicted the firing of others in the population and their information content with respect to spatial location and sequence position. We were able to identify independent populations of place cells and sequence-encoding cells concurrently in CA1. Similar proportions of cells from both categories occurred as has been previously reported. However, contrary to previous reports, sequence-encoding cells in our experiment occurred in the presence of spatial cues. Additionally, we identified a third population of cells that were preferentially active during rest but did not encode repeatable sequences. The three types were not spatially clustered within dorsal CA1. In all cases, the interaction within functionally-defined populations was greater than between these populations. These data suggest that sub-populations of hippocampal pyramidal cells with distinct functional properties exist. *1. O'Keefe, J., and Dostrovsky, J. Brain research (1971). 2. Villette, V., et al. Neuron 88.2 (2015): 357-366. 3. Gauthier, J.L. and Tank, D.W. BioRxiv 207043 (2017) 4. Aronov, D., et al. Nature 543.7647 (2017): 719.*

Disclosures: D.M. Grijseels: None. **K. Shaw:** None. **C. Barry:** None. **C.N. Hall:** None.

Poster

324. Mechanisms of Episodic and Episodic-Like Memory

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Title: Recall memory in the object recognition task is dependent of the care given by the mothers

Authors: *L. DÍAZ[1], M. D. DORANTES-NIETO[2], A. UGARTE[2], A. TRUJILLO[3], C. CORTES[4], J. EGUIBAR[5]
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Abstract: We selectively bred two sublines from Sprague-Dawley (SD) rats in base of their spontaneous yawning frequency. High-yawning rats (HY) yawn 22 times/h and low-yawning rats yawn two times/h. These sublines also differ in their maternal care, because HY dams build nests of poor quality and perform atypical retrieving respect to SD and both sublines spent less time with their pups compared with SD dam. The mother, siblings and nest have great impact in the development of the newborn. In this sense cross-fostering is an adequate technique to evaluate the role of maternal care on behavioral traits in adulthood. We employed female rats from HY, LY and SD at three months of age that were reared by their natural mother (controls), and by the other two types of mother (cross-fostered groups), from these combinations we obtain seven groups with 6 subjects (Ss) in each group. All Ss were maintained under standard animal room conditions and with free access to rodent pellets and purified water. All experiments were done between 1000 to 1600. Using the object recognition task in an open-field arena, in the first trial Ss were freely allowed 5 min to explore two objects of the same form and weight (marble cube); after 30 min delay period one of the objects was changed with a different form: a triangle pyramid or a cylinder of marble with the same size and weight as the cube. All Ss allowed to explore the arena by 5 min, and 6 h later one of the objects changed and an additional 5 min free exploration allowed. Our results showed that in the short-term memory (30 min) LY females reared by SD (SD-LY) dams explored 70% more than LY raised by their natural mother (χ^2 = 50.4, $P \leq 0.001$), and if a HY dam was raised by SD dams their exploration scores decreased 42%

(χ^2= 18.4, $P \leq 0.001$). In long-term memory SD-LY dams increased 23% their exploration respect to control (χ^2 = 53.2, $P \leq 0.001$). On the other hand, SD produced in LY dams showed a reduction of 50% respect to the control (χ^2 = 25, $P \leq 0.001$). We conclude that the type of maternal care given is capable to induce changes in the memory capacities of the female rats in adulthood probably due to epigenetic mechanisms given by nest conditions.

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Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 325.01/DDD14

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Intramural Research Program

Title: Orbitofrontal cortex lesions disrupt anticipatory autonomic responses to reward magnitude in macaque monkeys

Authors: *J. HWANG, P. L. NOBLE, E. A. MURRAY
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Abstract: Neurons in the macaque orbitofrontal cortex (OFC) encode the sensory properties, magnitude and subjective value of expected and received outcomes, typically foods and fluids. Subjective value is reflected not only in neural activity, but also in autonomic responses. Indeed, both neural activity and pupil diameter changes, a measure of sympathetic autonomic arousal, are correlated with magnitude of expected reward (Mitz et al., J. Neurosci. Methods, 2017). However, previous research has not identified how the value coding in OFC is linked with autonomic arousal. To answer this question, we compared rhesus monkeys with bilateral excitotoxic lesions of OFC (N = 4) and unoperated controls (N = 4) on a reward magnitude task in which five visually presented images were assigned to five different fluid reward amounts (0, 0.2, 0.4, 0.8 and 1.6 ml). Monkeys were required to maintain fixation at the center of a monitor screen for the duration of each trial, which consisted of image presentation (cue period), an unfilled interval with no cue (delay period), and reward delivery. Monkeys received the amount of reward assigned to the single image displayed on that trial. Pupil size, which was continuously measured while the monkeys performed the task, served as our measure of autonomic arousal. To test whether the monkeys' pupillary responses differed based on anticipated reward amounts, we performed one-way ANOVA and calculated Spearman's rank correlation coefficients. The groups did not differ in the number of sessions required to exhibit a significant autonomic

response during the cue period within a single daily session or across 4 consecutive days. In addition, the pupil size change during both the cue period and delay period was positively related to the reward magnitude in both groups. Compared to the controls, however, monkeys with OFC lesions showed a late onset of differentiated pupillary responses during the cue period and a significant impairment in sustaining arousal during the delay period. At the same time, autonomic responses to unsignaled reward and to changes in luminance were intact, demonstrating that OFC lesions did not affect the basic physiology of the pupil. Our findings show that OFC is necessary for acquiring the normal pattern of autonomic arousal in anticipation of different reward magnitudes. In particular, the data suggest that subjective value representations in OFC sustain autonomic arousal for biologically significant events.

Disclosures: J. Hwang: None. **P.L. Noble:** None. **E.A. Murray:** None.

Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Whitehall and Brain and Behavior Foundations to C.M.G.
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Title: Orbital cortex activity encoding of associative information underlying goal-directed actions

Authors: *C. CAZARES[1], C. GREMEL[2]
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Abstract: The orbitofrontal cortex (OFC) is necessary for performance of goal-directed decision-making, with deficits observed in disorders such as alcohol dependence. However, whether OFC circuit activity contributes to associative information necessary for goal-directed control is not clear. Goal-directed actions are by definition under a strong action-outcome contingency control; actions are continually adjusted using feedback from prior actions until they are successful. Hence, OFC circuit activity may contribute to prior action history, confidence in the current decision, and successful execution of the appropriate decision. To investigate representation of goal-directed associative information within OFC, we developed a self-paced, un-cued modified version of the rodent Progressive Hold Down (PHD) task that requires a mouse to make a sustained single lever press response to earn a valued outcome. This allowed us

to observe ongoing action feedback behaviorally in a trial-by-trial manner, as both expected and delivered outcomes dictate adjustments in future lever-press duration. Using in vivo photometry to measure calcium activity in OFC projection neurons during behavior, our preliminary data show increased calcium transients prior to action onset. These OFC calcium transients prior to action onset were often of a higher magnitude when the future action performance was successful. In addition, we also observed increases in OFC calcium transients that were dependent on outcome delivery, but not outcome expectancy. Single unit in vivo recordings via chronic indwelling multi-channel electrodes showed up modulation and down modulation of single putative OFC neurons during the lever-press initiation and offset, as well as periods of sustained modulation throughout the duration of the action. This suggests that sub-populations of OFC neurons encode separate aspects of action-contingency information. Importantly, it appears that alcohol dependence modulates putative single unit encoding of action properties. Thus far, our results suggest the OFC encodes associative information including action feedback, and that alcohol dependence may disrupt such processing thereby hindering goal-directed decision-making.

Disclosures: C. Cazares: None. **C. Gremel:** None.

Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

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NIH BRAIN Initiative 1R01NS104923-01 from NINDS

Title: Nodal perturbation disrupts value representations and coherent neural dynamics across the fronto-striatal network

Authors: *J. I. SEDILLO, S. QIAO, B. PESARAN
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Abstract: The orbital frontal cortex (OFC) is anatomically interconnected with sensory, limbic, and motor-association areas. It has been shown to participate in multiple operations regarding valuation, reinforcement learning, and flexible cognitive function**.** We implanted two rhesus macaques with large-scale semi-chronic microdrives capable of simultaneous extracellular recording and intracortical microstimulation (ICMS) from multiple brain areas in the fronto-striatal network (FSN). We tested the hypothesis that the OFC encodes action-outcome value associations with effector-specific representations as part of the FSN. We trained two male monkeys to perform a reward-driven reinforcement learning choice task using a reward drift

model to assign reward magnitudes to two different stimuli with different shapes. This task assesses the monkey's ability to decode the varying reward signals and respond with either reach or saccadic effectors to implement a choice towards the target with optimal value**.** Choice performance using either reach or saccade consisted of immediate and delayed trials (1-1.5s) that were randomly interleaved (1:3) for each effector block. We used open-loop bipolar continuous tetanic ICMS to perturb multiple sites within the OFC to investigate its role in effector-specific valuation during behavior. We found that multiple sites in the OFC are involved with action-outcome value representations. For example, bipolar continuous 100 Hz tetanic ICMS (biphasic, charge-balanced 20 µA, 100 µs/ phase) in the medial OFC decreased reaction times ($P = .0170$, Wilcoxon rank sum test) for the delayed-reach condition and decreased reward sensitivity indicated by choice performance on the psychometric curve. In comparison, increased reaction times ($P < .0001$) and reward sensitivity was observed for the delayed-saccadic condition during stimulation in the same area. These perturbations indicate disruptions/enhancement of effector-specific value representations possibly encoding decision variables related to recent experience and response outcomes. Our evidence also shows topographically distinct value representations decoded from the beta band of local field potentials (LFP) in the lateral OFC and caudate. Furthermore, adaptive and flexible goal-directed behavior involves temporally precise coordination within task-relevant distributed neural networks. Our large-scale coverage allows the analysis of interactions between frontal and striatal networks during decision making. These analyses provide insight into coherent neural dynamics distributed across the FSN during a decision-making task.

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Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 325.05/DDD18

Topic: H.01. Animal Cognition and Behavior

Support: ANR NeuroEffort

Title: Value based decision making across ventro-medial Prefrontal Cortices in monkey

Authors: *E. C. LEVY[1,3], E. CHAVRET-RECULON[2], C. I. JAHN[4], S. BOURET[4,5]
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Abstract: All species adjust their behaviors by optimizing the ratio between costs and benefits. In complex species, action selection involves comparing the value associated with distinct

courses of actions, which rely upon the prefrontal cortex. More specifically, recent studies in humans have identified the ventromedial prefrontal cortex (VMPFC) as a key node for value-based decision making, but the underlying physiological processes remain unclear. Here, we used an electrophysiological approach in behaving monkeys to further understand the dynamic relation between neuronal activity in the vmPFC, evaluation and decision processes. We trained one monkey to perform a sequential cost-benefit choice task involving sequences of actions. Each trial starts with a visual cue indicating how many actions (bar presses) the monkey must perform on a given lever (left or right) in order to obtain a given reward (volume of juice). In a fraction of these trials, the monkey is offered a choice before the end of the sequence. The animal can choose to complete the initial sequence to obtain the associated reward (default option) or to switch to the alternative lever to perform the alternative options, defined by a given number of squeeze and a given reward size. This choice is indicated by explicit visual cues indicating the costs and benefits associated with each option, which the monkey selects by squeezing the corresponding lever. We conducted a preliminary analysis on 74 single VMPFC units (area 14). In agreement with previous studies most VMPFC neurons (59/74, 80%) encoded the monkeys willingness to work. The relation between VMPFC firing and engagement in the task encompassed several trials, reflecting a slow state function rather than an event-related function. In addition, many VMPFC neurons encoded the monkeys choice in the default vs alternative frame. Indeed, 27 neurons responded at the time of the choice cue (requiring the monkey to choose between default vs alternative option), vs only 16 at the cue signaling sequence onset, and requiring the monkey to engage in the sequence, or not. Moreover, half of VMPFC neurons (n=37) encoded the monkey's decision in the default vs alternative frame, especially around the time of the decision itself. Thus, the firing of VMPFC neurons is strongly associated with both the internal changes in willingness to work and with value-based decision making. Altogether, this data supports the idea that vmpfc activity is strongly related to a subjective and internal component of value based decision making and can predict choices. Future analysis will enable us to further charatcerize the nature and the dynamic of this relation.

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Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 325.06/DDD19

Topic: H.01. Animal Cognition and Behavior

Support: NIDA IRP

Title: Optogenetic inactivation of medial orbitofrontal cortex fails to affect economic choice in well-trained rats

Authors: *M. P. GARDNER[1], J. C. CONROY[1], C. V. STYER[1], T. HUYNH[1], G. SCHOENBAUM[2]
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Abstract: How humans and animals make choices when confronted with complex and diverse options remains an active area of research within neuroscience. One attractive hypothesis is that particular brain regions compress the complex feature space of each of the available offers to a single dimension of utility in order to make rational decisions between options. There has been considerable evidence that several frontal brain regions, in particular the orbitofrontal cortex (OFC), contribute to this process of value determination, yet much of this evidence arises from neural correlates measured through fMRI or single-unit recordings in humans and monkeys. To directly address whether OFC is necessary for making decisions between biologically relevant goods which differ across features and size, we inactivated the OFC of rats using halorhodopsin during the choice period of an economic choice task. The task was developed to mimic those used in primate single-unit recording studies showing neural correlates of value in OFC. We previously showed that lateral OFC is not necessary for successful behavior on the task. In fact, rats were able to continue to make decisions based not only on the amount of food available but on the type of food as well. There is also considerable evidence that the medial portion of the OFC (mOFC) is a critical region for computing the value of different offers. Here we show that inactivation of mOFC in rats (n = 6) using the light-sensitive hyperpolarizing protein halorhodopsin does not impact behavior on the task in well-trained rats. We further found successful manipulation of mOFC using halorhodopsin in the same rats as their behavior was disrupted on the progressive ratio task, a task previously shown to be mOFC dependent. This result, combined with our prior findings of lateral OFC inactivation, suggests that economic choices between offers with multiple different features likely depends on a value computation distributed across a network of several brain regions encoding a variety of pertinent associative information. We are currently looking at how OFC is involved in economic choice behavior when confronted with these choices for the first time under different conditions. Preliminary results suggest that normal OFC function becomes critical when rats are confronted with choices between offers which have never been experienced in the particular paired arrangement. This finding suggests that OFC might be necessary for determining the relationship between goods within a goods space, yet only during the initial exposure of the comparison.

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Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: 325.07/DDD20

Topic: H.01. Animal Cognition and Behavior

Support: R00AA021780
R01AA026077

Title: Functional influence of mediodorsal thalamic projections onto mouse lateral orbitofrontal cortex

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Abstract: Across species, different anatomical divisions of the mediodorsal thalamus (MD) project to and receive input from distinct prefrontal cortical regions implicated in different executive functions. While MD projections onto more medial and dorsal prefrontal areas have been studied in the context of various cognitive tasks, the functional influence of excitatory MD relay neurons that project to the lateral orbitofrontal cortex (lOFC) has not been explored in depth. We investigated the functional role of MD input onto the mouse lOFC during a decision-making task shown to be dependent on the OFC. This incentive learning task involves mice learning to leverpress for a rewarding outcome, experiencing a shift in motivational state and - importantly -- updating outcome value in the new motivational state through experience with the outcome. During an extinction test the following day, mice are expected to infer and use the updated representation of outcome value to control their leverpress actions. An intersectional virus strategy was used to chemogenetically attenuate MD --> lOFC projection neurons during the value updating epoch of the incentive learning task. Compared to fluorophore controls, mice with prior MD --> lOFC attenuation were impaired in their performance on the extinction test, suggesting an impairment in value updating following a state change. Thus, we hypothesized that excitatory MD --> lOFC input's influence over local lOFC circuit activity changes depending on motivational state. To examine this, we probed whether different motivational states alter presynaptic release from MD terminals onto lOFC neurons in a cell-type specific manner. Channelrhodopsin-2 (ChR2) was injected into the MD of transgenic mice that express a fluorescent reporter in parvalbumin-positive (PV) interneurons. Following chronic food restriction of experimental mice or free feed in control mice, whole-cell voltage-clamp recordings were performed from both pyramidal neurons and PV interneurons in the lOFC while MD terminals were photostimulated. Our preliminary data using paired-pulse or asynchronous release protocols suggest that there are state-dependent changes at the level of MD --> lOFC synaptic physiology. These studies contribute to our understanding of how distinct MD projections may be important for state-dependent decision-making.

Disclosures: E. Yalcinbas: None. **C. Gremel:** None.

Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant P20 GM113109-01A1

Title: Inactivation of the orbitofrontal cortex, basolateral amygdala, or mediodorsal thalamus during training impairs performance on a multiple-response/multiple-reinforcer operant devaluation task in rats

Authors: *H. FISHER, A. PAJSER, S. FOX, C. LONG, S. GILBERT, C. L. PICKENS
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Abstract: Devaluation is a task often used to model flexible goal-directed behavior, the ability to adaptively modify behavior when the value of a reinforcer changes. In rodents, there are many simplified versions of the devaluation task and the brain regions involved can differ depending on the task demands. We chose to use a multiple-response/multiple-reinforcer devaluation task that should require the basolateral amygdala (BLA), orbitofrontal cortex (OFC), and mediodorsal thalamus (MD). In order to determine the role of these brain areas in the learning the necessary associations, we inactivated each of these three brain regions during operant training and then tested the rats on devaluation without the brain areas inactivated. We implanted bilateral cannula into the BLA, OFC, or MD of male Long Evans rats. The rats then were trained on a multiple-response/multiple-reinforcer operant devaluation task. Five minutes prior to beginning each cued-trial training session, the rats were infused with either muscimol/baclofen (n= minimum of 6/group) or PBS (n=minimum of 8). We gave cued-trial operant training with lever-light compounds available during 40-sec trials. Two lever-light compounds were each associated with a different food pellet (earned for lever-pressing on an intermittent reinforcement schedule). Only one lever-light-food pellet combination was available during each training session. After the rats received four days of cued operant training, two days for each lever, each of the two reinforcers was devalued through selective satiety in two separate tests (one pellet sated in each test) and devaluation was assessed through choice tests in extinction. The control rats (PBS) showed a devaluation effect, but there was no devaluation in the BLA, OFC, or MD inactivation groups. These results show that the BLA, OFC, and MD regions are involved in learning the necessary associations to guide behavior after reward devaluation in our task. Future studies will determine how these brain regions communicate to support goal-directed behavior.

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Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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French National Institute for Agricultural Research (INRA) and AgreenSkills grant agreement number FP7-267196 to S.L.P.

Title: Noradrenergic modulation of the orbitofrontal cortex mediates flexibility of goal-directed behavior

Authors: *J.-C. CERPA[1,2], A. R. MARCHAND[1,2], M. WOLFF[1,2], S. L. PARKES[1,2], E. COUTUREAU[1,2]
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Abstract: For an organism, knowledge of the consequences of its actions and the ability to assign a value to these consequences are both crucial processes allowing an appropriate goal-directed response. The major role of prefrontal regions, e.g. insular and medial prefrontal cortices, for these processes has been very well described. However, the mechanism by which the organism quickly adapt this goal-directed response to unexpected environmental changes remains unknown. It is possible to study this ability using instrumental learning. Typically, during an initial phase, an animal must associate voluntary actions with the delivery of rewarding outcomes. Then, during a reversal phase, the animal must respond flexibly to a modification of these associations. Using this task and chemogenetic tools allowing specific inhibition of cerebral regions, we have recently demonstrated a crucial role of the ventrolateral orbitofrontal cortex (vlOFC) for flexible response adaptation during the reversal phase (Parkes et al., 2017). In the present study, we focused on the noradrenaline (NA) input to the vlOFC which has been commonly implicated in flexibility-requiring tasks. In a first experiment, using a toxin (anti-DβH saporin) we selectively depleted noradrenergic fibers in the vlOFC and showed a deficit of behavioral flexibility. Notably, this effect was not only specific to the reversal phase but also to vlOFC input since a similar depletion restricted to the medial portion of the prefrontal cortex had no effect. Using an intersectional chemogenetic approach aiming at selectively targeting the locus cœruleus (LC) input to the vlOFC, we are deciphering the time course of the involvement of this pathway during behavioural flexibility. Taken together, these results demonstrate a central role for noradrenaline input to the vlOFC in behavioural flexibility and reinforce the idea that the LC exerts a strong modulation of OFC functions.

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Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: 325.10/DDD23

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH097061

Title: Orbitofrontal neurons represent confidence irrespective of sensory modality and predict confidence-guided time investments

Authors: *T. OTT[1], P. MASSET[1], J. HIROKAWA[2], A. KEPECS[1]
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Abstract: Every decision we make is accompanied by a sense of confidence about its likely outcome. This sense informs subsequent behavior, such as investing more ―whether time, effort, or money― when reward is more certain. We previously showed that the firing of many orbitofrontal cortex (OFC) neurons encode statistical confidence about olfactory-discrimination decisions and OFC inactivation specifically impairs the ability of rats to optimally invest time waiting for reward. However, it is unknown if these neurons predict time investments and whether these neurons represent confidence across sensory modalities consistent with a metacognitive notion of confidence. Here we show that single OFC neurons represent abstract decision confidence and predict confidence-guided time investments. We trained rats to make choices based on evidence from two different sensory modalities (auditory discriminations or olfactory discriminations). After making a choice, rats had to wait in a choice port to obtain an uncertain, randomly delayed reward. The time rats were willing to wait for a potential reward provided a time investment, which reflected their decision confidence. Single OFC neurons encoded decision confidence and predicted rats' time investment trial-by-trial, seconds in advance of giving up on waiting. Furthermore, the same OFC neurons signal confidence and predict time investment irrespective of whether the sensory discrimination was olfactory or auditory. Orbitofrontal cortex thus contains a sensory-modality-general metacognitive representation of confidence useful for mediating confidence-guided economic decisions.

Disclosures: T. Ott: None. **P. Masset:** None. **J. Hirokawa:** None. **A. Kepecs:** None.

Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: 325.11/DDD24

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01MH097990

Title: Influence of DLPFC on OFC representation during decision-making

Authors: *Z. BALEWSKI[1], J. D. WALLIS[2]
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Abstract: Dysfunction of frontal cortex, including orbitofrontal (OFC) and dorsolateral (DLPFC) regions, has been implicated in many neuropsychiatric disorders, including mood disorders, obsessive-compulsive disorder, and addiction; many of these involve impaired decision-making. Pharmaceutical treatments, which broadly alter neural function, are often ineffective in reducing the prevalence or severity of mental illness. Brain-machine interfaces (BMIs) provide a more targeted manipulation of complex behaviors, for example to give paralyzed patients control of a computer or robotic arm. To implement these tools in the cognitive domain we first need to identify the computational processes implemented in frontal cortex. Specifically, we aim to understand how reward-predictive cues are translated into decisions. Previously our lab (Rich and Wallis, Nat Neuro 2016) trained a decoder to identify reward predictive cues on four value levels from ensembles of on average 10 primate OFC neurons. The decoder flip-flopped between the two available options while the subject made a decision. While the frequency and duration of these flips were predictive of choice behavior, there was no evidence of gradual ramping up toward the ultimately chosen option. OFC is anatomically connected to DLPFC, which may play a role in translating these vacillations into a decision. Using multi-site array electrodes in one subject, we simultaneously recorded OFC and DLPFC neurons while he selected between pairs of 16 cues using a lever. We trained multiple decoders on value and choice direction separately for both regions. With a more complex stimulus set, we continue to see flip-flopping in OFC based on value and no evidence of action information. In DLPFC we observe similar switching between the available options using either the value or action decoders. We are currently investigating whether DLPFC influences the vacillations in OFC, for example as an attention modulator, or instead “reads out” OFC serving as an accumulator for the ultimately chosen option.

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Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NIDA R21DA041791
NIMH R01MH097990

Title: Orbitofrontal-hippocampal interactions underlying reinforcement learning

Authors: *E. B. KNUDSEN[1], J. D. WALLIS[2]
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Abstract: The orbitofrontal cortex (OFC) is critical for learning and exploiting reinforcing stimuli in the environment. Orbitofrontal neurons exhibit responses to reward-predictive cues, but it is unclear how these responses arise. Recent experimental and theoretical work has positioned OFC as a computational substrate for modeling the abstract state-space underlying value-based tasks, much in the same vein as hippocampus' theorized role for spatial learning and memory. Despite this common theoretical underpinning, the interrelationships between these two distant regions remain poorly understood.

Using a simple reinforcement learning (RL) task, we identified a strong presence of theta phase resetting in OFC around critical events in the task. This resetting, prominent throughout a session, displayed a bistability, such that the degree of phase resets was significantly increased when subjects were required to update stimulus-outcome associations. To test the functional relevance of this signal, we disrupted it via temporally-linked, closed-loop microstimulation. This had the net effect of drastically reducing our subjects' ability to update value estimates for optimal task performance. There was no effect of stimulation on behavior if it was a) delivered during epochs when values were previously learned, b) delivered open-loop, or c) delivered at beta frequency.

We then recorded from hippocampus and OFC to determine if this theta signal had a common function. Indeed, the hippocampus and OFC showed a significant synchronization within the theta frequency band coincident with optimal behavioral performance and the emergence of stable value representations in OFC. Theta-linked hippocampal stimulation interrupted theta synchronization and disrupted behavior in an identical fashion to OFC stimulation. These results provide a causal link between OFC, hippocampus, and reinforcement learning, and provide crucial evidence for the role of hippocampal model-building in even the simplest RL behaviors.

Disclosures: E.B. Knudsen: None. **J.D. Wallis:** None.

Poster

325. Animal Cognition and Behavior: Decision Making: Orbitofrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: 325.13/EEE2

Topic: H.01. Animal Cognition and Behavior

Title: Value representations in the orbitofrontal cortex drive learning, not choice

Authors: *K. J. MILLER[1], M. M. BOTVINICK[2], C. D. BRODY[3]
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Abstract: Humans and animals make predictions about the rewards they expect to receive in different situations. In formal models of behavior, these predictions are known as "value representations", and they play two very different roles. Firstly, they drive choice: expected values of available options are compared to one another, and the best is selected. Secondly, they support learning: expected values are compared to rewards actually received, and future expectations are updated accordingly. The orbitofrontal cortex (OFC) is well established as a key region for representing and using value information, but its particular role remains the subject of heated debate. Does the OFC play a role in choice, in learning, or in both? Resolving this question has been difficult, because both ideas make similar predictions for typical laboratory tasks, in which the items to be learned about are identical to the items to be chosen between. In recent work (Miller, Botvinick, & Brody, 2017), we have adapted for rats a two-stage decision task from the human literature (Daw, et al., 2011) which breaks this identity, cleanly separating learning from choice. Electrophysiological recordings and optogenetic perturbations indicate that, contrary to prominent theories, the OFC does not directly drive choices. Instead, it supplies value information to a learning process that updates choice mechanisms elsewhere in the brain.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA039349

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National Science Foundation Cooperative Agreement No. DMR-1157490*

Title: Adolescent exposure to THC alters mean diffusivity in adult rat brain regions associated with learning and emotion

Authors: *R. J. DRAGONE[1], S. L. BLAES[1], S. C. WALL[1], M. M. BRUNER[5], L. M. COLON-PEREZ[2], A. W. BRUIJNZEEL[3], B. SETLOW[2], M. FEBO[4]
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Abstract: Cannabis use among adolescents is expected to increase as its use becomes legal in a growing number of states and countries. Despite this growth, little is known about the lasting impact of its chemical constituents on brain development. In this study, we sought to determine the impact of daily exposure to Δ9-tetrahydrocannabinol (THC) during adolescence on adult brain structure using a variety of MRI approaches.
Beginning on post-natal day 32, male and female Long Evans rats were given twice daily injections of vehicle or 2.5 mg kg^{-1} THC (i.p.) for three days, 5.0 mg kg^{-1} for 4 days, and 10.0 mg kg^{-1} for 4 days, for a total of 11 treatment days (as per Rubino et al. 2008, *Neuropsychopharmacology*). The treatment groups were the following: vehicle (n=8 females, 8 males); THC (n=8 females, 8 males). At 178 days of age, rats were sacrificed and brain tissue prepared for *ex vivo* imaging. Imaging data were collected at 4.7 Tesla using a two-shell 36 direction (6 low b value and 30 high b value) high angular resolution diffusion MRI (HARDI) sequence. Diffusion tensor images (DTI) were constructed using FMRIB software library (FSL), using DTIFIT. ROIs were selected a priori based on their known roles in various reward and cognitive functions. These were analyzed for estimates of fractional anisotropy (FA) and Mean Diffusivity (MD).
The results indicate prominent and sex-dependent effects of THC on DTI measures. In females, THC treatment during adolescence resulted in reduced MD values in hippocampal subregions and major white matter tracts, which suggest alterations in memory processing. In males, THC did not affect these regions, but instead reduced MD in nucleus accumbens and prelimbic cortex, which suggest effects related to reward seeking and substance use. In addition, ongoing work is taking advantage of the HARDI parameters used in the scans to conduct Neurite Orientation Dispersion and Density Imaging (NODDI) analyses.
The results of this work indicate that adolescent THC exposure alters brain developmental trajectories, which appear to differ between females and males. These imaging-based findings will help guide future behavioral assessments directed at memory and reward circuitry, and how these are differentially affected by THC in male and female rats.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Program #/Poster #: 326.02/EEE4

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH109548

Title: Contributions of the perirhinal cortex to spatial delay discounting

Authors: *M. KREHER[1], S. A. JOHNSON[2], J.-M. MIZELL[7], D. K. CHETRAM[1], D. T. GUENTHER[3], S. D. LOVETT[4], B. SETLOW[5], J. L. BIZON[8], S. N. BURKE[4], A. P. MAURER[6]
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Abstract: In order to optimize outcomes in the face of uncertainty, one must recall past episodes and extrapolate to the future by assigning values to different choices. This behavior requires an interplay between memory and reward valuation, functions carried out by activity across all brain regions. At the anatomical nexus of this interplay is the perirhinal cortex (PRC), in theory a hub integrating memory, reward, and prediction. The perirhinal cortex is densely directly connected to the amygdala and orbital frontal cortex (Burwell RD, Witter MP, & Amaral DG, 1995), regions that have been implicated in reward-based decision making. However, the PRC's role in value-based decision making, to our knowledge, has not been explored. Therefore, we tested the role of the PRC in a spatial delay discounting task, which allowed rats to choose between a 1-second delay for a small food reward and a variable delay for a large food reward, with the delay to the large reward increasing after delivery of each large reward and decreasing after each small reward. Thus, the rat could alternate sides to stabilize the delay or adjust the delay by consecutively choosing the same side (Breton YA, Seeland KD, Redish AD, 2015; Papale AE, Stott JJ, Powell NJ, Regier PS, Redish AD, 2012). When the PRC was bilaterally inactivated with the GABA(A) agonist muscimol, rats completed the task with a higher proportion of adjustments relative to controls (32% vs 8%; $P<.01$), indicating less stability in the time they were willing to wait for the large reward, and increased reaction times at the choice point of the maze. These results indicate that the PRC is required for stable valuation of reward and should be the target of further research on decision making.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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NIDA K99DA041493

Title: Sex differences in the relationship between risk-taking preference and escalation of cocaine self-administration in rats

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Abstract: Impaired decision making is known to be strongly associated with substance use disorders (SUDs). Previous work from our laboratory has shown that cocaine self-administration alters risky decision-making behavior, causing an increase in risky choice (risk taking). Furthermore, pre-existing individual differences in risk-taking behavior are positively correlated with subsequent cocaine intake. These studies are limited, however, in that only male subjects were used. Given the well-established sex differences in both risk taking and substance use, it is conceivable that the relationship between risk taking and cocaine self-administration may differ in females relative to males. To begin to address this hypothesis, male and female Long-Evans rats were first trained in the "Risky Decision-making Task" (RDT), in which they made discrete trial choices between a small, "safe" food reward and a large, "risky" food reward accompanied by increasing probabilities of mild footshock punishment.
After reaching stable performance, males and females underwent jugular catheter surgery followed by long-access cocaine self-administration (6 h, 0.5 mg/kg/infusion) for 14 days. There were no sex differences in total cocaine intake or in change in cocaine intake over days (escalation). There were also no significant correlations in males between risk taking and either total cocaine intake or escalation of cocaine intake. In contrast, although risk taking in females was not correlated with total cocaine intake, it was positively correlated with escalation of cocaine intake such that females who displayed greater risk taking (greater preference for the large, risky food reward) showed greater escalation of cocaine intake. The sex difference in this relationship between risk taking and escalation of intake is consistent with evidence that women progress from casual drug use to drug dependence more rapidly than males, but it also suggests that, at least at some doses, pre-existing risk taking may be a stronger predictor of the development of substance use problems in women than in men. Future experiments will extend these findings by examining whether cocaine self-administration causes similar increases in risk

taking in females as it does in males. Collectively, results from these experiments will have significant implications for understanding and treatment of impaired decision making in individuals with SUDs.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Program #/Poster #: 326.04/EEE6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH109548
McKnight Brain Institute

Title: Development of the spatial gradient along the dorsal-ventral axis of the hippocampus

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Abstract: The size of hippocampal place fields progressively increases from the dorsal to ventral region of the hippocampus (Jung et al., 1994; Maurer et al., 2005; Kjelstrup et al., 2008), leading to the hypothesis that there is a spatial gradient along the long axis of the hippocampus. Small place fields in the dorsal hippocampus are associated with spatial representation while broader fields in the ventral hippocampus facilitate emotional and homeostatic processing (Bannerman et al., 2004). Although the dorsal-ventral axis of transcription is differentiated at birth (O'Reilly et al., 2015), place cells and spatial selectivity do not appear for approximately 2 more weeks. Therefore, to understand the developmental trajectory of the spatial selectivity along the long-axis of the hippocampus, we characterized the expression of the activity-regulated immediate early gene, Arc, at ages P14 to P21. Pups underwent a two-epoch object exploration task, in which the position of two out of the four objects are swapped (Ramsaran, Westbrook, & Stanton, 2016). This design provides the capability to assess spatial selectivity as well as any potential correlates to object-place selectivity. Our preliminary data demonstrates that at P14, there is no significant difference in Arc activity between the dorsal and ventral regions of CA1, however by P21 a gradient is evident. In addition, this gradient is a result of increased expression of Arc in the dorsal region, as the activity in the ventral region remains relatively stable. Ongoing experimentation will seek to focus on the development of the spatial gradient in the CA3 region in addition to the previously studied CA1.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIA RO1 AG 049722
University of Florida, University Scholars Program

Title: Dissociable effects of advanced age on prefrontal cortical and medial temporal lobe ensemble activity

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Abstract: The link between age-related cellular changes within brain regions and larger scale neuronal ensemble dynamics critical for cognition has not been fully elucidated. The current study measured neuron activity within medial prefrontal cortex (PFC), perirhinal cortex (PER), and hippocampal (HPC) subregion CA1 of young and aged rats by labeling expression of the immediate-early gene Arc (Guzowski et al., 2001). 4- and 24-month old male Fisher 344 x Brown Norway rats were trained on an object-place paired association (OPPA) task that is dependent on this PFC-PER-HPC circuitry as well as an alternation task within the same testing apparatus. Although aged animals required more training to learn the object-in-place rule (Hernandez et al., 2015), all animals were trained to equivalent performance. The proportion of cells expressing Arc was quantified at baseline in a subset of rats sacrificed directly from the home cage, and following the OPPA and alternation behaviors in another subset. Additionally, the retrograde tracer cholera-toxin subunit B was injected into the prelimbic (PL) and infralimbic (IL) cortices within the PFC to identify cells within PER and CA1 that project to the medial PFC. Baseline Arc expression did not differ across age groups within CA1 or PER, but was elevated in aged rats relative to young within the PL and IL regions of the PFC. Within the CA1 of task-performing rats, no age-related differences in neuronal activity were observed in the entire neuron population or within CA1 pyramidal cells that project to PFC. Although behavior was comparable across age groups, behaviorally driven Arc expression was higher in the deep layers of both PER and PFC, and lower in the superficial layers of these regions in aged rats. Moreover,

age-related changes in activity levels were most evident within PER cells that project to PFC. These data suggest that the PER-PFC circuit is particularly vulnerable in advanced age.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Topic: H.01. Animal Cognition and Behavior

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K99/R00 NIDA to Caitlin A. Orsini
McKnight Brain Research Foundation to Jennifer L. Bizon
R01AG024671 to Jennifer L. Bizon
Pat Tillman Scholarship to Caesar M. Hernandez

Title: Female rats show greater impulsive choice than males in an intertemporal choice task

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Abstract: Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. All other things being equal, individuals prefer large over small rewards; however, individuals tend to more readily choose small over large reward options the longer they have to wait for the large reward (i.e., the value of the large reward is "discounted" by the delay to its delivery). Marked individual differences in intertemporal choices exist across the population, with preferences for small, immediate rewards (greater "impulsive choice") associating with many psychiatric disorders. While data from our lab (Orisini et al, 2016) and others strongly implicate sex and gonadal hormones in other aspects of decision making, such differences are poorly elucidated in the context of intertemporal choice. The goal of the current study was to characterize adult (4 mo.) male and female Fischer 344 × Brown Norway F1 hybrid (FBN) rats on an intertemporal choice task in which rats make discrete trial choices between a small, immediate reward and a large, delayed reward using a block task design. Estrous cycle was evaluated in female rats after stable baseline performance was achieved. Choice preference (% choice of the large, delayed reward) was used as the primary performance measure, and latency to respond during intermixed forced choice trials was analyzed as a measure of motivation to obtain the rewards. Compared to males, female rats

showed significantly greater preference for the small, immediate over the large, delayed reward (i.e., females showed greater "impulsive choice" than males). Consistent with less incentive motivation for the large, delayed reward, females also showed longer latencies to choose this option relative to males. Overall task motivation was not affected by sex, however, as males and females completed similar numbers of trials. These sex differences in intertemporal choice were also not secondary to differences in reward magnitude perception, as males and females showed equivalent preference for the large reward when there was no delay to its delivery. Finally, choice behavior in females was not altered across the estrous cycle. Considered together, these data demonstrate that female rats show greater impulsive choice than males, and suggest that sex differences in decision making may be a contributing factor to gender disparities across a range of neuropsychiatric disorders.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Title: Altered $GABA_B$ receptor signaling in basolateral amygdala may contribute to age-associated differences in intertemporal choice

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Abstract: The ability to choose adaptively among options that vary in time to arrival (i.e., intertemporal choice) is critical for navigating many aspects of everyday life. Most individuals will choose a large over a small reward in the absence of delays, but reliably "discount" the subjective value of the large reward if there is a delay imposed between the choice and its delivery. Greater discounting of large, delayed rewards (i.e., greater impulsive choice) is a hallmark of several neuropsychiatric disorders. In contrast, older adults exhibit less discounting

of delayed rewards compared to young adults (i.e., less impulsive choice). Impulsive choice is mediated by a network of limbic cortico-striatal brain structures, and recent findings indicate that the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) are particularly critical for regulating impulsive choice in young adults. Previous optogenetic and biochemical studies from our lab and others implicate altered excitability of BLA and mPFC in age-associated changes in intertemporal choice. The objective of the current study was to investigate specifically how changes in signaling at the extrasynaptic $GABA_B$ receptor contribute to age differences in intertemporal choice in Fischer 344 × Brown Norway F1 hybrid rats. In a first cohort of young and aged behaviorally naïve rats, RNA was extracted from tissue punches of the BLA and mPFC in order to evaluate expression of transcripts associated with excitatory and inhibitory signaling molecules using RT-qPCR. Transcripts for $GABA_B$ receptor subunits were significantly reduced in the aged BLA but not the aged mPFC relative to young adults. In additional experiments, cohorts of young and aged rats received surgically implanted guide cannulae targeting either the BLA or mPFC. After recovery from surgery, rats were trained on the intertemporal choice task. Using a within-subjects design, choice performance was evaluated following intra-cerebral infusion of either the $GABA_B$ receptor agonist, baclofen (0.03, 0.1, 0.3 µg/0.5 µl/hemisphere), or the $GABA_B$ receptor antagonist, CGP55845 (0.05, 0.15, 0.5 µg/0.5 µl/hemisphere). Baclofen infused into the BLA increased impulsive choice in both young and aged rats, whereas CGP did not alter choice performance in either age group. The effects appeared specific to the BLA as neither baclofen nor CGP55845 targeted to mPFC altered choice performance in either age group. Taken together, these data suggest that reduced $GABA_B$ receptor expression, particularly in the BLA, may contribute to age-associated decreases in impulsive choice.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Program #/Poster #: 326.08/EEE10

Topic: H.01. Animal Cognition and Behavior

Support: DARPA BTO Grant No. HR0011-17-2-0019

Title: Targeting GABAergic mechanisms to improve prefrontal cortical-mediated cognitive flexibility in a novel touchscreen-based reversal learning task

Authors: *L. ALTIDOR[1], T. S. GARMAN[1], S. RAMIREZ[1], A. M. CRIDER[1], D. G. LAMB[2], M. M. BRUNER[1], A. M. FINNER[1], E. W. DIRR[3], F. DELGADO[3], K. P. OLCZAK[3], A. P.

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Abstract: Cognitive flexibility is a core prefrontal cortical-dependent neurocognitive process that enables modification of one's behavioral strategy in response to a change in environmental contingencies. Reversal learning is a form of cognitive flexibility in which the learned reinforcement contingencies associated with a two choice discrimination are reversed (e.g., A+/B- becomes A-/B+). Therapies to enhance cognitive flexibility may have broad functional benefit to individuals engaged in some forms of learning (e.g., acquiring a new language) and may attenuate maladaptive behavior in conditions in which cognition is compromised. Based on previous work from our laboratory and others that implicates prefrontal cortical GABAergic signaling as critical for cognitive flexibility, the overarching goal of this study was to assess the efficacy of multiple approaches for modulating cortical GABAergic signaling on reversal learning. Adult male Brown Norway rats were trained in a novel reversal learning task in "touchscreen" operant chambers, in which visual stimuli are projected on a touch-sensitive video screen. In this task, rats initially received training sessions consisting of intermixed presentations of two pairwise visual discrimination problems (W+/X- and Y+/Z-). For each problem, touching the correct stimulus in each pair (W+ and Y+) earned a food pellet reward. Once rats learned to perform accurately on both problems (>80% correct on each), the contingencies were reversed for the stimuli in one of the problems, whereas they remained consistent for the other (W-/X+ and Y+/Z). In naïve rats, initial performance accuracy was markedly lower on the reversed problem in comparison to the consistent problem, but improved over the course of subsequent training. Rats were then tested in a within-subjects comparison of acute, systemic administration of 0, 1.0, and 2.5 mg/kg of the GABA(B) receptor agonist baclofen. Baclofen (2.5 mg/kg) significantly enhanced performance accuracy on the reversed problem compared to vehicle administration, with minimal effects on the consistent (non-reversed) problem. These results show that activation of GABA(B) receptors can enhance reversal learning, and in combination with previous findings from our laboratory (Beas et al., 2016, 2017), suggest that increasing cortical GABAergic activity can promote cognitive flexibility. Current experiments are evaluating whether electrical stimulation of the vagus nerve, which is an approved treatment for epilepsy, can similarly enhance reversal learning.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Topic: H.01. Animal Cognition and Behavior

Support: Defense Advanced Research Projects Agency (DARPA) BTO under the auspices of Dr. Douglas Weber and Dr. Tristan McClure-Begley through the DARPA Contracts Management Office Grant No. HR0011-17-2-0019

Title: Acute vagus nerve stimulation attenuates novelty-induced arc transcription in dorsal CA1

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Abstract: Vagus nerve stimulation (VNS) is currently an FDA-approved treatment for drug-resistant epilepsy, major depressive disorder, and migraine. Moreover, recent data have indicated that VNS may be beneficial for treating stroke (Kilgard et al., 2018), tinnitus (Tyler et al., 2017), and post-traumatic stress disorder (Noble et al., 2017), as well as for enhancing auditory discrimination (Engineer et al., 2017) and other cognitive functions (see Lamb et al., 2018). While the mechanisms of the clinical utility of VNS are not yet known, it is well established that VNS paired with sensory stimuli enhances cortical plasticity (e.g., Porter et al., 2012; Hulsey et al., 2016; Engineer et al., 2017; Borlan et al., 2018). Thus, it is likely that a potential mechanism of VNS efficacy is the ability of this treatment to modulate the expression of immediate-early genes, which are implicated in plasticity and known to be induced by behaviors associated with new learning. One such immediate-early gene is activity-regulated cytoskeletal (*Arc*) protein, which is involved in homeostatic synaptic scaling and hypothesized to be a nexus point for synaptic dysfunction in cognitive disorders (for review, see Shepherd and Bear, 2011). The current experiment investigated the extent to which VNS can modulate behaviorally-driven *Arc* transcription during two distinct epochs of novel object exploration in adult (4-months old) Brown Norway rats. Critically, because the distribution of *Arc* mRNA in the nucleus versus the cytoplasm occurs at distinct time points following neuron spiking, its subcellular location can reveal the activity history of neurons during two different epochs of behavior 20 min apart. This cellular compartment analysis of temporal activity by fluorescence *in situ* hybridization (catFISH; Guzowski et al., 1999) therefore enables distinct VNS parameters to be compared within an individual animal. Within the CA1 subfield of the dorsal hippocampus, high frequency VNS (60μs pulse width, 500mA, 50Hz, 0.8s train duration) paired with object exploration resulted in a significant decrease in the proportion of *Arc* positive cells following exploration when compared to animals that received no stimulation. This reduction in *Arc* expression was not observed when animals received low frequency stimulation during the behavioral epoch (60μs pulse width, 500mA, 2Hz, 20s train duration). These data suggest that VNS paired with salient behavioral events may operate to enhance plasticity by promoting the sparsification of active neural ensembles to increase signal-to-noise ratios.

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Poster

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Florida Department of Health 7AZ06
McKnight Brain Institute Fellowship
McKnight Brain Research Foundation

Title: Hippocampal, perirhinal, and lateral entorhinal contributions to mnemonic discrimination in young and aged rats

Authors: *S. A. JOHNSON[1,4], S. M. TURNER[1], K. N. LUBKE[1], K. E. FERTAL[1], A. P. MAURER[1,2], J. L. BIZON[1,4], S. N. BURKE[1,4,3]
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Abstract: Memory requires that similar episodes be represented distinctly. Notably, many symptoms of age-related memory loss appear to derive from a decreased ability to distinguish between similar events (e.g., Stark et al. 2013). In a rodent version of the mnemonic similarity task that tests this ability, we have shown aged rats are selectively impaired in distinguishing a learned target object from similar lure objects (Johnson et al. 2017), and that disrupting neural activity in the dorsal CA3 in young adult rats impairs mnemonic discrimination. Given work in animal models and, more recently, human functional neuroimaging studies, implicating the perirhinal and entorhinal cortices in age-related decline in mnemonic discrimination (Berron et al. 2018; Maurer et al. 2017; Reagh et al. 2018; Ryan et al. 2012), the present study investigated activation of neural ensembles across medial temporal lobe and hippocampal regions during mnemonic similarity task performance in young and aged rats. F344 x Brown Norway F1 hybrid rats (young adult 6-8 m, aged 26-30 m) were behaviorally characterized and trained on a target-lure LEGO object discrimination task in which feature overlap of a well-learned target object (S+) to lures (S-) was systematically varied (Johnson et al. 2017). To assess neural ensemble activation as it relates to mnemonic discrimination performance, rats completed two behavioral epochs with distinct versus similar objects, then brain tissue was rapidly extracted and prepared

for fluorescent in situ hybridization (FISH) against the immediate early gene Arc. The proportion of neurons expressing Arc was systematically counted from regions of interest across the lateral entorhinal cortex (LEC), perirhinal cortex (PRC), CA3, and CA1. Consistent with previous studies, aged rats showed a reduction in the proportion of neurons active during mnemonic discrimination in superficial layers of PRC. This effect was also observed in output layers of LEC. In contrast to medial temporal lobe regions, aged rats showed a greater proportion of neurons active in hippocampus, particularly in CA3 and the proximal portion of CA1. Of note, while the size of neural ensembles active across regions did not correlate with performance on behavioral epochs immediately prior to tissue collection, a greater proportion of neurons active in the proximal CA1 was observed in rats that showed better abilities discriminating similar objects over the course of initial behavioral training. Our results directly parallel findings from older adults and support the emerging view that circuit level dysfunction across the medial temporal lobe and hippocampus contributes to age-related memory loss.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Program #/Poster #: 326.11/EEE13

Topic: H.01. Animal Cognition and Behavior

Support: MH109548

Title: Laminar differences in velocity modulation of hippocampal local field potential

Authors: *S. D. LOVETT[1], J. P. KENNEDY[2], Y. ZHOU[3], Y. QIN[4], S. N. BURKE[5], A. SHEREMET[6], A. P. MAURER[7]
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Abstract: Local field potential oscillations, which arise from large-scale synaptic activity over a population of neurons, are hypothesized to play a fundamental role in the organizing the timing of single neuron action potentials to promote the formation of cogent cell assemblies (Lisman & Idiart, 1995). During active behavior and REM sleep, the hippocampal LFP is dominated by gamma oscillations (50-120 Hz) and the 4-12 Hz theta rhythm (Vanderwolf, 1969; Bragin et al., 1995). As the frequency and power of both these oscillations are modulated by running speed and other behaviors (Montgomery and Buzsaki, 2008; Ahmed and Mehta, 2012; Zheng et al., 2015), and theses oscillations are primarily generated by ionic flux related to synaptic activity,

then it stands to reason that increases in power are a consequence of more afferent input into the hippocampus.. While there is a well-defined organization of afferent input across the hippocampal laminae (Amaral and Witter, 1993), to our knowledge, there has yet to be an explicit investigation of changes in local-field potentials across layers of the hippocampus as a function of velocity. A simple hypothesis is that increased running velocity is associated with a uniform increase in all synapses independent of afferent location (e.g., radiatum power increases as much with velocity as the lacunosum-moleculare). Alternatively, the entorhinal cortex containing path integration-related information may eclipse the CA3 input field. These mutually exclusive hypotheses were tested in the current study.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Topic: H.01. Animal Cognition and Behavior

Support: McKnight Pre-Doctoral Fellowship
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K99/R00 NIDA
McKnight Brain Research Foundation
R01AG024671

Title: Aged rats do not use basolateral amygdala during outcome evaluation in an intertemporal choice task

Authors: *C. M. HERNANDEZ, III[1], C. A. ORSINI[2], C. C. LABISTE[1], A.-R. WHEELER[1], T. W. TEN EYCK[1], M. M. BRUNER[1], S. M. SINGHAL[3], C. J. FRAZIER[3], B. SETLOW[2], J. L. BIZON[1]
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Abstract: Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. Such decisions require integration of existing reward representations (prior experience) with valuation of the organism's current wants and needs (incentive motivation). Moreover, evaluation of the outcome received (is it more or less than expected) is critical for driving future choices. Prior studies in both humans and rodents show that relative to young adults, aged subjects are better able to delay gratification, and generally prefer large, delayed over small, immediate rewards. While the neural circuit changes that mediate these age differences in intertemporal choice are unknown, lesion and

electrophysiological studies consistently implicate the basolateral amygdala (BLA) in motivation and affective decision making. The current experiments used optogenetic approaches to determine the effects of temporally discrete BLA inactivation on choice behavior during an intertemporal choice task. Young adult (6 mo) and aged (24 mo) Fischer 344 x Brown Norway F1 hybrid rats were surgically implanted with guide cannulae targeting BLA through which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was delivered and optic fibers were implanted. Rats were subsequently trained on an adjustable-delay intertemporal choice task in which preference for small vs. large rewards was evaluated in the presence of increasing delays to large rewards. Upon reaching stable performance, light-induced BLA inactivation was performed using a within-subjects design such that BLA was inactivated at discrete phases of the task: the period before choice (deliberation), the delay interval prior to large reward delivery (delay), a 4 s period during reward (outcome) or the intertrial interval (ITI). BLA inactivation during the ITI, delay interval or large reward delivery had no effect on behavioral performance. In contrast, BLA inactivation during deliberation *increased* young rats' choice of the large, delayed reward, whereas BLA inactivation during the small reward outcome *decreased* their choice of the large, delayed reward. The effects of BLA inactivation during deliberation were replicated in aged rats, while there was no effect of BLA inactivation during the outcome phase of the task in aged rats. These data indicate that in young adults, there are multiple BLA circuits that exert opposing influences on decision making. Importantly, however, aged rats fail to use the BLA to process information about outcome to guide future choices. These data may help explain the robust age-associated differences in intertemporal choice evident across aging populations.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 326.13/EEE15

Topic: H.01. Animal Cognition and Behavior

Support: DARPA Contracts Management Office Grant No. HR0011-17-2-0019

Title: Effects of vagus nerve stimulation on selective attention in Brown Norway rats

Authors: *D. G. LAMB[1,6,2], T. S. GARMAN[3], S. RAMIREZ[3], A. CRIDER[3], M. M. BRUNER[3], E. W. DIRR[4], F. DELGADO[4], K. P. OLCZAK[4], A. P. MAURER[3,2,4,5], K. J. OTTO[4,2], S. N. BURKE[3,2], B. SETLOW[1,2], J. L. BIZON[3,2]
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Abstract: Selective attention is a prefrontal cortical-mediated executive function that serves as a building block for many aspects of higher-order cognition. Enhancement of selective attention may offer broad functional benefits across a range of cognitively challenging circumstances and for the treatment of cognitive disorders. Prefrontal cortical acetylcholine and norepinephrine have been particularly implicated in attentional processes, and vagus nerve stimulation (VNS) can modulate cortical levels of these neurotransmitters via projections through the nucleus tractus solitarius. In the current studies, the effects of VNS were tested in Brown Norway rats (~4 mo.) using a 5-choice serial reaction time task in which rats had to respond to brief presentations of visual stimuli in a touchscreen operant chamber. Within each test session, five stimulus durations (ranging from 0.7-0.05s) were presented in a randomized fashion. Under baseline conditions, rats showed a systematic reduction in accuracy with decreasing stimulus durations. On test days in which VNS (60μs pulse width, 500μA, 50Hz, 0.8s train duration) followed correct choices, rats showed a reliable improvement in accuracy at short stimulus durations compared to baseline (no stimulation) conditions. VNS further produced a reduction in trial omissions as well as an increase in premature responses, consistent with greater task vigilance. In contrast to these enhancing effects on performance, VNS impaired accuracy at long stimulus durations relative to baseline. The effects of VNS were compared with those resulting from systemic administration of either donepezil (an acetylcholinesterase inhibitor, 0.1, 0.3, 1.0 mg/kg) or atomoxetine (a noradrenergic transporter blocker, 0.3, 1.0, 3.0 mg/kg), which were assessed using a within-subjects design. In agreement with previous literature, both drugs enhanced accuracy relative to vehicle conditions, suggesting that the beneficial effects of VNS may act through these modulatory neurotransmitter systems. Funding: This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) BTO under the auspices of Dr. Douglas Weber and Dr. Tristan McClure-Begley through the DARPA Contracts Management Office Grant No. HR0011-17-2-0019.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

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Title: Perforant path fiber loss results in mnemonic similarity task deficits in rats

Authors: *S. M. TURNER[1], S. A. JOHNSON[1], J. J. FLINT[1], K. L. ROBERTSON[1], J. A. NICK[1], S. D. LOVETT[1], J. L. BIZON[2], S. N. BURKE[1], A. P. MAURER[1]
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Abstract: The observation that entorhinal input into the hippocampus declines in old age is well established across human studies and in animal models (Barnes and McNaughton, 1980; Yassa et al., 2011; Rogalski et al., 2012; Bennett and Stark, 2016). This loss of perforant path fibers is exaggerated in Alzheimer's disease and Mild Cognitive Impairment (Gómez-Isla et al., 1996; Kordower et al., 2001; Stoub et al., 2005), with additional research suggesting that perforant path integrity in cognitively normal adults is predictive of progression to Alzheimer's Disease and more generally of episodic memory impairment (Stoub et al., 2014). Together, this suggests that, at least in the early stages, diseases of pathological cognitive aging are cortical disconnection disorders (Hyman et al., 1984). However, evidence linking perforant path changes to cognitive decline has been largely correlational, as invasive mechanistic studies in humans are not feasible. Thus, the current project aimed to 1) Replicate the finding perforant path fiber loss in aged rats in the same data modality as used in humans - DTI, and 2) Test the causative role of perforant path fiber loss in behavioral decline by performing a unilateral knife cut to disconnect the entorhinal cortex from the hippocampus in the right hemisphere. Our preliminary data suggest a decline in perforant pathway fractional anisotropy between 6 and 28 months of age in Fischer 344 x Brown Norway F1 hybrid rats. When young male rats received a right hemisphere perforant path knife cut and were tested on the rat variant of the mnemonic similarity task (Johnson et al., 2017), there was a significant impairment in the abilities of lesioned animals to discriminate between objects with high levels of feature overlap. This deficit was not observed in the sham group that received a cut to cortex that did not involve white matter. Interestingly, a significant difference in mnemonic similarity task performance between the perforant path knife cut and sham group was not observed in female rats. Together these data support the view that perforant path fiber loss is a consequence of normal aging that is ubiquitous across species. Moreover, the integrity of perforant path fibers is critical for an animal's ability to resolve mnemonic interference.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

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McKnight Brain Research Foundation to SNB and JLB

Title: Normal aging increases susceptibility to human wild type tau in transentorhinal cortex

Authors: *J. A. MCQUAIL[1], S. A. JOHNSON[1], M. N. LITENSKI[1], S. GHAY[1], S. L. ROSSI[2], P. CHAKRABARTY[1], B. I. GIASSON[1], S. N. BURKE[1], P. R. RAPP[2], J. L. BIZON[1]
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Abstract: Intracellular inclusions comprised of hyperphosphorylated tau are among the earliest pathological features of Alzheimer's disease (AD), the most prevalent age-associated neurodegenerative disorder. Initially manifesting in area 35 of the transentorhinal cortex, tau pathology has been described as progressing in an anatomically directed manner, propagating to synaptically interconnected regions throughout the medial temporal lobe. Distinct from AD, these same neural circuits are highly sensitive to the effects of normal aging, exhibiting neurophysiological and synaptic changes that associate with memory loss. The overarching goal of the current study is to directly investigate interactions between aging and tau pathology using approaches that model the anatomical specificity of the human disease. Young adult (6 mo) and aged (24 mo) Fischer 344 × Brown Norway rats received a stereotaxic delivery of an AAV containing human wild type tau-eGFP (AAV-hWTtau) or eGFP alone (AAV-CON). Two months after surgery, sections from one hemisphere were processed for immunofluorescence to evaluate phosphorylation and conformational alterations in tau, using antibodies to AT8 and Alz50. Expression of eGFP was robust in area 35 across all groups and did not differ with age. In both young and aged rats that received AAV-hWTtau, immunoreactivity for AT8 and Alz50 was reliably detected in both area 35 and the monosynaptically connected CA1 subfield of hippocampus. In the AAV-hWTtau condition, eGFP neurons in area 35 of aged rats showed

increased AT8 in somatodendritic compartments, less AT8 in axons and markedly reduced soma size relative to young rats. The other hemisphere of each brain was cleared using iDISCO procedures and processed for immunohistochemistry to localize hyperphosphorylated tau (AT8). Using volume imaging, AT8 immunopositive cell bodies were visualized within area 35 and monosynaptically interconnected structures, including CA1. Consistent with observations from traditional histological sections, qualitative observations of cleared tissue confirmed that aged rats receiving AAV-hWTtau showed overall less AT8-immunoreactivity in axons compared to young rats in the same condition. Together, these observations indicate that aged neurons appear to have increased susceptibility to the deleterious effects of human wildtype tau and establish the methodology to detect 3-dimensional spread of tau pathology in the medial temporal lobe of aged rats. Ongoing work will apply quantitative anatomical and biochemical methods to compare abnormal tau species and synaptic integrity in area 35 and CA1 in this model.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 326.16/EEE18

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA036534

Title: Effects of inactivation of the lateral habenula on risky decision making

Authors: *S. L. BLAES[1], C. A. ORSINI[1], H. HOLIK[1], J. L. BIZON[3], B. SETLOW[2]
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Abstract: Cost-benefit decision making is critical for adaptive behavior, and impairments in decision making are associated with a range of psychiatric disorders. The lateral habenula (LHb) is a brain region thought to play a key role in some forms of cost-benefit decision making, potentially through its role in signaling “negative prediction errors” (which occur when the consequence of an action or event is less optimal than expected). Lesions or inactivation of the LHb cause alterations in some forms of decision-making, but its role in decisions involving risk of explicit punishment is unclear. To address this question, male Long Evans underwent surgery to implant bilateral cannulae targeting the LHb and were then trained in a Risky Decision Making Task (RDT) in which they made discrete trial choices between a small, “safe” food reward and a large, “risky” food reward accompanied by varying probabilities of footshock

punishment. Once stable performance was achieved, rats received microinfusions of baclofen/muscimol or vehicle into the LHb followed by testing on the RDT, using a randomized, within-subjects design. While inactivation of the LHb with baclofen/muscimol had no effect on choice of the large, risky reward in the group as a whole, rats' performance under vehicle conditions revealed a strong bimodal pattern of choices; some rats showed a strong preference for the large, risky reward ("risk-taking"), whereas others showed a strong preference for the small, safe reward ("risk-averse"). Separate analyses of the effects of LHb inactivation on choice performance in these two subgroups of rats revealed opposing effects on choice performance. Specifically, LHb inactivation reduced choice of the large, risky reward in the risk-taking subgroup, but increased choice of the large, risky reward in the risk-averse subgroup. Ongoing experiments are further evaluating whether these distinct effects of LHb inactivation reflect inherent differences in the recruitment of neural circuits during decisions that involve risk in "risk-taking" versus "risk-averse" subpopulations.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

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Program #/Poster #: 326.17/EEE19

Topic: H.01. Animal Cognition and Behavior

Support: Toyota Motor North America

Title: A mechanistic model of memory and schema consolidation for preventing catastrophic interference in neural networks

Authors: *T. J. HWU[1], J. L. KRICHMAR[1,2]
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Abstract: Humans and other animals develop mental schemas of their environments, allowing them to recognize different scenarios and behave appropriately according to the situation. The complementary learning systems theory suggests that schemas are acquired through a gradual learning system in the neocortex combined with a fast learning system via the hippocampus to consolidate episodes of experience (McClelland, McNaughton, and O'Reilly, Psych Review, 1995). However, it has been shown that information matching a preexisting schema can be learned very rapidly (Tse et al., Science, 2007). Although there exist theories of how schemas are stored and processed, we have an incomplete understanding of the neural mechanisms that achieve this. To address this, we created a systems level computational model of schema consolidation that examines the interactions of several brain areas. Replicating the experiment

from Tse et al., our model uses a multi-layer contrastive Hebbian network (CHN) to train paired associations (PAs) between food cues and their corresponding locations. We show that the representation of spatial layouts as schemas in the medial prefrontal cortex (mPFC) supports the retrieval of different PAs according to context. The model also suggests that the indexing behavior of the ventral hippocampus (vHPC) gates neurons in intermediate layers of the CHN depending on their involvement within the current schema. This causes the learning of a new schema to not interfere with the storage and recall of prior schemas. Furthermore, oscillations in the dorsal hippocampus (dHPC), which alternate between clamping and unclamping the output layer of the CHN, are necessary to drive learning. Finally, our simulations show the vital role of neuromodulation, as the locus coeruleus detects uncertainty in the mPFC according to how strongly information fits within a prior schema. It uses this to consolidate new information into an existing schema when consistent with a prior schema, and drive the encoding of this information into a new schema when it is inconsistent. The present work provides a mechanistic explanation of how schemas are formed and recalled. Moreover, the model provides inspiration for creating context-dependent memories and avoiding catastrophic forgetting in artificial neural networks.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 326.18/EEE20

Topic: H.01. Animal Cognition and Behavior

Title: Systemic administration of 5-HT_6 receptor agonist and antagonists at active and sub-active doses during memory consolidation and amnesia

Authors: *A. MENESES, L. APARICIO-NAVA
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Abstract: Serotonin or 5-hytryptamine (5-HT) $_6$ receptor antagonists have pro-memory and/or anti-amnesic effects. Certainly, not all researchers report pro-memory and/or anti-amnesic effects of 5-HT_6 receptor antagonists and agonists. These inconsistencies might be due to drug administration timing, memory task or memory phase used. To our knowledge serotonergic 5-HT_6 receptor tone remains little explored; hence, we are addressing it by testing systemic administration of 5-HT_6 receptor drugs with differential intrinsic activity. Thus, the antagonists SB-399885 (SB-399) and SB-357134 (SB-357) as well as the agonist EMD 386088 (EMD) at active and sub-active doses are tested in autoshaping Pavlovian/instrumental short- (STM) and long-term memory (LTM) and amnesia. Automatized autoshaping is bridging translational testing between rodents and humans, measuring memory, neural markers and pharmacological

effects. Both SB-399 (10.0 mg/kg) and SB-357 (10.0 mg/kg) increased CR% in STM and LTM and prevented decrements of scopolamine- or dizocilpine-induced. EMD at 1.0 mg/kg had did not affect STM but increased CR in LTM (24-h) and reversed STM induced-amnesia by scopolamine or dizocilpine. SB-399 (10.0 mg/kg) or SB-357 (10.0 mg/kg) prevented LTM (24-h)-amnesia. Systemically sub-active doses of SB-399 or SB-357 (both at 5.0 mg/kg) plus EMD (2.5 mg/kg) had no effect on STM but facilitated LTM (24-h) and prevented scopolamine-induced STM amnesia. SB-EMD co-administration di not alter the scopolamine- or dizocilpine-induced decreased CR; thus indicating that both drugs exerted their effects via 5-HT_6 receptor.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

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Program #/Poster #: 326.19/EEE21

Topic: H.01. Animal Cognition and Behavior

Support: Max Planck Society

Title: Neural activity suppression in the mediodorsal thalamus precedes the occurrence of hippocampal ripples

Authors: *M. YANG, N. LOGOTHETIS, O. ESCHENKO
Max Planck Inst. For Biol. Cybernetics, Tuebingen, Germany

Abstract: Highly synchronized oscillations, or ripples (~200Hz), are generated in the hippocampus (HPC) during awake immobility or non-REM (NREM) sleep and has long been suggested to mediate the hippocampal-cortical communication underlying memory consolidation. The medial prefrontal cortex (mPFC) receives direct input from the HPC and many mnemonic processes depend on these two brain regions. The HPC-mPFC pathway is considered critical for consolidation of declarative memory and is currently one of the most studied memory-related pathways. A memory-supporting network is, however, not limited by the HPC and the mPFC. The thalamic mediodorsal (MD) nucleus is likely a part of an extended memory network. The MD is reciprocally connected with the mPFC and has long been implicated in different mnemonic functions. Our fMRI-based mapping of the whole brain activity associated with ripples occurrence suggested that silencing of a subset of subcortical regions, including thalamus, may reduce interference for hippocampal-cortical communication (Logothetis et al., 2012).
We characterized neural activity in the MD around times of the hippocampal ripples in spontaneously behaving rats. Generally, the MD population activity was strongly suppressed around ripples. A substantial reduction of the MD firing occurred 0.4 - 2.4 sec (mean: 1.1 ± 0.1

sec) before the ripple peak and lasted for 2.1 ± 0.2 sec. Moreover, the degree of MD activity suppression correlated with the ripple amplitude. The ripple-associated decrease of the MD firing rate was the strongest and the most consistent during awake immobility. In contrast, during NREM sleep bidirectional modulation of the MD activity was observed: the MD firing was actually enhanced around ripples that were temporally coupled with sleep spindles, while it was decreased around spindle-uncoupled ripples. Our results suggest possible competitive interaction between the hippocampal-cortical and thalamo-cortical networks supporting 'off-line' and 'on-line' information processing, respectively.
Logothetis, N. K., Eschenko, O., Murayama, Y., Augath, M., Steudel, T., Evrard, H. C., . . . Oeltermann, A. (2012). Hippocampal-cortical interaction during periods of subcortical silence. Nature, 491(7425), 547-553. doi:10.1038/nature11618

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

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Program #/Poster #: 326.20/EEE22

Topic: H.01. Animal Cognition and Behavior

Support: NSERC-CREATE to KI
Alberta Innovates Health Solutions to MT and DRE
Canadian Natural Sciences and Engineering Research Council (Discovery grant) to MT and DRE

Title: Triggering k-complexes and spindles during NREM sleep in rats by electrical stimulation of deep cortex

Authors: *K. IYER, M. J. ECKERT, M. TATSUNO, D. R. EUSTON
Canadian Ctr. For Behavioural Neurosci., Lethbridge, AB, Canada

Abstract: Non-rapid eye movement (NREM) sleep is thought to play a key role in memory consolidation. Evidence suggests that the offline replay of memories occurs during oscillatory events in NREM sleep, specifically slow oscillations and sleep spindles. Previous studies have shown that transcranial direct current stimulation in both humans and rats results in better memory consolidation. However, the exact stimulus parameters which lead to the strongest memory enhancement have not been fully explored. Here, we tested whether pulsatile stimuli might be useful for triggering consolidation-related oscillations in the cortical local field potential (LFP) and how evoked responses varied as a function of sleep state. We delivered stimulation via bipolar electrodes located in deep layers of dorsal medial frontal cortex (Paxinos and Watson areas Cg1 and M2) and recorded electrical potentials via bipolar electrodes located

in M1 motor cortex for cortical LFP and just above CA1 for hippocampal LFP. Stimulation consisted of brief biphasic electrical pulses (500uA square pulse with 0.2 msec per phase, delivered every 3-sec) during slow-wave sleep (SWS) in four male Fisher Brown Norway rats. EMG (electromyogram) electrodes in the neck muscle were used to identify rest and waking states. LFP recordings obtained from the frontal cortex and hippocampus were used to divide the sleep periods into NREM sleep and REM sleep, based on theta(5-10 hz)/delta(1.5-4 hz) power ratio. LFPs were recorded during three epochs, a one-hour stimulation period and two one-hour no stimulation periods before and after ('pre-stim' and 'post-stim' periods). The pulsatile stimulation reliably triggered an evoked response in the cortical LFP. During slow-wave sleep, the stimulation-evoked LFP was visually similar to naturally occurring k-complexes followed by spindle activity. Quantitatively, we found that the rate of spindle occurrence during stimulation periods was significantly higher than during equivalent slow-wave periods in the pre-stim period before stimulation began. Qualitative observations suggested that the evoked response are state-dependent in that stimulation during waking states did not trigger spindles while stimulation during the transition from waking to SWS occasionally triggered high-amplitude spindles, a separate phenomenon from the low-amplitude spindles associated with memory consolidation. In sum, the results show that stimulation over frontal cortex with brief pulses can increase spindle density in a state-dependent manner. This method may be useful for future studies which attempt to boost memory via transcranial or intracranial stimulation.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

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Program #/Poster #: 326.21/EEE23

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust PhD studentship

Title: Modelling the influence of reward on offline activity: Replay of hippocampal-accumbens activity supports learning in a stochastic reinforcement learning task

Authors: *E. ROSCOW, N. F. LEPORA, M. W. JONES
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Abstract: Experience-dependent patterns of neural activity are replayed during periods of quiet rest and sleep. Replay is best-characterised in CA1 of the hippocampus, where substantial evidence shows that memory consolidation depends on this offline activity. Preferential hippocampal replay of activity related to rewarding experiences is reported to be coordinated with reactivation of reward-responsive cells in the nucleus accumbens following learning. This

distributed offline activity may underlie the integration of reward into memory, potentially improving learning efficiency.
To test this, we developed a stochastic, spatial reinforcement learning task for rats, in which rewards are delivered at each of three goal locations on a Y-maze with different probabilities. Successful learning depends on acquiring reward probability distributions by integrating reward information over many trials, as well as learning to alternate between goal locations rather than revisit one successively. The stochastic nature of the task allows reward outcome (delivery or withholding of reward) to be distinguished from reward prediction (high, medium or low expectation of reward).
6 adult male Lister hooded rats were trained daily on the task, and began performing significantly above chance after 33 trials ($p = 0.03$). With a moderate difference between reward probability at goal locations (75%, 50% and 25% respectively), rats reached a peak of 64% optimal behaviour after 6 hour-long training sessions. With a bigger difference in reward probability (87.5%, 50% and 12.5%), rats reached a peak of 74% optimal behaviour.
Behaviour was modelled using a Dyna-Q reinforcement learning algorithm, which updates estimates of the value of state-action pairs based on expected reward. The algorithm was trained to predict rats' actions on each upcoming trial based on the complete history of actions taken and rewards obtained up to that point, and parameters were optimised for each individual rat. The Dyna-Q model showed strongest predictive accuracy when endowed with replay between trials and between sessions, consistent with offline activity biased by reward contributing to learning in the face of uncertain outcomes.
We are now testing model predictions using chronically recorded multiple single-unit activity from dorsal CA1 of the hippocampus and the nucleus accumbens, during Y-maze training sessions and surrounding periods of rest and sleep.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Program #/Poster #: 326.22/EEE24

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH60670
UCLA Dept. of Integrative Biology & Physiology

Title: Effects of optogenetic activation of the locus coeruleus during sleep on hippocampal replay

Authors: *B. A. GROSS[1], K. SWIFT[2], M. FRAZER[1], M. MAHONEY[3], G. R. POE[1]
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Abstract: The locus coeruleus (LC), the main source of norepinephrine (NE) throughout the brain, is silent during rapid eye movement (REM) sleep and just before non-REM sleep spindles. We posited that these periods of LC silence are required for the incorporation of new memories into preexisting memory circuits. We have previously shown that preventing these sleep silent periods, via optogenetic stimulation of the LC, after a hippocampal-dependent altered learning task led to reductions in CA1 spindle density and REM theta power and a decrease in ripple-spindle coupling, which were correlated with poorer task performance. In addition, this LC stimulation resulted in CA1 spatial mapping abnormalities, i.e. lower place field stability and abnormal place field expansion. Here, we investigated the effects of our LC stimulation paradigm on sleep replay. Using variable length Markov chain (VLMC) models trained on firing sequences during sleep of identified place cells, we found that LC stimulated animals had approximately half the number of significant sequences during non-REM sleep compared to controls. In the control animals, roughly half of the significant sequences were forward or reverse replay of the run sequence—greater than 20 times the proportion of ordered replay occurring in the LC stimulated animals. These results provide further support for the importance of sleep-specific LC silent periods in accurate memory consolidation.

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Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

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Topic: H.01. Animal Cognition and Behavior

Support: DFG Grant "Cellular Mechanisms of Memory Consolidation" for Matthew Larkum
Advanced ERC Grant "Active Dendrites and Cortical Associations" for Matthew Larkum
Human Brain Project "Systems and Cognitive Neuroscience SGA1" for Matthew Larkum

Title: Parahippocampal feedback input to layer 1 gates dendrite-dependent learning in cortex

Authors: *G. DORON, J. SHIN, C. BOCKLISCH, M. VON HEIMENDAHL, M. BRECHT, M. LARKUM
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Abstract: The hippocampus (HPC) and related parahippocampal structures play a vital role in transforming experience into long-term memories that are then stored in the cortex, however the cellular mechanisms which designate single neurons to be part of a memory trace remain unknown. In order to examine associative cortical memory formation we developed a behavioral paradigm using cortical microstimulation in which rats and mice were trained to report the direct stimulation of somatosensory cortex (S1). Pharmacogenetic inhibition of perirhinal cortex (PRh) projections to Layer 1 (L1) of S1 as well as optogenetic activation of dendritic targeting interneurons during behavioral training resulted in learning deficits, suggesting a critical role of L1 in memory formation. We further investigated the cellular mechanisms of information transfer between PRh and S1 using juxtacellular recordings in PRh in awake head-restrained rats during learning. We found that firing and burst rates in deep layers of PRh is increased a few seconds after microstimulation in S1. Spectral analysis of local field potential (LFP) at a similar time window after microstimulation revealed an increase in theta frequency in PRh and S1 during this time window, suggesting a mechanism for information transfer between these regions during memory formation. Finally, we examined the role of feedback activity on microstimulation-learned engrams retrieval by generating somatic & dendritic input patterns in a single-neuron detection task following microstimulation learning. We found that simulated dendritic input was sufficient for memory retrieval. Overall, our data are consistent with dendritic-dependent information transfer and memory formation via cortical L1.

Disclosures: G. Doron: None. **J. Shin:** None. **C. Bocklisch:** None. **M. von Heimendahl:** None. **M. Brecht:** None. **M. Larkum:** None.

Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 326.24/EEE26

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1U19NS104590

Title: Ca^{2+} imaging of network mechanisms of long-term memory consolidation

Authors: *A. D. GROSMARK[1], F. T. SPARKS[2], M. J. DAVIS[3], J. ZHANG[1], A. LOSONCZY[1]
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Abstract: The mechanisms by which SWR-related activity lead to stable or unstable spatial-coding outcomes remains little understood. Moreover, limits on the sensitivity and speed of Ca^{2+}-imaging techniques, as well as the absence of well-defined Ca^{2+}-analogues of established biomarkers of 'offline' activity such the LFP-detected SWRs, have restricted the accessibility of

'offline' activity to Ca^{2+}-imaging. We have successfully developed and implemented combined chronic CA1 LFP recordings with simultaneous fast (60 Hz) two-photon Ca^{2+} imaging to stably track the activity of genetically identified mouse CA1 principal neurons over weeks of 'online' spatial behavior and 'offline' resting. I employ a behavioral paradigm designed to test the cross-day stability of CA1 'online' spatial representations as well as test for evidence of 'offline' replay. This project aims to predict the diverging cross-day spatial-coding stability outcomes of place cells by their recruitment to and replay in SWR events - to link long-term spatial memory to the 'offline' SWR-related replay activity thought to underlie memory consolidation. Our preliminary results recorded under this paradigm demonstrate: 1) that joint LFP recording and Ca^{2+}-imaging is an effective tool for studying fast neural dynamics, such as SWR-related responses, 2) stable and unstable cross-day spatial coding of CA1 place cells, 3) the first reported Ca^{2+}-imaging of SWR-associated place cell replay of a recent non-local spatial experience, and 4) that SWR-recruitment predicts long-term spatial stability outcomes. Ongoing work will directly relate the replay of memory ensembles to their spatial coding stability during treadmill running, and in turn relate these to various behavioral variables including memory performance and proximity to reward.

Disclosures: A.D. Grosmark: None. **F.T. Sparks:** None. **M.J. Davis:** None. **J. Zhang:** None. **A. Losonczy:** None.

Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 326.25/FFF1

Topic: H.01. Animal Cognition and Behavior

Support: Dutch National Research Agenda
Studienstiftung des Deutschen Volkes, Phd scholarship

Title: CA1 maintains working memory representation of stimulus identity during trace conditioning

Authors: *J. L. KLEE[1], F. P. BATTAGLIA[2]
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Abstract: Establishing associations between stimuli that are discontinuous in time is a central element of intelligent behavior but also poses a complex problem for neural networks. While a multitude of lesion studies have pointed towards the hippocampus as a key entity in enabling trace conditioning, a form of classical conditioning during which CS and US are non-overlapping, very little is known about the underlying neurophysiology. In this context, we

combine an appetitive auditory trace conditioning paradigm in head fixed mice with high density silicon probe electrophysiological recordings from the hippocampus CA1 region. We find that single cells in CA1 exhibit robust sensory evoked responses to sounds and reward as well as CS+ specific and learning dependent sustained responses during the trace interval. In addition, we find a learning dependent and CS+ specific increase in CA1 theta and gamma power during the trace period. Finally, we employ template matching to show that patterns of evoked responses after CS presentations are replayed during Sharp Wave Ripples and that this replay is stronger for templates representing the CS+. In combination, these results suggest that the hippocampus contributes to trace conditioning by maintaining working memory representations of stimulus identity, possibly enabled by increased replay of task relevant information during Sharp Wave Ripples.

Disclosures: J.L. Klee: None. **F.P. Battaglia:** None.

Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 326.26/FFF2

Topic: H.01. Animal Cognition and Behavior

Support: ISF 968-13 (SB)
ISF 1916-13 (SB)
National Institute of Psychobiology in Israel 110-14-15 (SB)

Title: Dissecting brain plasticity patterns of alcohol-memory dynamics - Formation, reconsolidation and extinction

Authors: *S. BARAK[1], H. LAUFER[2], Y. ASSAF[3,2]
[2]Sagol Sch. of Neurosci., [3]Dept. of Neurobio., [1]Tel Aviv Univ., Tel Aviv, Israel

Abstract: Alcohol relapse is often driven by cue-alcohol associative memories, thus, disruption of cue-alcohol memories is a potential therapeutic strategy for alcohol relapse prevention. Extinction of the cue-alcohol association by prolonged or repeated exposure to cues alone reduces craving temporarily, but the memory often recovers, evoking relapse. Current memory theories hold that memories undergo a transient instability period through a process termed reconsolidation, during which they become labile. Reconsolidation is triggered by memory reactivation, typically via a brief exposure to the cue alone. Therefore, procedural resemblance between extinction and reconsolidation may lead to non-effective relapse treatments. Here, we dissociated between the brain mechanisms underlying extinction and reconsolidation of alcohol-related memories. We used diffusion tensor imaging (DTI), which is considered a microstructural probe that identifies learning-induced structural changes. Mice were scanned

before and after the formation of a context-alcohol associative memory in an alcohol-conditioned place preference (CPP) procedure, followed by scans after a short (reconsolidation) or long (extinction) exposure to the context alone. DTI analysis revealed that the formation of alcohol-associated memories led to changes in the cortex and mesolimbic system, which was different between mice that learned the association and preferred the alcohol-associated compartment, compared to non-learners. Strikingly, extinction and reconsolidation processes led to differential brain plasticity profiles in several brain regions, which also displayed differential synaptic density and expression of plasticity-related genes. Our findings suggest that formation and extinction of alcohol-associated memories induce similar changes in brain plasticity. In contrast, reconsolidation affects brain plasticity in a fashion similar to non-learning. These results provide critical neurobiological evidence for the difference between formation, reconsolidation and extinction of memories.

Disclosures: H. Laufer: None. **Y. Assaf:** None.

Poster

326. Animal Cognition and Behavior: Executive Function: Learning and Memory II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 326.27/FFF3

Topic: H.01. Animal Cognition and Behavior

Support: World Premier International Research Center Initiative from the Japan Ministry of Education, Culture, Sports, Science, and Technology (MEXT)
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Research Foundation for Opto-Science and Technology
Japan Foundation for Applied Enzymology
Life Science Foundation of Japan

Title: Function of the adult-born neurons in memory consolidation during sleep

Authors: *D. KUMAR[1], I. KOYANAGI[1], A. C. RUIZ[2], P. VERGARA[1], Y. SUGAYA[2], S. SRINIVASAN[1], M. KASUYA[1], T.-S. YU[3], K. VOGT[1], M. MURATANI[1], T. OHNISHI[1], S. SINGH[1], C. M. TEIXEIRA[4], P. NONDHALEE[1], T. NAOI[1], T. J. MCHUGH[5], S. G. KERNIE[3], M. KANO[2], T. SAKURAI[1], M. YANAGISAWA[1], M. SAKAGUCHI[1]
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Cell Biology, Columbia Univ. Col. of Physicians and Surgeons, New York, NY; [4]Emotional Brain Institute, Nathan Kline Inst., New York, NY; [5]RIKEN Ctr. for Brain Sci., Saitama, Japan

Abstract: Mammalian sleep contains rapid eye movement (REM) and non-REM sleep, both could employ different mechanisms for memory consolidation. Previous reports showed that memory-associated odor stimulation during non-REM sleep enhanced memory consolidation[1]. In addition, boosting slow oscillations or inhibiting sharp wave-ripples during non-REM sleep potentiated or interfered with memory consolidation[2,3]. On the other hand, REM sleep deprivation inhibited memory consolidation[4]. However, the memory circuit that is responsible for memory consolidation during each sleep stage has not been clearly shown. We have shown that hippocampal adult-born neurons are incorporated in memory circuits after learning[5]. Therefore, we silence the activities of the adult-born neurons during specific stages of sleep after learning using optogenetics, which provides reversibility in intervention with higher time resolution and target specificity. The intervention reveals that the activities of the adult-born neurons is necessary for memory consolidation during specific stage of sleep.
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1. Rasch B et al., Science, 2007, v315, p1426
2. Marshall et al., Nature. 2006, v444, p610
3.Girardeau et al., Nat Neurosci, 2009, v12, p1222
4. Ravassard et al., Cerebral Cortex. 2016, v26, p1488
5.Arruda-Carvalho et al., J Neurosci., 2011, v31, p15113

Disclosures: D. Kumar: None. **I. Koyanagi:** None. **A.C. Ruiz:** None. **P. Vergara:** None. **Y. Sugaya:** None. **S. Srinivasan:** None. **M. Kasuya:** None. **T. Yu:** None. **K. Vogt:** None. **M. Muratani:** None. **T. Ohnishi:** None. **S. Singh:** None. **C.M. Teixeira:** None. **P. Nondhalee:** None. **T. Naoi:** None. **T.J. McHugh:** None. **S.G. Kernie:** None. **M. Kano:** None. **T. Sakurai:** None. **M. Yanagisawa:** None. **M. Sakaguchi:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.01/FFF4

Topic: H.01. Animal Cognition and Behavior

Support: N00014-12-0850 from Office of Naval Research

Title: Memory interactions across wakefulness and sleep: Consolidation and reconsolidation of auditory classification learning in a songbird

Authors: *T. P. BRAWN[1], H. C. NUSBAUM[2], D. MARGOLIASH[3]
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Dept. of Psychology, Chicago, IL; [3]Organismal Biol. and Anat., Univ. of Chicago Dept. of Organismal Biol. and Anat., Chicago, IL

Abstract: Memory consolidation strengthens and stabilizes new memories, a process that benefits from sleep. We have shown sleep-dependent consolidation in starlings operantly trained to classify novel starling songs. Classification accuracy improved after sleep but not after waking retention. Learning two similar classification tasks produced interference that impaired performance on both tasks after waking retention but recovered after sleep. Here, we examine how memories are maintained in the presence of multiple interfering stimuli encountered over one or more days as well as the relationship between learning, sleep structure, and post-sleep memory. In the first study, starlings were trained and tested on one or two auditory memory classification tasks and retested at later times in the day. Starlings that only learned one task exhibited stable performance across the day. In contrast, starlings that learned both tasks showed impaired performance on both, but with asymmetrical effects such that retroactive interference developed during the learning of the second task whereas proactive interference developed subsequent to learning the second task. Next, we examined whether sleep-consolidated memories could be destabilized by memory reactivation and reconsolidated by sleep. Starlings were trained on one task and retested at multiple time points over the next 3 or 5 days. Starlings were also trained on additional classification tasks on the subsequent days. We found that sleep-consolidated memories were destabilized and impaired if the interference was encountered after, but not before, the memory of the first task was reactivated by retrieval, and that sleep reconsolidated the impaired memory. Finally, we examined the structure of starling sleep in relation to task performance. Starlings were trained on one or two classification tasks and retested after waking and sleeping retention. We implanted starlings with EEG electrodes and chronically recorded EEG and infrared videos for 56 hours during each experimental session. Starlings expressed a mammalian-like pattern of sleep characterized by initially high levels of SWS that decreased across the night and initially very low levels of REM sleep that increased. Critically, classification training led to an increase in SWS during the first hour of sleep that correlated with post-sleep performance improvements. This series of studies indicates that long-term memory formation involves a dynamic process of sleep-dependent consolidation, use-dependent destabilization, and sleep-dependent reconsolidation.

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Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.02/FFF5

Topic: H.01. Animal Cognition and Behavior

Support: ONR MURI N000141310672
ONR MURI N000141612829
University of Arizona Undergraduate Biology Research Program

Title: Targeted memory reactivation during sleep facilitates spatial memory consolidation in rats

Authors: *E. E. HOWARD, M. CONTRERAS, B. HARPER, E. ARMSTRONG, R. PADGETT, J.-M. FELLOUS
Psychology, Univ. of Arizona, Tucson, AZ

Abstract: Following acquisition, new memories undergo a time-dependent consolidation process. Many human and animal studies suggest that consolidation involves spontaneous memory reactivation during specific phases of sleep. Recent studies have focused on the selective reactivation of memories by exposing subjects to learning-associated cues, such as auditory or olfactory stimuli, during non-rapid eye movement sleep. However, the mechanism by which targeted memory reactivation modulates memory consolidation is not fully understood. In this study, we investigated whether auditory cueing during post-learning sleep influenced spatial memory consolidation and recall performance in rats. Adult male Brown Norway rats were chronically implanted with 14-tetrode hyperdrives targeted to dorsal CA1 of the hippocampus with local field potentials in the medial prefrontal cortex. We trained rats to receive rewards from peripheral feeders on an open-field maze. During the learning phase, a subset of feeders was rewarded, and a sound was played at these locations. After the animals learned the cued locations, the sound was played again during sleep. Rats completed a distractor task on the maze, followed by another sleep session, and memory was tested during a subsequent recall phase. Conditions with no sound or a different sound played during post-learning sleep were used as controls. Preliminary findings show that the same sound condition facilitated memory consolidation compared to the other conditions. This finding suggests that playing the same learning cue during sleep strengthened the spatial memory for the particular set of locations associated with this cue. We investigate the effect of this targeted reactivation on sharp-wave ripple and sleep spindle densities, as well as cue- and oscillation-associated cell activity. These results may provide insights into potential applications of targeted memory reactivation to normal and pathological memory consolidation.

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Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

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Program #/Poster #: 327.03/FFF6

Topic: H.01. Animal Cognition and Behavior

Support: VA Merit 5I01BX002661-03

Title: Can we erase fearful memories? A role of sleep

Authors: *R. SHARMA, P. SAHOTA, M. THAKKAR
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Abstract: Purpose: Newly formed memories are labile initially, but through the process of consolidation, they can enter permanent stores and become resistant to disruption or interference. Permanently stored memories can be again made labile through a process of reactivation. Reactivated memories can again become resistant to disruption or interference through the process of reconsolidation. Sleep is a requisite for memory consolidation. Is sleep necessary for reconsolidation? **Methods:** To address this question, we used male C57BL/6J mice and exposed them to contextual conditioning [conditioned stimulus (CS) = Context A; unconditioned stimulus (US) = foot shock)] followed by fear reactivation on Day 2. During reactivation, a set of mice were exposed to paired (Context A; CA group) or neutral (Context B; CB group) context without any US for 2 min. Percent time spent in freezing behavior was measured. Subsequently, one subset of mice, from each group (CA-SD and CB-SD groups), underwent sleep deprivation. The second subsets (CA-NSD and CB-NSD groups) of mice were allowed to sleep. On the following day (Day 3) fear memory recall testing was performed by exposing all four groups to CS (without US) for 12 min. Percent time spent in freezing behavior was monitored. **Results:** Two-way ANOVA suggested a significant main effect of context and sleep deprivation. Subsequent Bonferonni's post-hoc test suggested that only mice in the CA-SD group showed a significant reduction in freezing during fear memory recall testing. **Conclusion:** These results suggest that sleep is necessary for reconsolidation.

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Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

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Program #/Poster #: 327.04/FFF7

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1R15GM122058-01

Title: The effects of sleep deprivation on stress granules in *Caenorhabditis elegans*

Authors: *M. K. DOUGHERTY, C. SAUL, M. NELSON, J. C. TUDOR
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Abstract: Stress granules (SGs) are non-membrane bound aggregates of messenger ribonucleoprotein. It has been shown in cells *in vitro* that suppression of the mammalian target of rapamycin (mTOR) pathway and its non-mammalian orthologue target of rapamycin (TOR) is associated with an increase in SG formation. It has also been shown that the mTOR pathway is suppressed in response to sleep deprivation in mice. Despite the possible connection via the TOR/mTOR pathway, there has not been any previous evidence directly linking sleep deprivation with SG formation. Our present investigation uses the microscopic, transparent, and genetically tractable nematode, *Caenorhabditis elegans* as a model for examining SG formation in response to sleep deprivation. *C. elegans* experience two different types of sleep, developmentally-timed sleep and stress-induced sleep. Developmentally-timed sleep occurs between the different larval stages of the worm, while stress-induced sleep occurs in response to a stressor, such as heat or UV shock. These different types of sleep are mediated by different mechanisms, and mutant strains have been developed that are deficient in the mediators of each type of sleep. We developed two novel strains of *C. elegans* that model sleep deprivation that have GFP-labeled TIA-1 protein, a key component of SGs. Through analysis and quantification of SG levels in the sleep-deprived mutant and the sleeping wildtype, we analyzed the impact of sleep deprivation on SG formation. Preliminary imaging shows an increase in SG formation after UV stress, and current work involves imaging sleep-deprived animals. This work will explore novel mechanisms by which sleep deprivation affects neuronal function.

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Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.05/FFF8

Topic: H.01. Animal Cognition and Behavior

Title: Low acetylcholine during early sleep is crucial for motor memory consolidation: Support for the synaptic homeostasis theory

Authors: *S. INAYAT, .. QANDEEL, M. NAZARIAHANGARKOLAEE, S. SINGH, I. Q. WHISHAW, M. MOHAJERANI
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Abstract: The study investigated the contributions of Acetylcholine (ACh) synaptic activity in relation to the synaptic homeostasis theory of sleep-related memory storage. We hypothesized that during the early phase of sleep, characterized by slow wave electroencephalographic activity and reduced ACh tone, a downscaling of overall synaptic strength happens that improves synaptic signal-to-noise ratio and facilitates motor memory consolidation. Therefore, upregulation of ACh levels during early sleep would disrupt the consolidation of motor

memories. To test this hypothesis, mice were trained and then evaluated on two motor tasks; rotarod and skilled-forelimb reaching. For the rotarod task, 58 C57 Black/6J (wild-type, WT) and 17 transgenic mice were used. Mice were trained on rotarod on day 1 and immediately after motor training, ACh was either upregulated or downregulated for the subsequent post-learning sleep period. In WT mice, physostigmine was used to increase ACh levels while a combination of scopolamine and mecamylamine was used for decreasing ACh levels. In transgenic mice clozapine-N-oxide was used to decrease ACh levels. A memory test given on Day 5 following training showed that increasing ACh for post-learning sleep was associated with poorer performance while decreasing ACh levels resulted in normal motor performance. As a control, increasing ACh levels in post-learning sleep 24 hours after training also did not disrupt performance. Oxotremorine and nicotine were used to selectively activate muscarinic and nicotinic ACh receptors during post-learning sleep and showed a relatively larger involvement of muscarinic ACh receptors compared to nicotinic ones on motor performance. For the skilled-forelimb reach task, 21 WT mice were trained/tested for 9 days and each day either saline (n=10) or physostigmine (n=11) was given immediately after training. Physostigmine slowed learning and diminished success scores as compared to mice given saline. Home-cage filming and electrophysiology showed that increasing ACh levels with physostigmine altered sleep structure and decreased slow-wave activity duration and power in the first hour of post-learning sleep. These results suggest that post training slow-wave sleep, associated with low cholinergic levels, is optimal for motor memory consolidation. The early phase of sleep therefore may contribute to motor memory consolidation by providing a homeostatic state that is optimal for the selective synaptic formation required to establish motor memory.

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Poster

327. Behavioral Aspects of Memory (Re)Consolidation

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Program #/Poster #: 327.06/FFF9

Topic: H.01. Animal Cognition and Behavior

Support: Department of Veterans Affairs Merit Research Award (I01BX002661).

Title: A single episode of binge alcohol drinking causes sleep disturbance, disrupts sleep homeostasis and downregulates equilibrative nucleoside transporter 1

Authors: *M. M. THAKKAR[1], P. SAHOTA[2], R. SHARMA[1]
[1]Neurol., HSTMV Hospital/University of Missouri, Columbia, MO; [2]Neurol., Univ. of Missouri Columbia Sch. of Med., Columbia, MO

Abstract: Binge alcohol drinking, a risky pattern of alcohol consumption, has severe consequences toward health and well-being of an individual, his family and society. Although, binge drinking has detrimental effects on sleep, underlying mechanisms are unknown. We used adult male C57BL/6J mice and exposed them to a single, four-hour session of binge alcohol self-administration, in stress-free environment, to examine neuronal mechanisms affecting sleep. We first verified binge pattern of alcohol consumption. When allowed to self-administer alcohol in a non-stressful environment, mice consumed alcohol in a binge pattern. Next, effect of binge drinking on sleep-wakefulness was monitored. While sleep-wakefulness remained unchanged during drinking session, significant increase in non-rapid eye movement (NREM) sleep was observed during 4 hours of active period post-binge, followed by increased wakefulness, reduced sleep during subsequent sleep (light) period; although the timing of sleep onset (at lights-on) remained unaffected. Next, electrophysiological and biochemical indicators of sleep homeostasis were examined using sleep deprivation-recovery sleep paradigm. Mice exposed to binge-drinking did not show an increase in cortical theta power and basal forebrain adenosine levels during sleep deprivation; NREM sleep and NREM delta power did not increase during recovery sleep suggesting that mice exposed to binge alcohol do not develop sleep pressure. Our final experiment examined expression of genes regulating sleep homeostasis following binge drinking. While binge drinking did not affect adenosine kinase and A1 receptor, expression of equilibrative nucleoside transporter 1 (ENT1) was significantly reduced. These results suggest that binge alcohol consumption-induced downregulation of ENT1 expression may disrupt sleep homeostasis and cause sleep disturbances.

Disclosures: M.M. Thakkar: None. **P. Sahota:** None. **R. Sharma:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

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Program #/Poster #: 327.07/FFF10

Topic: H.01. Animal Cognition and Behavior

Support: University of Verona "Bando di Ateneo per la Ricerca di Base" (2015)

Title: Reconsolidation of appetitive memory and sleep: Functional connectomics and plasticity

Authors: *L. PADOVANI[1], C. TESORIERO[2], A. L. VYSSOTSKI[3], M. BENTIVOGLIO[2], C. V. CHIAMULERA[1]
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Abstract: Memory re-consolidation is the process of update or modification of consolidated memories after their reactivation. Sleep is well-known to play a role in memory consolidation, but no information is given on whether reconsolidation of memories after their reactivation also occurs during sleep or whether sleep somehow affects memory reactivation. Studies of fear memory conditioning showed a theta synchronization between amygdala and hippocampus, and theta-gamma cross-frequency coupling in hippocampal CA1 area during reactivation. Although hippocampus and basolateral amygdala (BLA) are involved in appetitive memory reactivation as shown by Wells et al (2011), however it is not known their reciprocal functional and temporal connectivity modes during this stage.
The aim of the current study is to assess differences in memory reconsolidation when appetitive memory reactivation is performed during the sleep or awake phases, at both behavioural and electrophysiological levels. Particularly, we focus on the study of Local Field Potential (LFP) patterns in dorsal CA1 and BLA and their modulation during awake/sleep phases.
LFPs were recorded in freely moving rats exposed to a behavioural protocol of appetitive memory reactivation (or no reactivation). Briefly, we used a sucrose self-administration paradigm with the following stages, 1), training, 2), forced abstinence, 3), reactivation (RET) or no-reactivation (NORET), and, 4), relapse test. All the stages were performed during the awake phase, except for memory reactivation which took place either during awake or sleep phases. Behaviour and theta-gamma powers in CA1 and BLA were assessed.
Behavioural data showed a significantly different responding measured as Inter Response Time (IRT, seconds) between RET-awake and RET-sleep groups, with the former showing lower mean IRT compared to the latter, i.e. faster responding. However, no difference in responding was observed at relapse test.
LFPs from CA1 and BLA were analysed by extracting theta and gamma powers from each subject during stage 3) and by comparing their means. Two-way ANOVA showed a main effect of RET/NORET condition (but not of sleep/awake), with greater theta and gamma powers for NORET compared to RET. However, this effect was observed for each frequency band in the spectrum, thus suggesting that the observed differences are possibly due to methodological differences between RET/NORET groups.

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Poster

327. Behavioral Aspects of Memory (Re)Consolidation

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Program #/Poster #: 327.08/FFF11

Topic: H.01. Animal Cognition and Behavior

Support: CONACyT 250870

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DGAPA-PAPIIT IN208616

Title: Early consolidation window is vulnerable to induction of state dependent memory by amnesic drugs

Authors: *A. HERNANDEZ-MATIAS, D. OSORIO-GÓMEZ, F. BERMUDEZ-RATTONI
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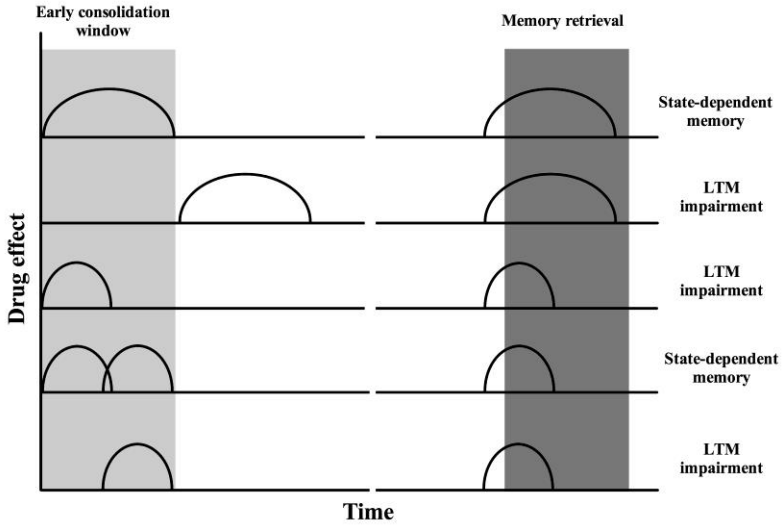
Abstract: Memory consolidation refers to the post-learning processes by which the information is stabilized and strengthened into long-term memory. In general, newly formed memories are labile and susceptible to many amnesic agents that disrupts long-lasting memory establishment. This consolidation hypothesis has been recently challenged by a memory integration hypothesis, which suggests that new memories are liable to incorporation of the neurobiological state induced by amnesic drugs in a state-dependent memory manner. In this study, we evaluated the effects of a protein synthesis inhibitor, a RNA synthesis inhibitor, or an NMDA receptor antagonist infused into the insular cortex of male Wistar rats on object recognition memory. Our results revealed that administration of a protein synthesis inhibitor, the RNA elongation inhibitor and an NMDA antagonist generated a state-dependent recognition memory when infused after a specific period of time and before retrieval. Interestingly, all amnesic drugs used in this study could not generate state-dependent memory when infused outside the early consolidation window. Therefore, we suggest that there are sensitive windows when drugs effects could become an attribute of the recognition memory from the period of time that recognition memory is impaired. In general, state-dependent memory is produced by amnesic drugs only for a specific period of time, and not outside that period, whereas memory consolidation impairments rely on sensitive windows and time of administration.



Disclosures: A. Hernandez-Matias: None. **D. Osorio-Gómez:** None. **F. Bermudez-Rattoni:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.09/FFF12

Topic: H.01. Animal Cognition and Behavior

Support: T32AG052363
R01AG038747
R01NS056218
R01AG057424

Title: Simultaneous assessment of cognitive function, circadian rhythm and spontaneous activity in aging mice

Authors: *S. LOGAN[1], D. OWEN[1], S. CHEN[2], W.-J. CHEN[2], Z. UNGVARI[1], J. FARLEY[1], A. CSISZAR[1], A. SHARPE[3], M. LOOS[4], B. KOOPMANS[4], A. RICHARDSON[1], W. E. SONNTAG[1]
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Abstract: Cognitive function declines substantially with age in both humans and animal models. In humans, this decline is associated with decreases in independence and quality of life. Although the methodology for analysis of cognitive function in human models is relatively well-established, similar analyses in animal models have many technical issues (e.g. unintended experimenter bias, motivational issues, stress, and testing during the light phase of the light dark cycle) that limit interpretation of the results. These caveats, and others, potentially bias the interpretation of studies in rodents and prevent the application of current tests of learning and memory as an overall healthspan assessment in rodent models of aging. The goal of this study was to establish the methodology to assess cognitive function in aging animals that addresses many of these concerns. Here, we use a food reward-based discrimination procedure with minimal stress in C57Bl/6J male mice at 6, 21 and 27 months of age, followed by a reversal task to assess behavioral flexibility. Importantly, the procedures minimize issues related to between-experimenter confounds and are conducted during both the dark and light phases of the light dark cycle in a home-cage setting. During cognitive testing, we also were able to assess multiple measures of spontaneous movement and diurnal activity in young and aged mice including distance moved, velocity, and acceleration over a 90h period. Both initial discrimination and reversal learning significantly decreased with age and, similar to rats and humans, not all old

mice demonstrated impairments in learning with age. These results permitted classification of animals based on their cognitive status. Analysis of movement parameters indicated decreases in distance moved as well as velocity and acceleration with increasing age. Based on these data, we developed preliminary models indicating that, as in humans, a close relationship exists between age-related movement parameters and cognitive ability. Our results provide a reliable method for assessing cognitive performance with minimal stress and simultaneously provides key information on movement and diurnal activity. These methods may represent a novel approach to developing non-invasive healthspan measures in rodent models that can be standardized across laboratories.

Disclosures: S. Logan: None. **D. Owen:** None. **S. Chen:** None. **W. Chen:** None. **Z. Ungvari:** None. **J. Farley:** None. **A. Csiszar:** None. **A. Sharpe:** None. **M. Loos:** None. **B. Koopmans:** None. **A. Richardson:** None. **W.E. Sonntag:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.10/FFF13

Topic: H.01. Animal Cognition and Behavior

Support: PICT-2013-1020. Los sistemas modulatorios endógenos como determinantes de la expresión de la memoria a largo plazo durante las fases de consolidación y reconsolidación.
CONICET -PIP 11220120100170CO Estudio de los mecanismos que determinan la formación, expresión y labilización de una memoria visual de largo término en un minicerebro 2013-2015.

Title: A memorytrace built in conjunction with a stressor is privileged: Reconsolidation-resistant memories in the crab neohelice

Authors: *A. DELORENZI[1], V. A. MOLINA[2], P. N. FERNÁNDEZ LARROSA1[1], F. J. MAZA[1], L. BLOISE[1], H. GONZALEZ[1]
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Abstract: The dynamics of memory processes are conserved throughout evolution, a feature based on the hypothesis of a common origin of the high-order memory centers in bilateral animals. Reconsolidation is just one example where, for instance, in crabs and humans both expressed or unexpressed memories can enter reconsolidation only if a surprise is presented during reactivation sessions. Our view is that, during reconsolidation, endogenous

neuromodulators determine the probability of the memory to guide behavior by decreasing or increasing its behavioral expression, disturbing neither its persistence nor its capacity to be reactivated. The possibility to interfere long-term memory expression during reconsolidation has been proposed as a potential clinical approach to treat traumatic memories. However, several pieces of evidence in humans and rodents show that both robust fear memories or stressful events applied before acquisition promote reconsolidation-resistant memories, i.e., memories that are resistant to the interfering effect of drugs on memory reconsolidation. Is the induction of reconsolidation-resistant memories part of the dynamics of memory processes conserved throughout evolution? In the semiterrestrial crab Neohelice, memory reconsolidation is triggered by a short reminder without reinforcement since the onset of reconsolidation depends on errors in outcome prediction. Here, we showed that an increase in the salience of the aversive stimulus boosts memory strength; nonetheless, the proteins synthesis inhibitor cycloheximide still disrupted the reconsolidation process. However, crabs stressed by a water-deprivation episode before a strong training session build up a memory that was reconsolidation-resistant. We tested whether these reconsolidation-resistant effects can be challenged by changing the parametric conditions of memory-reactivation sessions; multiple (three) memory reactivations without reinforcement were not able to trigger the labilization-reconsolidation of this apparent resistant memory. Overall, the present
findings suggest that reconsolidation-resistant memories can be another feature of the dynamics of memory processes conserved throughout evolution. Memories built in conjunction with stressors are privileged. Consequently, its ability to guide behavior should not be put at risk after each memory reactivation episode.

Disclosures: A. Delorenzi: None. **V.A. Molina:** None. **P.N. Fernández Larrosa1:** None. **F.J. Maza:** None. **L. Bloise:** None. **H. Gonzalez:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.11/FFF14

Topic: H.01. Animal Cognition and Behavior

Title: Behavioural tagging: A general approach to understand the mechanism of long term memory formation

Authors: *M. NASEEM[1], S. PARVEZ[2]
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Abstract: Aim: We aimed to investigate the novel mechanism of “Behavioural Tagging” which is thought to be involved in long term memory (LTM) formation and to find the key factors playing role in consolidation of LTM.

Methods: Behavioural tagging is a process which explains how to stabilizeshort-term memory induced by a weak stimulus and transforms it into long lasting memorieswhen exposed to a novel environment in a critical time window. Here we have shown thathow the process of "Behavioural Tagging" provides both setting of learning tags as well assynthesis of plasticity related proteins (PRPs) to stabilize LTM in adult Wistar rats. Thereforethe expression of these LTP specific PRPs at the cellular as well as molecular level have beenshown to play a significant role in both maintaining long term potentiation (LTP) andmemory storage. Furthermore to confirm the relationship between behavioural tagging, PRPsand LTM, we investigated the effects of PRPs inhibitor.
Results: The results here indicated that memory consolidation-like events take place in various regions of the brain including prefrontal cortex and these LTP-specific PRPs are critical for the consolidation of an abiding plasticity and memory storage which are the essential components in LTM formation.
Conclusion: In conclusion our findings provide evidences for the possible role of LTP-specific PRP i.e., PKM-ζ, activated by the process of behavioural tagging in long term memory formation.**Keywords:** LTP-Specific-Plasticity Related Proteins, Prefrontal Cortex, Behavioural Tagging, long term memory

Disclosures: M. Naseem: None. **S. Parvez:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.12/FFF15

Topic: H.01. Animal Cognition and Behavior

Support: RSF Grant 14-15-00685
RFBR Grant 16-04-01848

Title: Experience-specific anterograde amnesia: Impairment of memory consolidation prevents its subsequent reacquisition in young chicks

Authors: *K. ANOKHIN[1,2,3], D. BEZRIADNOV[2], D. GAEVA[1], A. TIUNOVA[2]
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Abstract: Memory can be experimentally disrupted by a variety of ways, for example by NMDA receptor antagonists or inhibitors of protein synthesis administered prior to memory consolidation or reconsolidation. It is natural to assume that once the effects of such drugs vanish it should be possible to reacquire the initially impaired experience. In this study we tested an

opposite hypothesis - that damage to a specific memory prevents its subsequent reacquisition. Here we examined this possibility in a model of long-term memory formation in young chicks. Day-old chicks were trained in the one-trial passive avoidance task (Cherkin, 1968) by presenting them a 2-mm white bead dipped in a bitter-tasting substance, methylanthranilate. Training was preceded by administration of protein synthesis inhibitor anisomycin (80 mkg intracranially), or NMDA receptor antagonist MK-801 (0.4 mg/kg intraperitoneally or 5 mkg intracranially). Both drugs caused amnesia which was permanent, and no spontaneous recovery of memory was observed. Next, the second training was given to amnestic animals either using the same object ("Retraining" group) or a novel one - a bead of a red color ("Novel training" group). Interval between the first and second training was 2 or 24 h, and the retention test was given from 30 min to 48 h after the second training. During the test chicks were presented for 10 s with a dry bead identical to the one used for training. Chicks were also presented next with a dry metal bead which was used as a neutral (discriminating) stimulus. Pecking or avoidance of the aversive bead was recorded, and a percentage avoidance score was calculated for each group. The second training of the amnestic chicks for the same stimulus failed to produce avoidance memory for all the between-training and training to test intervals. We call this phenomenon an experience-specific anterograde amnesia (ESAA) and discuss its possible neural bases.

Disclosures: K. Anokhin: None. **D. Bezriadnov:** None. **D. Gaeva:** None. **A. Tiunova:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.13/FFF16

Topic: H.01. Animal Cognition and Behavior

Support: NSERC Discovery Grants to RJM, RJS

Title: Maintenance of contextual fear memories and context discrimination acquired in the absence of the hippocampus

Authors: D. C. GIDYK, R. J. MCDONALD, *R. J. SUTHERLAND
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Abstract: One prominent view of the hippocampus is that it is essential for acquisition and initial maintenance of certain long-term memories. In particular, it has been hypothesized that the longevity and precision of episodic memory both require the hippocampal participation at the time of learning. We tested these ideas by damaging the rat hippocampus before contextual fear conditioning. We showed that after one contextual fear conditioning episode, non-hippocampal networks can acquire, maintain, and express context memory, apparently normally, for up to 30 days[1]. In a separate previous experiment using our discriminative fear conditioning to context

procedure, we discovered that context discrimination is supported by non-hippocampal networks for up to three days[2]. These findings confirm earlier reports that non-hippocampal networks can acquire and express a version of context memory. However, the discovery that non-hippocampal context memory exhibits normal longevity and is not lacking detail requires further investigation. In the present experiment, rats with or without damage to the hippocampus were exposed to a single contextual fear conditioning episode, then tested for context discrimination 1, 7, or 15 days later. To ensure damage to the hippocampus completely disrupted hippocampal function, rats were also trained and tested on the spatial cue version of the Morris Water Task (MWT). The results are: 1) damage to the hippocampus was very extensive and caused a large disruption of spatial learning in the MWT; 2) similarly extensive hippocampal damage did not affect the maintenance of contextual fear memory at any retention interval; 3) rats with extensive hippocampal damage exhibited intact context discrimination ability at all retention intervals. The present findings do not support the ideas that the longevity or details of contextual fear memory depend upon the hippocampus. Moreover, further exploration of the mnemonic capacities of non-hippocampal networks may help resolve recurrent theoretical questions about memory consolidation, its dependence on the hippocampus and its importance in remote long-term memory[3,4]. [1] Gidyk, D. C., McDonald, R. J. & Sutherland, R. J. (2016). *Society for Neuroscience Abstracts*, San Diego, CA[2] Lee, J. Q., Sutherland, R. J., & McDonald, R. J. (2017). *Hippocampus*.[3] Sutherland, R. J., & Lehmann, H. (2011). *Current opinion in neurobiology*, 21(3), 446-451.[4] Lee, J. Q., Zelinski, E. L., McDonald, R. J., & Sutherland, R. J. (2016). *Neuroscience & Biobehavioral Reviews, 71*, 154-166.

Disclosures: D.C. Gidyk: None. **R.J. McDonald:** None. **R.J. Sutherland:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.14/FFF17

Topic: H.01. Animal Cognition and Behavior

Support: 18-BR-04-03
NRF-2017M3C7A1048089
NRF-2018M3C7A1024148

Title: Role of the posterior parietal cortex in fear recovery after extinction

Authors: *B. JOO, S. LEE, J. KOO
Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: Relapse of extinguished fear is a major challenge to clinical treatments of fear-related anxiety disorders (e.g., exposure therapy). The extinction of conditioned fear does not eliminate

fear memory itself. For example, presentation of conditioned stimulus (CS; e.g., tone) can induce fear response again with outside of an extinction context ('renewal') or re-experience of aversive shock ('reinstatement'). Considerable researches have suggested that the posterior parietal cortex (PPC) mediates visual and spatial information processing and the recognition of context, such as novel object placement task. However, its role in the context-dependent relapse of extinguished fear response has not been explained. Accordingly, we investigated whether the PPC plays a role in fear renewal and reinstatement which are differentially elicited by context alternation. In Experiment 1, the effects of the reversible inactivation of PPC on the fear renewal were examined. It is known that the fear renewal is occurred in the original fear acquisition context (ABA renewal) or in a context distinct from the conditioning and extinction contexts (ABC renewal). Inactivation of PPC attenuated the ABC renewal but not ABA renewal. In Experiment 2, fear reinstatement was not affected by the inactivation of PPC. In experiment 3, optogenetic inhibition of PPC (Light-ON) selectively blocked ABC renewal but this effect was not shown in Light-OFF trial. The results revealed that inactivation of PPC prevented ABC renewal, but not ABA renewal and reinstatement. In conclusion, the PPC is critical for the fear recovery in the new context, but not for the return of fear in the old context that previously have been explored.

Disclosures: B. Joo: None. **S. Lee:** None. **J. Koo:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.15/FFF18

Topic: H.01. Animal Cognition and Behavior

Support: NSERC Discovery Grant 355934

Title: Overtraining transforms the role of the perirhinal cortex in object recognition memory

Authors: *H. LEHMANN, J. MACKENZIE
Psychology, Trent Univ., Peterborough, ON, Canada

Abstract: Evidence from lesion and neural activation studies suggest that the perirhinal cortex (PRH) plays a critical role in object recognition memory. The neural network supporting a memory, however, can be altered with many learning reinstatements (overtraining), to the extent that a given structure may no longer be required for it. This raises the possibility that overtraining may reduce the contribution of the PRH to an object recognition memory. The current study examined this issue by assessing PRH activation in the novel object preference test, which is commonly used to assess object recognition. Specifically, rats were given either 5 or 30 daily learning sessions during which they were allowed to investigate two identical sample objects. The rats were then given a recognition test in which a novel object replaced one of the

sample objects. Regardless of the reinstatement extent, the rats showed a significant preference for the novel object, but this preference was significantly greater in the 30-session group. Thus, overtraining produced a stronger object recognition memory. Ninety minutes following this recognition test, the rats were sacrificed, their brains removed, sectioned, and finally processed for the expression of the immediate early gene c-Fos, a marker of neural activity. Unbiased stereological quantification of c-Fos+ cells in the PRH revealed that, in contrast to control rats that did not receive any experimental manipulations, rats tested for novel object preference showed increased c-Fos expression in the PRH. Importantly, however, the 30-session group showed significantly fewer c-Fos+ cells in the PRH than the rats that only received five sample sessions. Hence, the overtrained rats, which showed the strongest object recognition memory, had less PRH activation. A second experiment examined the retrograde amnesic effects of PRH lesions on object recognition memory in rats that received the same training parameters as the rats in the immediate early gene experiment. The lesions impaired memory in the group that was limited to five learning session, whereas the memory was intact in the rats that received the overtraining (30 sessions). Combined, these findings suggest that overtraining or repeated learning reinstatements of an object memory causes neural reorganization of the memory and that this plasticity includes PRH disengagement.

Disclosures: H. Lehmann: None. **J. Mackenzie:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.16/FFF19

Topic: H.01. Animal Cognition and Behavior

Support: FAPEMIG - Foundation for Research Support of the State of Minas Gerais

Title: Effect of classical music on the extinction of fear memory in rats

Authors: *P. H. OLIVEIRA[1], D. H. PIETROBON[1], L. L. S. LEMOS[1], A. C. D. DE ANDRADE[1], C. M. F. TRZESNIAK[1], C. R. SARTORI[2], D. A. R. MOREIRA[1], R. S. FARIA[1]
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Abstract: INTRODUCTION: The memory process is divided into acquisition, consolidation, persistence and extinction. Studies suggest that the exposure to music is beneficial in acquiring and consolidating memory. However, little is known about how music could affect the extinction of memory. OBJECTIVE: To analyze the influence of the exposure to the Mozart's Sonata K448 and Classical Music on the extinction of fear memory in rats. METHODS: Sixteen pregnant Wistar rats were daily exposed to music or ambient sound, subdivided into the following groups:

G1-Mozart; G2-Classical; G3-Ambient sound and G4-Control (ambient sound). After delivery, offspring male rats were separated into the respective groups: G1-Mozart (n=24); G2-Classical (n=15); G3-Ambient sound (n=15); G4-Control (n=15), remaining the musical exposure according to the gestational period. On the 39th day, a Fear Conditioning test was performed, in which the groups G1-Mozart, G2-Classical and G3-Ambient sound were submitted to 3 shocks. On the 67th-71th days, the Extinction Test was performed, in which all animals were individually placed in the same shock chamber for 5 consecutive days (D1, D2, D3, D4, D5), but not receiving shock, being collected freezing time data. Statistical analysis was performed with one-way ANOVA, followed by the Tukey test, being significant $p<0.05$. RESULTS: On the D1-D2 days, G1-Mozart, G2-Classical and G3-Ambient sound groups presented higher freezing time compared to controls ($p<0.001$). On the D3, both G1-Mozart ($p=0.074$) and G2-Classical ($p=0.052$) in relation to control already tended to a shorter freezing time, while G3-Ambient sound still had a longer freezing time compared to controls ($p<0.001$). On the D4-D5 days, there were no differences between G1-Mozart or G2-Classical compared to G4-Control ($p>0.05$). On the D5, there was a longer freezing time in G3-Ambient sound compared to the other three groups ($p<0.05$). CONCLUSION: The results point to significant benefits of the exposure to music for more efficient extinction of fear memories. The positive effect of the exposure to Classical Music on the extinction of implicit aversive memory may contribute to the current knowledge about the environmental modulation of memory process. In psychopathological terms, this could help in cases of posttraumatic stress disorder.

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Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.17/FFF20

Topic: H.01. Animal Cognition and Behavior

Title: The effects of diet manipulation on learning, memory and anxiety

Authors: *K. PEDEMONTE, C. M. HERNANDEZ, J. M. FLINN
George Mason Univ., Fairfax, VA

Abstract: This study looks at the effects of autoclaving lab feed as well as the levels of soy content in lab feed. Autoclaving sterilizes and cleans equipment through heat and steam. However, autoclaving animal feed can not only affect key nutrients, but also increase the “hardness” of food pellets and produce toxic and carcinogenic products. An additional dietary factor that is often overlooked is soy (phytoestrogen) content. Evidence has found that

phytoestrogens have anxiolytic effects in both males and females when assessed in an elevated plus maze (Lephart et al., 2002) and open-field testing (McCarthy et al., 1997). Therefore, it is important to consider both autoclaving and soy content in animal feed when conducting behavioral neuroscience research. Ninety-six C57BL/6J male and female mice were assigned to one of four diet groups prenatally: (1) a non-autoclaved standardized Teklad 7012 (containing soy); (2) an autoclaved standardized Teklad 7012; (3) soy-free Teklad 2020SX; and (4) low-soy Teklad 2018SX. Neither the soy-free nor the low-soy diets were autoclaved. At 4 months of age, the mice were examined on behavioral tests including: Morris water maze (MWM), fear conditioning (FC), nesting, elevated zero maze (EZM), open field (OF), and grooming. Collapsed across sex, there were no significant differences in MWM, EZM, and OF between dietary groups. However, animals on Teklad 7012 and autoclaved Teklad 7012 extinguished the learned tone/shock pairing in FC significantly slower than animals on low-soy and soy-free diets. Animals on the standard Teklad 7012 diet created significantly better nests than the animals on any other diet. Additionally, animals on standard Teklad 7012 diet groomed less than the animals on low-soy and soy-free, but more than the animals on the autoclaved Teklad 7012. These data show that the dietary effects including autoclaving feed and amount of soy in diet have a significant effect on behavior and is therefore an important factor for behavioral researchers to consider.

Disclosures: K. Pedemonte: None. **C.M. Hernandez:** None. **J.M. Flinn:** None.

Poster

327. Behavioral Aspects of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 327.18/FFF21

Topic: A.09. Adolescent Development

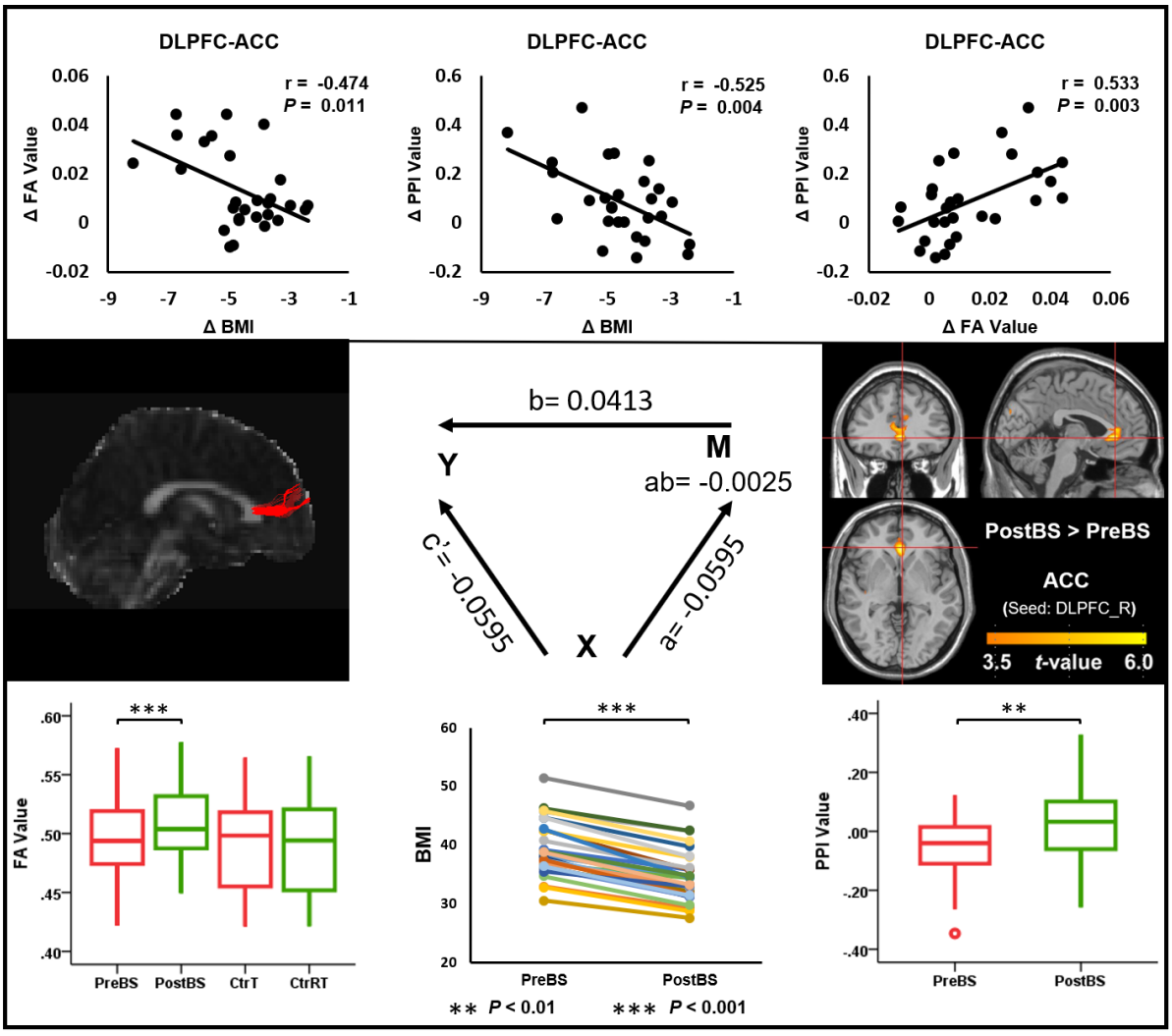
Support: NSFC Grant 81271549
NSFC Grant 81470816

Title: Laparoscopic sleeve gastrectomy induced structural connectivity changes between dorsolateral prefrontal cortex and anterior cingulate cortex

Authors: *Y. HU[1], G. LI[1], M. XU[1], L. LIU[1], Q. JIN[1], Y. NIE[2], G. JI[2], G.-J. WANG[1], Y. ZHANG*[1]
[1]Sch. of Life Sci. and Technology, Xidian Univ., Shaanxi, China; [2]Xijing Gastrointestinal Hosp., The Fourth Military Med. Univ., Xi'an, China

Abstract: Laparoscopic-sleeve-gastrectomy (LSG) is one of the most effective ways to treat obesity, and neuroimaging studies showed alterations in frontal-mesolimbic circuitry in obese patients after LSG, which included attenuated activation in mesolimbic/mesostriatal reward

circuits and diminished activation in dorsolateral prefrontal cortex (DLPFC). However, LSG-induced structural connectivity (SC) changes in the circuitry have not been studied yet. We tested the hypothesis that LSG-induced alterations in SC of frontal-mesolimbic circuitry were associated with improved functional connectivity (FC) in obese patients. Diffusion tensor imaging (DTI) and functional-magnetic-resonance-imaging (fMRI) cue-reactivity task with high- (HC) and low-calorie (LC) food cues were used to investigate brain structural and functional connections changes in 28 obese patients, who were tested before and 1 month after bariatric surgery (BS), and in 22 obese controls (Ctr) without surgery but tested at baseline and 1 month later. ANOVAs showed there were significant interaction effects (group × time) on fractional anisotropy (FA) between the right DLPFC-ACC tract due to significantly increased SC in LSG group (Fig 1), and its changes were correlated with changes in psychophysiological interaction (PPI) connectivity of right DLPFC-ACC (Fig 1). Both increases in SC and FC were associated with decreases in BMI (Fig 1). In addition, the relationship between weight-loss and increases in SC of right DLPFC-ACC can be fully mediated by increases in FC of right DLPFC-ACC (Fig 1). These findings suggest that LSG-induced weight-loss may alter SC of DLPFC-ACC by influencing its FC, reflecting a strengthening of top-down control post LSG.



Disclosures: Y. Hu: None. **G. Li:** None. **M. Xu:** None. **L. Liu:** None. **Q. Jin:** None. **Y. Nie:** None. **G. Ji:** None. **G. Wang:** None. **Y. Zhang*:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 328.01/FFF22

Topic: H.01. Animal Cognition and Behavior

Title: The histone chaperone Anp32E regulates H2A.Z eviction and turnover and regulates memory formation in the hippocampus

Authors: *G. STEFANELLI[1], M. BRIMBLE[4], K. NARKAJ[2], A. M. DAVIDOFF[4], B. J. WALTERS[5], I. B. ZOVKIC[3]
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Abstract: H2A.Z is a highly conserved variant of histone H2A, whose role as a memory suppressor we recently discovered (Zovkic et al. 2014). Specifically, H2A.Z is removed from chromatin after learning, and AAV-mediated H2A.Z depletion results in enhanced memory, suggesting that H2A.Z eviction promotes memory formation. However, the molecular mechanism underlying learning-induced H2A.Z removal remains uncharacterized. Studies in non-neuronal tissue recently identified Anp32E as an H2A.Z-specific histone chaperone that removes H2A.Z from nucleosomes, leading us to hypothesize that Anp32E-mediated removal of H2A.Z is crucial for memory formation. Here, we show that Anp32E and H2A.Z are simultaneously bound to several H2A.Z-enriched genes in the mouse hippocampus. In response to fear conditioning, H2A.Z and Anp32E are concurrently evicted from sites in which they co-localize. Moreover, Anp32E is functionally relevant for memory formation, as AAV-mediated knock-down of this chaperone in the hippocampus results in impaired memory, whereas Anp32E overexpression results in enhanced memory. Notably, manipulating Anp32E levels in cultured neurons and in the hippocampus results in altered gene expression of H2A.Z-regulated genes and altered accumulation of H2A.Z in different chromatin fractions. In addition, knock-down of Anp32E in primary hippocampal neurons results in impaired dendritic branching. Strikingly, simultaneous knock-down of Anp32E and H2A.Z results in rescue of altered gene expression, impaired dendritic branching and memory formation seen in Anp32E knock-down. Overall, our data suggest that Anp32E is a functional component of the molecular machinery regulating H2A.Z eviction during learning and turnover in neurons.

Disclosures: G. Stefanelli: None. **M. Brimble:** None. **K. Narkaj:** None. **A.M. Davidoff:** None. **B.J. Walters:** None. **I.B. Zovkic:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 328.02/FFF23

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant P20GM103423
The Pitt-Hopkins Research Foundation
The Penn Orphan Disease Center

Title: Targeting dna methylation to treat intellectual disability

Authors: H. SMITH, A. H. HOWARD, A. R. BOITNOTT, A. REDA, B. MALACHOWSKY, *A. J. KENNEDY
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Abstract: Haploinsufficiency of transcription factor 4 (Tcf4) leads to the extremely rare learning disability known as Pitt-Hopkins Syndrome (PTHS). We have recently shown that Tcf4-deficient hippocampal tissue from a mouse model of PTHS has altered expression of critical plasticity-related genes. Importantly, these genes were overexpressed in Tcf4-deficient tissue, correlating with a significant decrease in DNA methylation at these loci. Thus, the hypomethylation of genes activated after learning may be a key molecular phenotype of PTHS. Here, we determine the genome-wide sites of altered DNA methylation in Tcf4 (+/-) mice, a mouse line we have already developed that exhibits deficits in learning and memory, social interaction, ultrasonic vocalizations, and have altered synaptic plasticity. Then we test the hypothesis that these deficits can be ameliorated by increasing DNA methylation via the deletion of Tet1, a DNA demethylase that regulates learning and memory. These experiments test the overarching hypothesis that Tcf4 regulates synaptic plasticity, that its deficiency causes cognitive dysfunction, and that epigenetic mechanisms, specifically DNA methylation, can be utilized for the treatment of PTHS.

Disclosures: H. Smith: None. **A.H. Howard:** None. **A.R. Boitnott:** None. **A. Reda:** None. **B. Malachowsky:** None. **A.J. Kennedy:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

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Program #/Poster #: 328.03/FFF24

Topic: H.01. Animal Cognition and Behavior

Support: NSERC RGPIN-2017-05140

Title: Memory reconsolidation requires de novo synthesis of PKMζ

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Abstract: Following retrieval, many memories become temporarily labile and must be restabilized through the process of reconsolidation. Reconsolidation is widely recognized as a protein synthesis-dependent process but specifically which molecules are necessarily synthesized remains largely unknown. Research has demonstrated that PKMζ, an atypical protein kinase C isoform, is essential for maintaining long-term memories by preventing the endocytosis of GluA2-containing AMPA receptors from the postsynaptic membrane. Given this role of PKMζ in maintaining memory stability, we investigated whether disruption of PKMζ occurs during memory labilization and if de novo synthesis of PKMζ is necessary for reconsolidation. We trained rats in an auditory fear conditioning task. Following a retrieval test the next day, rats were sacrificed and their brains collected for Western blotting. Rats sacrificed 1h post-retrieval showed a significant decrease in PKMζ compared to those sacrificed 24h post-retrieval. In a second experiment, rats were trained in the same task. Immediately following retrieval, they were bilaterally infused with antisense oligodeoxynucleotides (ODNs) specific to PKMζ or a scrambled control into the basolateral amygdala. Rats were tested 24h following retrieval to determine the effect of these ODNs. Rats infused with PKMζ-antisense ODNs showed a significant impairment in memory performance at test compared to scrambled controls. These data suggest that during labilization, there is a reduced amount of PKMζ protein and failure to synthesize new PKMζ during reconsolidation prevents the restabilization process, significantly impairing long-term memory.

Disclosures: M. Bernabo: None. **K. Nader:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Program #/Poster #: 328.04/GGG1

Topic: H.01. Animal Cognition and Behavior

Support: NRF2012R1A3A1050385
NRF-2016R1D1A1B03931525

Title: The induction of a labile state during memory reconsolidation requires beta-adrenergic signaling

Authors: *C.-S. LIM[1,2], J.-I. KIM[3], C. KWAK[2], J. LEE[2], E. JANG[2], J. OH[2], B.-K. KAANG[2]
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Abstract: Memory reconsolidation is the process by which previously consolidated memories reenter a labile state through reactivation of the memory trace and are actively consolidated through *de novo* protein synthesis. Although extensive studies have shown that β-adrenergic signaling plays a critical role in the restabilization of reactivated memory, its role in the destabilization of long-term memory is not well-studied. In this study, we found that membrane excitability increased in hippocampal CA1 neurons immediately after the retrieval of contextual fear memory. Interestingly, this increase in membrane excitability diminished after treatment with propranolol (a β-adrenergic receptor antagonist), an NMDA receptor antagonist, and a PKA inhibitor. In addition, we found that administration of propranolol prior to, but not after, the retrieval of fear memory ameliorated the memory impairment caused by anisomycin, indicating that inhibition of β-adrenergic signaling blocks the destabilization of contextual fear memory. Taken together, these results indicate that β-adrenergic signaling via NMDA receptors and PKA signaling pathway induces a labile state of long-term memory through increased neuronal membrane excitability.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Support: NIMH 1R01MH101130
NARSAD Young Investigator Grant
PhRMA Research Starter Grant in Pharmacology/Toxicology
University of South Carolina ASPIRE I Grant
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Title: Deletion of PDE11A improves remote long-term social memory despite blocking recent long-term memory for that same event

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Abstract: System consolidation (SC) is a process by which certain types of information (e.g., social experiences) require the hippocampus for recent long-term memory (LTM) but then become increasingly independent of the HIPP and more dependent on the cortex for remote LTM. Here, we identify the first molecular manipulation—namely deletion of the phosphodiesterase 11A (PDE11A)—capable of *enhancing* remote LTM despite *blocking* recent LTM for that same event. PDE11A4, which degrades cAMP/cGMP and regulates glutamate signaling and protein synthesis, is selectively expressed in neurons of the subiculum, the superficial layer of CA1, and the adjacently connected amygdalohippocampal region. Thus, PDE11A4 is biochemically and anatomically positioned to regulate SC of social memories. In social odor recognition and social transmission of food preference (STFP), PDE11 mutant mice show normal short-term memory 15 minutes to 1 hour after training, no recent LTM 24 hours after training, and spontaneously improved remote LTM 7 days after training relative to WT littermates. At least in the case of STFP, the impaired recent LTM observed in adult PDE11A KO mice appears to correspond to weaker activation of ventral CA1; whereas, the improved remote LTM corresponds to stronger activation of SC-related extrahippocampal brain regions. An upregulation of NR1 and NR2A subunits in prefrontal cortex of PDE11A KO mice vs WT littermates, yet a downregulation of NR2A subunits in HIPP of KOs. We discuss our findings in the context of a working hypothesis: deletion of PDE11A produces transient amnesia by virtue of temporarily "misplacing" the memory (i.e., PDE11A deletion strengthens SC within the cortex ahead of schedule at the expense of prematurely erasing the memory from the HIPP).

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Program #/Poster #: 328.06/GGG3

Topic: H.01. Animal Cognition and Behavior

Support: CONACYT 237570
PAPIIT 203918

Title: c-Fos expression in amygdala after moderate and intense inhibitory avoidance training

Authors: *C. X. RUIZ-LOPEZ, A. C. MEDINA, P. BELLO-MEDINA, G. L. QUIRARTE, R. A. PRADO-ALCALA
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Abstract: Long-term memory formation is thought to depend on long-lasting changes in synaptic efficacy involving structural rearrangement of synapses. These processes are likely to require *de novo* protein synthesis. One of the first targets of plasticity-inducing stimuli appears to

be the activation of transcriptional factors, such as c-Fos. This protein has been used as a marker to identify brain regions that are activated in response to learning. On the other hand, several experimental findings suggest that typical amnestic treatments are ineffective when administered to subjects that have been over-trained or subjected to high foot-shock intensities in aversively learning. This protective effect has been found in a variety of learning tasks when treatments that disrupt normal activity are administered in several regions of the brain, including the amygdala. However, the mechanisms of this protective effect are unknown, and we do not know what regions are activated with this type of training, nor whether moderate and intense training recruit the same number of cells. In the present work we analyzed the number of c-Fos positive cells in amygdala after moderate and intense training. Rats were trained in a inhibitory avoidance task using different intensities of foot-shock (0.0, 1.0, and 3.0 mA). We also studied three controls groups: a cage group (rats that did not experience the inhibitory avoidance task), a 0.0 mA group (rats "trained" in the task, but the foot-shock was not delivered), and a shock-only group (rats that were placed in the shock compartment and received a non-contingent 3.0 mA foot-shock). The rats from each group were sacrificed 90 min after training for immunohistochemical c-Fos protein detection in the anterior basolateral (BLa) and lateral (LA) amygdala. A significant high number of neurons expressed c-Fos in BLa, but not in LA, in the 3.0 mA group compared with the rest of groups. In particular, the BLa has been suggested to play modulatory roles in fear memory. We conclude that long-term neuroplastic changes in the amygdala, which are dependent upon c-Fos expression, may be required for the formation of memory of intense training; the fact that there were no significant changes in c-Fos expression in the 1.0 mA group does no exclude the possibility that this protein is involved, within a different time-window in the amygdala, in the formation of memory of moderate aversive training. We thank Norma Serafín, Bertha Islas, Leonor Casanova, Nydia Hernández, Omar González, and Ramón Martínez for technical assistance.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: PICT 2015-1199
CONICET PhD Grant
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UBACYT 2014-2017
PIP CONICET 2014

Title: Model and remodel the trace: Actin cytoskeleton's role in different memory processes

Authors: *C. MEDINA, V. DE LA FUENTE, A. ROMANO
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Abstract: Memory consolidation is the process by which new information is encoded in a stable form in neural circuits. Once a memory is already consolidated, certain types of reminders of the learning event (i.e. a short re-exposure to the training context) might induce memory labilization and a process of reconsolidation is required to re-stabilize the memory trace. When the reminder of the learning event is prolonged in time, an extinction memory may form, consisting in a new memory trace which temporarily inhibits the expression of the original one. Long-term memory has been associated with morphological changes in the brain, in strict correlation with changes in synaptic efficacy. Such plasticity is proposed to rely on dendritic spines as a sort of neuronal canvas on which these changes can take place. These small actin-rich protrusions from dendrites provide a suitable biochemical compartment to locally control and integrate different inputs, due to spatial confinement. Therefore, spine number, morphology and underlying actin polymerization level can modulate synaptic efficacy in many different ways. Depolymerization of actin cytoskeleton is mainly regulated by a family of actin-binding proteins termed ADF/cofilin, becoming an attractive target to study processes underlying dendritic plasticity. Using a contextual fear conditioning paradigm in mice, we have found that pharmacological induction of depolymerization of actin filaments through an intra-hippocampal injection of BMS-5 –a potent inhibitor of LIM kinase, which is in turn an inhibitor of ADF/Cofilin activity– causes an impairment in memory consolidation and reconsolidation. On the other hand, when favoring stabilization of actin filaments by intra-hippocampal injection of Jasplakinolide immediately before a reminder session that usually elicits reconsolidation of memory, the consolidation of an extinction memory was facilitated. Moreover, extinction was impaired when direct actin cytoskeleton depolymerization was induced by intra-hippocampal administration of Latrunculin-A immediately after a prolonged reminder session. In addition, western blot analysis of synaptoneurosome-enriched hippocampal fraction obtained after a short reminder session that leads to reconsolidation showed an increased P-Cofilin/Cofilin ratio, implying a diminished depolymerization activity by this factor, therefore favoring stabilization of actin filaments. All of these results support the role of actin cytoskeleton dynamics in the morphological changes which underlie different memory processes.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

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Program #/Poster #: 328.08/GGG5

Topic: H.01. Animal Cognition and Behavior

Support: Yale/NIDA Neuroproteomics Center Pilot Project Grant

Title: Effects of garcinol administration on microtubule dynamics following cocaine-cue memory retrieval

Authors: *M. S. MONSEY[1], A. N. FRANKLIN[3], S. G. RUIZ[3], T. T. LAM[2], A. C. NAIRN[4], J. R. TAYLOR[5]
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Abstract: Sustained abstinence from cocaine use is frequently compromised by exposure to stimuli that have previously been associated with drug taking. Such cues trigger drug-associated memories leading to craving and relapse. Our previous work has shown that altering cocaine-cue memories by interfering with the reconsolidation process is a potential therapeutic tool to prolong abstinence. We have previously shown that the histone acetyltransferase (HAT) inhibitor, garcinol, can impair the reconsolidation of cocaine-cue memories in a manner that is reactivation specific, temporally constrained, and long lasting. Here, we examined the neuroproteomic profile of the lateral nucleus of the amygdala (LA) following cocaine-cue memory retrieval and systemic garcinol administration. Rats underwent 12 d of cocaine self-administration where lever presses resulted in an i.v. infusion of cocaine that was paired with a cue. Next, rats underwent lever extinction for 8 d followed by cue reactivation and were sacrificed 90 m later. LA tissue was collected for proteomic analysis using a label free quantitative approach (LCMS/MS) with a significance cutoff of $p<0.05$ and False Discovery Rate of 1% or less. Our results showed significant regulation of 14 proteins, half of which were identified as regulators of microtubule dynamics. One of these proteins, Rho guanine nucleotide exchange factor 2 (ARHG2), was significantly upregulated in the LA following garcinol administration ($p<0.05$) and is associated with changes in α-tubulin acetylation. This led us to investigate whether in addition to being a HAT inhibitor, garcinol might also be inhibiting acetylation on other proteins, such as α-tubulin. To test this we used primary cortical and striatal cell cultures. Cells were grown for 14 d and then treated with garcinol (5uM) or vehicle and collected at 5 or 15 m after application. Cells were then processed for Western blotting. Results show that garcinol significantly decreased levels of α-tubulin acetylation (K40) at 5 m ($p < 0.05$) but not at 15 m in cortical and striatal cultures. These data indicate that not only is garcinol a HAT inhibitor but it may also exert effects by changing levels of α-tubulin acetylation. Future experiments will assess garcinol's effect on human neuroblastoma (SH-SY5Y) and cortical (HCN-2) cell lines. Behavioral studies will use specific inhibitors of α-tubulin acetylation following cocaine-cue memory retrieval to reduce reinstatement. Collectively, these data support the hypothesis that garcinol may be used as a novel tool to interfere with the reconsolidation of cocaine-cue memories possibly through altering microtubule dynamics.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Program #/Poster #: 328.09/GGG6

Topic: H.01. Animal Cognition and Behavior

Support: CNPQ 306777/2016-9
CNPQ 140300/2018-0

Title: Glutamate NMDA receptors in thalamic nucleus reuniens have a subtype-specific role in memory destabilization and reconsolidation

Authors: *F. TROYNER, L. J. BERTOGLIO
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Abstract: Glutamate NMDA receptors are essential for plasticity that supports memory processing in several brain areas, including the amygdala, the hippocampus (HPC) and the medial prefrontal cortex (mPFC). Two NMDA receptor subtypes have received attention due to their roles in memory destabilization (the NR2B-containing subtype) and reconsolidation (the NR2A-containing subtype). The nucleus reuniens (NR) of the thalamus is reciprocally connected with the HPC and the mPFC and has been identified as a hub for functional integration between them during memory processing. Therefore, we hypothesized that glutamatergic activity through NMDA receptors in the NR would be essential for memory destabilization and reconsolidation, both processes dependent on the functional connectivity between HPC and PFC, and that NR2B and NR2A-containing NMDA receptors would have different roles. Male Wistar rats were fear conditioned to a context A and 24 h later submitted to a memory reactivation session in the same context. In the subsequent days, they were re-exposed to context A (Test A) and exposed to a novel unpaired context B (Test B). In the first experiment, infusing a selective antagonist of NR2B-containing NMDA receptors into the NR before reactivation prevented fear memory destabilization, since animals which received a reconsolidation blocker (clonidine) right after the session did not show a decrease in freezing behavior during Test A. Animals infused with vehicle or a selective NR2A-containing NMDA receptor antagonist presented a significant reduction in the time spent freezing during Test A when compared with that respectively expressed in the reactivation session, indicating that the reconsolidation blocker had an effect on fear memory. Neither NR2B nor NR2A antagonist interfered with memory expression during reactivation session or Test B. In the second experiment, animals were contextually fear conditioned and then systemically administered with the alpha-2 adrenoceptor antagonist yohimbine to induce a more generalized fear memory, which has been shown to be less prone to destabilization and reconsolidation. Infusing a selective NMDA receptor agonist into the NR immediately after reactivation induced fear memory updating, since animals presented a

reduction in freezing behavior during Test B when compared to vehicle-treated animals. Collectively, present results indicate a subtype-specific role of NR NMDA receptors in memory destabilization and reconsolidation.

Disclosures: F. Troyner: None. **L.J. Bertoglio:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Program #/Poster #: 328.10/GGG7

Topic: H.01. Animal Cognition and Behavior

Support: CONACYT 250870
CONACYT FOIINS 474
PAPIIT IN208616

Title: Insular cortex glutamatergic NMDA receptors participate in the maintenance of addictive memory

Authors: *E. GIL LIEVANA[1], J. LUIS ISLAS[2], R. GUTIERREZ[2], A. BONCI[3], R. A. MCDEVITT[4], F. BERMUDEZ-RATTONI[5], P. MORENO-CASTILLA[5]
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Abstract: The insular cortex (IC) is a brain structure that has been related mainly to visceral control, stimuli salience and recognition memory. Recent studies indicate that IC is also related to addictive behaviors, however, little is known about its participation in the formation and maintenance of addictive emories. Therefore, in this work, we study the cellular mechanisms in the IC involved in the acquisition and maintenance of addictive memory associated with a context. Using the in vivo optogenetic technique in a transgenic TH-cre mouse, we studied the VTA-IC dopaminergic pathway. We observed that the stimulation of the dopaminergic neurons in the VTA produced strong conditioning place preference (PP), while the stimulation of the dopaminergic terminalsin the IC did not. In addition, we determined using the in vivo microdialysis technique the extracellular concentration of different neurotransmitters during the acquisition and retrieval of PP task. Our results indicated that during the acquisition of PP, only the extracellular concentration of dopamine increased in the CI. Interestingly, during the retrieval of PP, the extracellular concentrations of glutamate, dopamine and norepinephrine increased in the IC. Given these results, we performed pharmacological manipulations with different receptor antagonists involved in the maintenance of the PP in the IC. We found that one intracortical injection of an NMDA receptor antagonist just after the first post-test trial impaired PP

maintenance and start to induce an accelerated extinction process. Conversely, injections of glutamate AMPA, D1 and D2 dopaminergic and β-adrenergic receptors antagonists in the IC did not affected the maintenance of the addictive memory generated by optogenetic stimulation in the VTA.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 328.11/GGG8

Topic: H.01. Animal Cognition and Behavior

Title: Developmental features of AMPAR trafficking-dependent memory

Authors: M. OPENDAK, 10016[1], R. ZANCA[2], *R. M. SULLIVAN[3], P. A. SERRANO[4]
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Abstract: Although infants are able to learn and remember, infant memory processes are attenuated compared to the adult, including the phenomenon of infantile amnesia. However, mechanisms for this attenuated infant memory have remained elusive. The existing literature has identified intracellular molecular events that are critical in memory formation, although this has yet to be described for infants. To fill this gap, we explored the molecular substrates of memory using a rat model of threat/fear learning and describe a complex, dynamic cascade that shows at least 3 mechanistic transitions as pups approach independence from the mother. In Experiment 1, pups underwent amygdala-dependent odor-shock (0.5mA) conditioning in early life during three distinct phases of threat learning: 1) Early infancy (<postnatal day PN10), when pups do not learn threat; 2) Transitional (PN10-15), when pups learn amygdala-dependent fear learning but it can be switched off by maternal presence via social buffering of the shock-induced corticosterone (CORT) stress hormone response; 3) Adult-like, when pups learn threat and it cannot be switched off by maternal presence or CORT blockade. Our results show that, amygdala memory molecules were not engaged in pups too young to exhibit fear learning. As pups reach a developmental age of amygdala-dependent fear conditioning, some aspects of the molecular memory cascade emerge, including PKMz-dependent upregulation of GluA2 and downregulation of GluA1. A more adult-like molecular cascade was seen in the oldest pups (PN17), with PKMz-dependent upregulation of both GluA1 and GluA2. In Experiment 2, we dissociated age and molecular events by shutting off the amygdala-dependent learning during odor-shock conditioning, where memory mechanism were also shut down. Specifically, at PN12

but not PN17, we shut down learning with pharmacological CORT blockade during conditioning and memory mechanisms were similarly shut off. Taken together, these results identify unique features of memory processes across early development: we provide novel evidence that GluA1/2 expression is differentially utilized and is sensitive to PKMζ inhibition for an amygdala-dependent avoidance memory. The partial recruitment of adult molecular mechanisms in the infant may help provide one explanation of why memories are not as well retained in early life.

Disclosures: M. Opendak: None. **R. Zanca:** None. **R.M. Sullivan:** None. **P.A. Serrano:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Program #/Poster #: 328.12/GGG9

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant RMH100650A
NIH Grant RMH109945

Title: Overexpression of GluN2B(E1479Q) within the basal and lateral amygdala enables the modification of a strong fear memory via reconsolidation

Authors: *C. A. DE SOLIS[1], M. GALDAMEZ[3], C. U. GONZALEZ[3], S. W. WOODARD[3], C. E. SALINAS[3], J. N. MILLER[3], J. M. PERISH[4], O. H. PINEDA[3], R. HOLEHONNUR[5], A. SANDOVAL[3], J. E. PLOSKI[2]
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Abstract: Memory retrieval does not initiate the reconsolidation process for some memories rendering pharmacotherapies designed to disrupt reconsolidation ineffective, in particular, strong memories have been shown to be difficult to disrupt via reconsolidation blockade and this is likely due to the inability of these memories to destabilize upon retrieval. In an effort to understand the molecular basis for why weak and strong fear memories differ in their requirements to initiate reconsolidation, we recently determined that training-dependent changes in the N-methyl D-aspartate receptor (NMDAR) subunit composition occur at basal and lateral amygdala (BLA) synapses that correlate with a strong memory's inability to be modified upon retrieval. We then demonstrated that genetically increasing the NMDAR GluN2A/GluN2B ratio is sufficient to block retrieval-induced memory destabilization and this prevents an existing memory trace from being modified via reconsolidation updating. Now we would like to determine if increasing the GluN2B/GluN2A ratio via overexpression of GluN2B or

GluN2B(E1479Q) mutant might enhance the initiation of reconsolidation. GluN2B(E1479Q) contains a point mutation in the PDZ domain of GluN2B which leads to higher surface levels of the subunit by inhibiting phosphorylation-driven endocytosis (Sanz-Clemente et al., 2010). In order to examine these questions, we generated lentiviruses designed to express these subunits from a TRE3G promoter. Injecting these viruses into the BLA of α-CaMKII-tTA mice allows us to restrict expression of the GluN2B transgenes to excitatory neurons and also enables expression of the transgene to be selectively expressed before or after fear conditioning training using doxycycline (Dox) (Holehonnur et al., 2015). Here, we examine how the overexpression of GluN2B and GluN2B(E1479Q) influences the consolidation, extinction and the initiation of reconsolidation of weak and strong Pavlovian auditory fear memories. We found that overexpression of GluN2B or GluN2B(E1479Q) within BLA neurons prior to fear conditioning led to an increase in LTM freezing levels. STM was not affected in either condition. Extinction was not affected due to overexpression of GluN2B(E1479Q) or GluN2B(WT) at the time of extinction learning. Increasing GluN2B at the time of reconsolidation with GluN2B(E1479Q), but not GluN2B(WT), allowed for pharmacologically induced amnesia of a strong fear memory. This amnesia was found to be dependent on retrieval. Increasing GluN2B(E1479Q) at the time of reactivation did not affect the initiation of reconsolidation for a weak fear memory.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 328.13/GGG10

Topic: H.01. Animal Cognition and Behavior

Support: HHMI
NS053415

Title: The pre- and postsynaptic compartments of *Aplysia* sensorimotor neuron synapses form positive feedback loops and act as one functional unit during consolidation of learning-related facilitation by 5HT

Authors: *I. JIN, E. R. KANDEL, R. D. HAWKINS
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Abstract: Intermediate- and long-term synaptic plasticity generally require coordinated pre- and postsynaptic mechanisms. Thus, the transition from presynaptic short-term facilitation (STF) to

intermediate-term facilitation (ITF) induced by 5HT at *Aplysia* sensory-to-motor neuron synapses requires the recruitment of postsynaptic mechanisms and activation of protein synthesis in both neurons. We previously found that presynaptic ApNT acts on ApTrk autoreceptors to form a self-perpetuating presynaptic positive feedback loop that is sufficient to drive the synapses from STF to ITF (Jin et al., 2016, 2017). Presynaptic ApNT also recruits postsynaptic mechanisms of facilitation by enhancing spontaneous release of glutamate, which acts on postsynaptic mGluR5 receptors. In addition, ApNT acts through both anterograde and retrograde signaling to form a trans-synaptic positive feedback loop (Jin et al., 2017). The presynaptic feedback loop appears to be the main self-perpetuating force driving consolidation: (1) activation of presynaptic PKA produces an increase in the signal intensity of ApNTpHluorin in the presynaptic neuron that grows over time ($p < 0.01$) without any clear growth over time in the postsynaptic neuron ($p > 0.05$); (2) Selective activation of presynaptic ApTrk receptors produces an increase in the signal intensity of calcium orange in the presynaptic neuron that grows over time ($p < 0.001$), without any clear growth over time in the postsynaptic neuron in analogous experiments ($p > 0.05$). On the other hand, the trans-synaptic feedback loop acts to orchestrate cellular activity in both the presynaptic and the postsynaptic neurons. For example, activation of protein synthesis by ApTrk receptor signaling in each synaptic compartment also depends on signaling from the other synaptic compartment: (1) activation of presynaptic protein synthesis by presynaptic ApTrk receptor signaling is reduced by injection of siRNA against ApNT into the postsynaptic neuron; (2) activation of protein synthesis in the postsynaptic neuron by postsynaptic ApTrk receptor signaling is reduced by bath application of MPEP, a potent inhibitor of mGluR5 ($p < 0.01$). These results suggest that protein synthesis in the presynaptic neuron depends on postsynaptic mechanisms and protein synthesis in the postsynaptic neuron requires presynaptic mechanisms, so that the pre- and postsynaptic compartments act as one functional unit. In summary, a presynaptic feedback loop acts as the driving force while a trans-synaptic feedback loop coordinates cellular activity in the pre- and the postsynaptic neurons during the consolidation of learning-related facilitation induced by 5HT.

Disclosures: E.R. Kandel: None. **R.D. Hawkins:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Program #/Poster #: 328.14/GGG11

Topic: H.01. Animal Cognition and Behavior

Support: BBSRC NIG
Royal Society of Edinburgh CRF
ARUK small fund

Title: Behavioral tagging and capture: Memory persistence and memory-activated neuronal ensembles in old age

Authors: *S.-H. WANG, A. GROS, A. LIM, V. HOHENDORF, N. WHITE
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Abstract: Our daily memories of insignificant events fade away quickly. However, when a memory-modulating event is introduced before or after memory encoding, memories can persist longer. Using a rodent spatial task that mimics human daily experience of locating objects, we found that a novel event can facilitate the persistence of spatial memory (Wang et al., 2010). This phenomenon shares the same principle of facilitating long-term potentiation in synaptic tagging and capture (Redondo and Morris, 2011). Using this spatial task, we recently showed that the memory decline in middle age (c.a. 12 months) is associated with an impaired encoding or synaptic tagging mechanism (Gros and Wang, 2018). This study aims to: characterise memory impairment in older age (c.a. 20 month) by using this task; investigate if training in young protects memory impairment; visualise the cellular signature in the hippocampus for memory representation. We trained male Lister-Hooded rats to find rewards in an open arena in a sample trial and to search for more rewards among multiple locations in a choice trial. Their memory was probed in a test trial with multiple locations no rewards and the time spent searching in previous rewarded, correct location or incorrect locations were scored blindly. The results showed that memory declined in old age, which was not facilitated by a novel modulating event. Encoding and modulating with high level of rewards were required to keep the memory in old age. Prior training of this task in young and in mid-age was partially effective at delaying the memory decline. Finally, we used fluorescence in situ hybridization (FISH) to explore the activation of neuronal ensembles in the hippocampus in this task. We found that in young rats, the neurons activated by the encoding overlapped with neurons activated by the memory-modulating event in CA1.

Disclosures: S. Wang: None. **A. Gros:** None. **A. Lim:** None. **V. Hohendorf:** None. **N. White:** None.

Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 328.15/GGG12

Topic: H.01. Animal Cognition and Behavior

Support: CNPq 141973/2015-3
CNPq 306777/2016-9

Title: Dorsal hippocampal kappa opioid receptors modulate contextual fear memory reconsolidation in rats

Authors: *F. VANZ, V. F. LINARTEVICHI, M. GIACHERO, T. C. M. DE LIMA, L. J. BERTOGLIO
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Abstract: Reconsolidation is a dynamic and adaptive process allowing the incorporation of new information into consolidated memories. Kappa opioid receptors (kORs) are expressed in brain regions involved in fear memory reconsolidation, including the dorsal hippocampus (DH). The present study sought to investigate the contribution of DH kORs to contextual fear memory reconsolidation. Male Wistar rats were fear conditioned to context A (3 shocks 1.0 mA, 3s). On the next day, they were briefly reexposed to the context A to reactivate the established memory and then bilaterally infused into the DH with vehicle (VEH), a selective kOR antagonist *nor*-binaltorphimine (*nor*-BNI; 0.3, 1.0, 3.0 or 10 nmol/hemisphere) or a selective kOR agonist GR 89696 (0.1, 0.3 or 1.0 nmol/hemisphere) 0 or 6 h later. To investigate the treatment effects on reconsolidation animals were reexposed to the paired context A on days 1 and 8 (Tests A1 and A2). The potential treatment effects on memory generalization were assessed by exposing the animals to a novel and unpaired context B on days 2 and 9 (Tests B1 and B2). Freezing behavior was measured as an index of memory in both cases. In experiment 1, infusing *nor*-BNI 1.0 nmol immediately after reactivation session increased the time spent freezing in both Tests B1 and B2 when compared with respective VEH groups (Test B1: VEH = 15 ± 3% *vs. nor*-BNI 1.0 = 48 ± 10%; Test B2: VEH = 27 ± 3% *vs. nor*-BNI 1.0 = 55 ± 7%). On the other hand, no effect was observed when *nor*-BNI 1.0 nmol was infused 6 h after reactivation session (experiment 2) (Test B: VEH = 11 ± 2% vs. *nor*-BNI 1.0 = 14 ± 1%). In experiment 3, infusing GR 89696 1.0 nmol immediately after reactivation session reduced the time spent freezing time in both Tests A1 and A2 when compared with respective VEH groups (Test A1: VEH = 82 ± 2% *vs.* GR 89696 1.0 = 43 ± 6%; Test A2: VEH = 78 ± 3% *vs.* GR 89696 1.0 = 39 ± 5%). However, this effect was no longer observed when GR 89696 1.0 nmol was infused 6 h after the reactivation session (experiment 4; Test A: VEH = 74 ± 3% *vs.* GR 89696 1.0 = 78 ± 3%) or when animals were pretreated with *nor*-BNI in a sub-effective dose (experiment 5) (Test A1: VEH ± GR 89696 1.0 = 51 ± 7% *vs. nor*-BNI 0.3 ± GR 89696 1.0 = 82 ± 3%; Test A2: VEH + GR 89696 1.0 = 48 ± 6% *vs. nor*-BNI 0.3 + GR 89696 1.0 = 72 ± 4%). Altogether, present results suggest the DH kORs play an important negative modulatory role in contextual fear memory reconsolidation.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 328.16/GGG13

Topic: H.01. Animal Cognition and Behavior

Support: CAPES
CNPq

Title: Protein kinase C activity in prelimbic cortex is necessary for reconsolidation and persistence of a reactivated contextual fear memory in rats

Authors: *T. R. DA SILVA[1], A. SEGANTINE[1], A. RAIMUNDY[1], L. BERTOGLIO[2], R. ANDREATINI[1], C. STERN[1]
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Abstract: An expanded time-window to mitigate reactivated fear memories has been shown, however, the mechanisms underlying the reactivation-induced memory persistence are not understood. Considering the role of protein kinase C (PKC) in the late stages of long-term memory formation, and the prelimbic cortex (PL) role in fear memory persistence and reconsolidation, this study sought to investigate whether PKC activity in PL could be important for reconsolidation and/or persistence of a reactivated fear memory. Male Wistar rats with bilateral implant of guide cannulas aimed at the PL underwent contextual fear conditioning that consisted of familiarization to the Context A on day 1, fear conditioning (Context A-shock pairing) on day 2, a brief Context A reexposure to memory reactivation on day 3, and subsequent Context A reexposures to estimate the drug effects on days 4 and 11 (TestsA1 and A2). Independent groups of rats received vehicle (VEH) or the selective PKC inhibitor cheleritrin (CHE; 1 or 3nmol/0,2µL/side) immediately, 6, 9, 12 or 18 hours after memory reactivation. A control group had the memory retrieval, or its reactivation omitted by the i.p. administration of nimodipine 16mg/kg, and after 6 hours they received VEH or CHE 3nmol. Freezing behavior was assessed as an index of fear memory. Data was analyzed using repeated measures ANOVA followed by Newman-Keuls test ($p \leq 0.05$). When infused into the PL immediately after memory reactivation, CHE (1nmol) significantly reduced the time spent freezing during TestA1 and A2, indicating a role for PKC in memory reconsolidation. VEH-treated animals presented a similar percentage of freezing during reactivation, Test A1 and A2. The groups treated with CHE 1 or 3 nmol intra-PL 6, 9 or 12 hours after memory reactivation presented less freezing behavior than controls during TestA2, indicating a role for PKC in memory persistence. No changes in the levels of freezing behavior during Test A1 were observed in the groups treated with CHE (1 or 3nmol) 6, 9 or 12 hours after memory reactivation. CHE 18 hours after reactivation presented no changes in freezing expression.When the memory retrieval or its reactivation were omitted, the

infusion of CHE 6 hours after did not change the freezing expression during Test A1 or Test A2.These results corroborate the role of PL in fear memory reconsolidation, indicating the PKC activity as a mechanism involved in this process. Moreover, the present findings indicate that the PKC activity in PL until 12 hours after memory reactivation and reconsolidation is involved in memory persistence, confirming the existence of an expanded time-window to selectively impair the persistence of reactivated fear memories.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Program #/Poster #: 328.17/GGG14

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Clinical Infectious Diseases Research Initiative
South African Medical Research Council
South African National Research Foundation
Department of Science and Technology South African Research Chair Initiative

Title: Interleukin-13 signaling influences long-term potentiation of spatial learning

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Abstract: Background
Pro-inflammatory cytokines are known to play a role in the bidirectional communication between brain and immune system. Recently, anti-inflammatory cytokines have been shown to also be expressed in the central nervous system (CNS), and to be essential for cognitive function. We recently showed that IL-13—possibly from immune cells—plays a role in the regulation of cognitive functions by stimulating astrocytes to produce brain derived neurotrophic factor that is known to play a significant role in memory formation.
In this study we aim to address the role of type 2 cytokine signaling via IL-4Rα on cognitive functions, in order to define IL-13 target cells involved, as well as the underlying molecular mechanism. We further address the consequence of inhibited signaling of IL-13 via IL-4Rα, leading to impairment of reference memory, but not learning.
Materials and Methods
To investigate immunological-relevant genes influencing cognitive function, mouse models

deficient of IL-4Rα, IL-4/IL-13, and IL-4Rα/IL-13 were analyzed for their influence on learning and memory using the Morris water maze (MWM) as described by Brombacher et al. Data were recorded using the EthoVision XT 8 automated tracking system (Noldus Information Technology, Leesburg, VA). Statistical analysis was performed using ANOVA and Bonferroni post hoc test or Student t test. Groups were run in alternating order on successive training days, and animal protocols were approved by the independent Animal Ethics Research Committee at the University of Cape Town. To gain insight into cellular infiltrates, Flow cytometry and histological analyses were conducted from brain parenchyma. qPCR and ELISA were employed to investigate local cytokine environment to assess systemic upregulation of cytokine production.
Results
We show that IL4Rα or IL4Rα/13 deficiency does not impair learning in comparison to wild type control mice—whether simple or complex—however, reference memory is impaired. From loss of function approach, using the MWM, we demonstrate that IL-13 signaling via IL-13RαII is not the cause for observed impairment of memory formation.
Conclusions
While both IL-4 and IL-13 are known to be required for learning and memory, failure to signal via the common receptor IL-4Rα, impairs only reference memory, but not learning. This suggests that possible compensatory mechanisms and pathways employed in the absence of IL-4Rα are effective to uphold the processes of learning, but not sufficient to support reference memory, indirectly suggesting that IL-13 is critical for the process of memory formation.

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Poster

328. Molecular Mechanisms of Memory (Re)Consolidation

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Topic: H.01. Animal Cognition and Behavior

Support: NIH R01, NS086933-01
NINDS Diversity Supplement NS086933
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Title: Examining the role of AKT isoforms on spatial learning and memory in AKT mutant mice

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Abstract: AKT is a protein kinase involved in synaptic plasticity and behavior and is often implicated in neurological disorders in which memory and cognition are impacted, such as

schizophrenia and Alzheimer's disease (AD). Behavior and memory formation involve activity-dependent changes that ultimately strengthen or weaken specific neuronal connections, and these activity-induced changes are commonly referred to as synaptic plasticity. Importantly, dysregulation of these activity-dependent changes has been implicated in schizophrenia, AD, and intellectual disability. There is ample evidence that links AKT signaling and protein synthesis in these processes; however, AKT is expressed in the brain by three distinct isoforms. The specific role each isoform may play in regulating memory, behavior, and synaptic plasticity remains unknown. Previous work from our lab found three major findings: 1) AKT isoforms demonstrate different patterns of regional and cellular expression in the brain; 2) removal of specific AKT isoforms differentially regulate the expression of hippocampal synaptic plasticity and protein synthesis; 3) AKT isoforms serve differential roles in cognition and memory formation. In the present study, we sought to further delineate the roles of each isoform by examining the effects of specific isoform removal in both floxxed and knockout mouse strains under various working memory tasks. Then, using a Cre/lox system, we examined whether the observed deficits in AKT1 mutants were due to the removal of AKT1 from the brain or the absence of AKT1 during development. To generate mice that have a conditional *AKT1* or *AKT2* removal in excitatory neurons in the forebrain, we bred $Akt1^{loxP/loxP}$ or $Akt2^{loxP/loxP}$ with *Camk2α*-Cre mice on a C57/BL6 background. We found that the removal of AKT isoforms differentially effects spatial learning and memory, and likely contribute to the cognitive impairments in disease states in an isoform specific function.

Disclosures: D.J. Peterson: None. **J. Levenga:** None. **H. Wong:** None. **C. Hoeffer:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.01/GGG16

Topic: H.01. Animal Cognition and Behavior

Support: NIH NINDS R01 NS045940

Title: Seizure-induced cognitive impairment in pregnancy and preeclampsia: Effects of prolonged seizures and anti-seizure treatments

Authors: *A. C. JOHNSON, M. J. CIPOLLA
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Abstract: Preeclampsia (PE), a hypertensive disease of pregnancy, can result in de novo seizures known as eclampsia. Eclamptic seizures, including generalized tonic-clonic seizures and status epilepticus (SE), often result in amnesia lasting days. While a brief seizure may cause minimal

injury, recurrent and prolonged seizures such as during SE can impair memory and cognition. Whether PE increases the susceptibility to seizure-induced memory impairment remains unclear. Magnesium sulfate (MgSO4) is more effective at reducing the incidence of recurrent eclamptic seizures than anti-convulsants such as diazepam (Dz); however, whether MgSO4 or Dz treatments are protective from SE-induced memory impairment in PE is unknown. Here, we tested the hypothesis that SE would cause greater memory impairment than a single seizure in PE versus the normal pregnant and nonpregnant states, and compared the protective effects of MgSO4 and Dz on seizure-induced cognitive dysfunction. Female Sprague Dawley rats (n=6-8/group) were either virgin, nonpregnant (NP), normal pregnant (Preg; d19-20) or with PE (induced by a high cholesterol diet gestational d7-20). The chemoconvulsant pentylenetetrazol (PTZ; i.p.) was used to compare the effect of one tonic-clonic seizure versus SE on cognition. Rats received one PTZ injection (60mg/kg) to induce a single seizure, multiple PTZ injections (5-40mg/kg; 10 min intervals) to induce SE including multiple tonic-clonic seizures lasting 30 mins, or vehicle (CTL). Rats having seizures received MgSO4 (270mg/kg i.p.) or Dz (10mg/kg i.p.) 20 min after PTZ or SE. Short-term memory was tested 24 hours post-seizures using a novel object recognition task and recognition index calculated: (novel object time)/(total object time). Data are mean ± SEM and comparisons made using a one-way ANOVA with post hoc Bonferroni test. SE impaired short-term memory in Preg and PE rats, demonstrated by decreased recognition indices compared to CTL (0.49 ± 0.04 vs. 0.69 ± 0.06, $p<0.05$ and 0.46 ± 0.07 vs. 0.70 ± 0.05, $p<0.05$) that was unaffected by MgSO4 or Dz in PE rats (0.49 ± 0.12 and 0.42 ± 0.08, respectively) and Preg rats (0.46 ± 0.08 and 0.51 ± 0.04, respectively). A single seizure did not affect short-term memory in either group, and short-term memory was unaffected by seizures in NP rats. In conclusion, short-term memory impairment after SE in Preg and PE, but not in NP rats suggests pregnancy increases the susceptibility to seizure-induced cognitive dysfunction. Neither MgSO4 nor Dz treatment improved cognition after prolonged and recurrent seizures, highlighting the importance of prevention of eclampsia and seizure cessation to maternal cognitive health.

Disclosures: A.C. Johnson: None. **M.J. Cipolla:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.02/GGG17

Topic: H.01. Animal Cognition and Behavior

Support: MRC UK G0800329
Wellcome Trust 110157/Z/15/Z

Title: Structural and functional reorganisation in the brain of macaques following fornix transection

Authors: *V. PELEKANOS[1], S. CHAKRABORTY[2], S. MASON[1], E. PREMEREUR[3], D. J. MITCHELL[4], A. H. BELL[1], A. C. LEE[5], A. S. MITCHELL[1]
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Abstract: The fornix, the white matter pathway in the primate brain that connects the extended hippocampal system to the limbic thalamus, mammillary bodies, and frontal cortex, has a critical role in episodic memory, as revealed by monkey lesion (Gaffan, 1994; Buckley et al., 2008) and human neuroimaging studies (Metzler-Baddeley et al., 2011; Rudebeck et al., 2009). In the present study, we used monkey neuroimaging combined with lesions to investigate the role of the fornix, and anatomically related structures, in rapid learning of episodic-like information. Eight age-matched young adult male macaques were scanned using diffusion-weighted magnetic resonance imaging (MRI) and resting-state functional MRI. Four animals underwent surgeries to receive selective bilateral fornix transections. Before and after the surgeries, these animals were scanned after extensive training on the object-in-place scene discrimination (OIP) task which measures episodic-like memory in monkeys. The other four animals, trained on a passive fixation task for an independent experiment, remained as unoperated controls. We employed diffusion tensor imaging to quantify white matter properties, which, preoperatively, showed increased fornix microstructural integrity in the OIP-trained monkeys compared to controls. Postoperatively, we found lesion-related structural and functional connectivity changes. Specifically, microstructural integrity in alternative major white matter pathways, like the cingulum bundle, was associated with learning on the OIP task, whereas the resting-state results suggested marked changes within the default-mode network (Mantini et al., 2011). Together, our results solidify the contribution of the fornix in episodic-like memory, and further demonstrate lesion-induced neural reorganisation in the primate brain, underlying its capacity for plasticity.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

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Program #/Poster #: 329.03/GGG18

Topic: H.01. Animal Cognition and Behavior

Support: NSF Career 1565410 (IAM)

Title: Behavioral strategies and source of directional signal for reorientation in sighted and blind animals

Authors: *C. M. GAGLIARDI, M. R. LOPEZ, M. C. GARZA, T. I. ERESANARA, I. A. MUZZIO
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Abstract: Reorientation - regaining one's bearings after becoming lost - is a fundamental problem of navigation. In lost animals the internal sense of direction is unreliable; therefore, disoriented navigators must reorient only using external cues. Across sighted species it has been shown that spatial geometry, i.e. the shape of a navigable space, plays a critical role in reorientation, even when other directionally informative cues, such as landmarks and objects, are present. Since vision allows a navigator to quickly and precisely process the external layout, it is unknown if blind navigators, who rely on sequential exploration to form detailed representations of space, use the same strategies and neural mechanisms as sighted subjects to reorient. Here we investigated how blindness affects behavioral strategies and the source of directionality during reorientation. First, we used a classic reorientation paradigm where disoriented animals have to find a reward in a rectangular environment containing a polarizing tactile cue. We found that both sighted and blind animals search equally often in the rewarded location and the symmetrically opposite corner, indicating the use of geometry for reorientation, disregarding the tactile cue. Then, we investigated whether the use of geometry during reorientation is contingent upon the area that the animal can explore or it merely requires the presence of tactile surface boundaries using the classic paradigm. We found that sighted mice could reorient using both the affordable navigable space and surface boundaries, but showed better performance in the later condition. Conversely, blind animals could only reorient using the affordable navigable space, suggesting that two-dimensional surface boundaries are not efficient for disoriented blind mice. We are now investigating if the directional signal necessary for reorientation arises from the same brain region/s in sighted and blind animals. To this end, we are using chemogenetic silencing to determine the role of the retrosplenial cortex and postsubiculum, two areas that are critical for landmark control of head direction. These results will be critical to understand the cognitive architecture of reorientation and determine the role of vision in this process.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.04/GGG19

Topic: H.01. Animal Cognition and Behavior

Title: Hippocampus-retrosplenial cortex interaction for memory formation and retrieval

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Abstract: The hippocampus and retrosplenial cortex (RSC) both play important roles during memory acquisition, consolidation and retrieval. However, it is unclear how the two brain structures may interact at each of these memory processes. Anatomically, there is a dense reciprocal connection between the dorsal hippocampus and RSC, suggesting a potential two-way communication between them. Here we employed in vivo electrophysiology and optogenetic approaches to study hippocampus-RSC interaction in freely-behaving mice. We first recorded neural activity from the dorsal hippocampus and RSC simultaneously and confirmed coordinated activity between the two brain regions at both the local field potential (LFP) and single-neuron levels. Hippocampal LFP displayed discrete fast ~200 Hz oscillations, known as sharp-wave ripples that are believed to be important for memory consolidation. On the other hand, the RSC LFP displayed a characteristic broad-band oscillation. This RSC oscillation shifted sequentially from fast (~300 Hz) to slow (~30 Hz) frequencies immediately prior to hippocampal ripples, signifying an orchestrated and controlled influence on hippocampal ripples. Consistently, most of the RSC neurons exhibited increased activity, which was phase-locked to the RSC oscillation. Immediately after hippocampal ripples, a small percentage of the RSC neurons, most likely interneurons, also increased their activity after a short latency of ~5 ms, suggesting a monosynaptic connection from the hippocampus to RSC. In contrast, the remaining RSC neurons, most likely pyramidal neurons, decreased their activity after ~25 ms, which are likely suppressed by the local interneurons. These above results indicate a two-way communication between the hippocampus and RSC during memory consolidation: the RSC influences hippocampal ripple activity through a coordinated fast-to-slow oscillation, while the hippocampus mainly inhibits RSC activity through direct activation of RSC local interneurons. In a second set of experiments, we trained mice with a contextual or trace fear conditioning procedure and optogenetically silenced the hippocampal projection to the RSC. Preliminary results revealed that the hippocampus-to-RSC pathway is required for retrieval of long-term (1 month) but not short-term (1 day) fear memory. Our ongoing effort is to determine the role of hippocampus-RSC connections at different stages of memory formation processes and advance our current understanding of memory associated circuits.

Disclosures: A.N. Opalka: None. **J. Liu:** None. **H. Liang:** None. **D.V. Wang:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.05/GGG20

Topic: H.01. Animal Cognition and Behavior

Support: ACBB: Science without Borders (CNPq – Brazil)

Title: Optogenetic silencing of retrosplenial cortex disrupts sensory associative memory

Authors: *A. BOTTURA DE BARROS[1], T.-Y. LEE[2], V. SAMBORSKA[2], M. PANAYI[3], T. AKAM[3], D. M. BANNERMAN[3], M. M. KOHL[2]
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Abstract: Numerous studies implicate the hippocampus and neocortex in associative memory. Still, it is unclear if and/or how sensory and contextual information is stored in these regions. The retrosplenial cortex (RSC) is known to reciprocally connect to the hippocampal formation and to sensory areas. Although RSC has been previously described as important for processing spatial information, this connectivity suggests that the RSC might be involved in hippocampus-neocortex interplay and more generally required in the formation and storage of sensory associative memory. This notion is supported by RSC-lesion and -inactivation studies that produced impairments in associative memory.
Here, we aimed to develop an associative memory task in mice and performed precise optogenetic manipulations of RSC activity to understand its role in facilitating the association of neutral sensory stimuli. We developed an aversive preconditioning behavioural paradigm in mice which allows us to test associations between neutral stimuli. We used the red-shifted opsin, Jaws, to inactivate the RSC during different phases of the task to investigate the role of this structure in sensory associative learning.
Our results show that control mice successfully learn the preconditioned association in our task. Optogenetic silencing of the RSC at the time when the mice form associations between neutral stimuli reduces performance to chance levels.
In summary, we establish a new sensory preconditioning task for mice allowing us to probe associative memory between neutral stimuli. Optogenetic silencing of RSC enables us to demonstrate the necessity of the RSC in this type of memory.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: Massey TBI Grand Challenge Award
American Epilepsy Society Junior Investigator Award
NIH BRAIN Initiative Grant R03MH111316

Title: Comparative dynamics of activity patterns in the retrosplenial cortex, visual cortex and hippocampus across sleep-wake states

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Abstract: The retrosplenial cortex (RSC) is a part of association cortex and has extensive interconnections with both sensory and limbic structures. The RSC is bidirectionally connected with the visual cortex and also receives substantial inputs from the hippocampal formation (specifically from CA1 and the subiculum). Functionally, the RSC is involved in visuospatial processing and memory, and lesions of the RSC lead to impairments in both fear conditioning and spatial learning. RSC neurons have been shown to encode both allocentric and egocentric spatial locations, as well as the head-direction of animals. To understand the detailed functional connectivity supporting this kind visuospatial encoding by cells in the RSC, we used large-scale simultaneous tetrode recordings from the visual cortex, CA1 and RSC in male Long-Evans rats. Here, we report on the neuronal activity patterns and cross-correlations seen among these three brain regions during distinct sleep-wake states. We compare our results to recent reports suggesting that RSC neurons are most likely to show maximal firing rates selectively during REM sleep.

Disclosures: F. Yang: None. **M. Ghosh:** None. **V. Hetrick:** None. **D. Siu:** None. **O.J. Ahmed:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Support: Nature Science Foundation of China (No. 91232721, 31400933, 81671106)
973Program" (2014CB541600, 2015CB759500)
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Title: A visual cue-dependent memory circuit for place navigation

Authors: H. QIN[1], L. FU[2], B. HU[1], X. LIAO[1], H. JIA[3,4], B. ZOTT[4,5], *A. A. KONNERTH[6,5], X. CHEN[1]
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Abstract: The ability to remember and to navigate to safe places is necessary for survival. Place navigation is known to involve connections from medial entorhinal cortex (MEC) to the hippocampus. However, learning-dependent changes in neuronal activity in distinct circuits remain unknown. Two pathways could be involved in visual place navigation. Here, we demonstrate that the MEC layer II - dentate gyrus (DG)-pathway is crucial for visually cued spatial navigation, while the connections from MEC layer III to hippocampal CA1 are not. In this study, we were able to record bulk calcium activity from the axon bundle of specific pathways in freely behaving mice. This was achieved by using an improved version of optic fiber photometry together with the layer-specific expression of the genetically encoded calcium indicator GCaMP5G in different spatial learning paradigms. We discovered the experience-dependent induction of a persistent task-associated (PTA) activity in the axons from MEC layer II to DG. This activity started at the onset of the task and terminated immediately after the localization of the target place. PTA activity followed place learning and its amplitude and duration strongly correlated with task performance. Moreover, PTA activity depended on continuous visual input and was elicited by visually guided navigation in a morris water maze or a radial eight-arm maze but not by locomotion in general. Electrophysiological tetrode

recordings in MEC layer II revealed that PTA population activity, on a single cell level, was created by both an increase in intermittently active neurons and by the de-novo development of persistently active neurons. Optogenetic inhibition of the MEC layer II - DG pathway completely and reversibly disrupted spatial navigation in trained animals, while it had no effect on different learning paradigms like fear conditioning. The MEC-Layer III - CA1 pathway, on the other hand, did not show activity patterns comparable to the experience-dependent PTA activity. Moreover, the optogenetic disruption of this pathway had no effect on spatial memory performance. Together, these findings suggest that the visual system, the MEC layer II and the dentate gyrus are essential hubs of a memory circuit for visually guided navigation. Also, the newly found PTA activity in MEC layer II neurons that project to DG is essential for successful visually cued navigation.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: 'Lendület' Program of the Hungarian Academy of Sciences (Grant No. LP2015-2/2015)
European Research Council (Grant No. StG 715043)

Title: The basal forebrain may provide a link between locomotion and learning

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Abstract: Cortical processing depends on brain states that influence animal behavior. Brain states are controlled by the coordinated activity of multiple subcortical neuromodulatory centers. Among these the basal forebrain has widespread cholinergic, GABAergic and glutamatergic projections thought to mediate multiple cognitive functions including learning, memory and plasticity. From these, the GABAergic projection has been implicated in controlling the locomotion-related theta oscillation in the hippocampus and the glutamatergic projection can directly control animal speed. On the other hand, cholinergic cells respond rapidly and reliably to reinforcement that is likely important for learning. Therefore we hypothesize a relationship between basal forebrain neuronal activity, locomotion and learning.

To directly test this, head-fixed mice were placed on a wheel and trained on an auditory Pavlovian cued outcome task in which two pure tones of different frequency predicted likely reward (water) or likely punishment (air puff). We quantified how well mice learned the task by measuring anticipatory licking after the tone predicting likely reward. This experimental design allowed mice to run or stay still voluntarily during the task. Additionally, stress levels induced by head-fixation and water restriction were tested by measuring corticosterone and adrenocorticotropic hormone levels from the blood. We monitored neuronal activity in the medial septum of the basal forebrain using tetrode electrodes. Therefore it was possible to examine whether there were correlated changes in basal forebrain neuronal activity, behavioural performance and learning across 'standing still' and running states, potentially influenced by differential levels of stress hormones.
We found that mice initially trained on a fixed wheel learned faster. When allowed to run freely, mice tended to run after reinforcement delivery, which could reflect approach (water) or escape (air puff) responses. Neurons displayed a diversity of responses to behaviourally relevant events with dominant subpopulations showing activation or suppression after air puff delivery. These medial septal cell types may convey locomotion-dependent learning signals via the septo-hippocampal pathway.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.09/GGG24

Topic: H.01. Animal Cognition and Behavior

Support: NSERC DG: 40352

Title: Distinct ripple-triggered cortical activity during natural sleep and wakefulness

Authors: *J. KARIMI ABADCHI[1], M. NAZARIAHANGARKOLAEE[2], T. KNOPFEL[3], B. L. MCNAUGHTON[4], M. H. MOHAJERANI[5]
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Abstract: Hippocampal sharp-wave ripple (SWR) events, the transient high frequency (100 - 250 Hz) oscillations in the hippocampal local field potential (LFP), are the main candidate for

facilitating reactivation of recently acquired memories in the hippocampal circuits. SWRs occur during both slow-wave sleep (SWS) and quiet wakefulness. Their co-occurrence with cortical slow oscillation (up- and down-states) and thalamocortical spindles during SWS is believed to mediate coordinated memory replay in the hippocampus (HPC) and the cortex (CTX). Coordinated reactivation of memory traces in the hippocampal-cortical circuits, mediated by SWR events, also occurs during periods of awake quiescence and immobility, particularly, during the pauses that animals make while they are performing a spatial task. However, there are major differences between SWS and awake reactivations. These differences probably stem from the different ways by which HPC and CTX communicate during different behavioral states. Recent research indicates that SWR-correlated activity of prefrontal cortex neurons equally shows both inhibitory and excitatory modulation. However, it is mainly biased toward excitation during SWS. It has also been shown that the hippocampal-cortical coordination is stronger during awake ripples compared to sleep ones, even though it seems there is no global synchronizing mechanism like slow-oscillation during quiet wakefulness. To further probe the differences in hippocampal-cortical interaction during sleep and wakefulness, we chronically monitored cortical activity in a large portion of the dorsal CTX in mice using wide-field optical imaging and simultaneously recorded hippocampal LFP from the pyramidal layer of the dorsal CA1 during both quiet wakefulness and natural sleep. We also collected and analyzed the same data under urethane anesthesia as a model of sleep. In line with the previous reports, we found an extensive ripple-triggered activation in the cortical areas during natural sleep and anesthesia. This activation was strongest in the retrosplenial cortex (RSC) compared to other dorsal cortical regions. Moreover, this activation was preceded by a period of silence, which probably reflects cortical down-states. In contrast, we found that RSC shows an abrupt inactivation during awake ripples, and we did not observe preceding down-states. Interestingly, this inactivation was mainly localized in the RSC and not in other cortical regions. Our data implicate RSC as one of the principal contributors to the ripple-triggered hippocampal-cortical interactions and support the idea that these interactions are state-dependant.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: DARPA Grant HR0011-18-2-0024

Title: Coherent theta and respiratory oscillations between sensory systems and the hippocampus

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Abstract: Spatial navigation provides an important window into understanding how neural activity gives rise to several components of cognition (e.g., attention, decision-making, sensorimotor processing, learning and memory). A recent proposal suggests that olfaction evolved primarily in the context of spatial navigation. Therefore, the rodent spatial learning and memory (SLM) model may be more ethologically valid when adding olfactory-spatial cues rather than using solely visual-spatial cues. The respiratory rhythm, arising from brainstem central pattern generators, is tracked by olfactory bulb respiratory oscillations (2-12 Hz in rodents) and recently shown to be capable of widespread coordination of neural activity implicated in cognition. The respiratory rhythm could be serving functions attributed to hippocampal theta, as it has been shown to coexist with theta in the hippocampus and olfactory bulbs at similar but separate frequencies. In this study, behavioral and electrophysiological methods were used with aims of 1: comparing spatial navigation and SLM in rodents across visual and olfactory modalities; and 2: assessing the roles of theta and respiratory oscillations in coordinating widespread neural activity during SLM and other related behaviors. Recordings of the local field potential (LFP) were obtained from the olfactory bulb, dorsal CA1 and DG of the hippocampus, piriform cortex, and primary visual cortex, concurrently with measures of respiratory rhythm in the nasal cavity, in freely behaving rats performing several tasks. Power and coherence spectral analyses and Granger causality are used to address cooperativity and causal relationships between areas. Spatial tasks included a four-arm radial maze, as well as navigation in an open field, with both tasks including phases with either visual or olfactory spatial cues present. Odor tasks involve passive odor sampling and a Go/No-Go odor discrimination task. Preliminary data suggest globally high coherence during spatial tasks between most areas measured with fluctuating patterns of theta and respiratory dominance over training and between areas. Odor tasks show high respiratory coherence within the olfactory circuit throughout, extending to the hippocampus during more difficult phases (e.g., rule reversal). Collectively, these studies aim to further characterize the potentially distinct yet complementary roles of hippocampal theta and olfactory bulb respiratory rhythms in the context of cognition.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP
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Hitchcock foundation pilot grant

Title: Renewal following extinction of remotely acquired conditioning depends on the postrhinal cortex

Authors: *N. E. DEANGELI, D. J. BUCCI, T. P. TODD
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Abstract: The postrhinal cortex (POR) is part of a network of posterior cortical regions involved in learning and memory. POR is critical for recent and remote context fear memory retrieval (Burwell, Bucci, Sanborn, & Jutras, 2004), but not for recent or remote cue fear memory retrieval (Bucci, Phillips & Burwell, 2000; DeAngeli et al., in preparation). Despite evidence that POR is not necessary for the retrieval of these cue fear memories, it may play a role in the context-specific expression of a cue fear memory after extinction (i.e renewal). Renewal, the recovery of responding to an extinguished conditioned stimulus that occurs when the CS is presented outside the extinction context, is impacted by hippocampal damage in some cases, but not others, suggesting that context encoding and retrieval might also depend upon other brain areas. As a parahippocampal structure, POR is well positioned to provide hippocampus with processed sensory information necessary for renewal.
In the present studies, rats received infusions of either inhibitory or control DREADDS into POR. Upon recovery, subjects were exposed to a single 8 min conditioning session in Context A, with three tone-shock pairings. Following a 28-day retention interval, rats were placed back in Context A for 20 min for a context retrieval test. The next day, the tone retrieval session occurred in Context B (different visual, olfactory, and tactile cues than Context A) with 20 presentations of the tone alone. Rats then underwent 7 days of extinction with 20 presentations of the tone alone in Context B each day. Following the last day of extinction training, rats were re-exposed to Context A for 20 min. On the next two days, renewal of extinguished fear was tested via 5 presentations of the CS each day. Each rat received one test session in Context A and one test session in Context B (counterbalanced). Freezing behavior was measured throughout the sessions as an indicator of conditioned fear. For Experiment 1, all rats received an IP injection of clozapine-n-oxide (CNO) 30 min prior to behavior on each extinction day. For Experiment 2,

rats received CNO injections prior to the renewal tests. Both manipulations resulted in impaired renewal in rats with temporary inactivation of POR versus controls. Thus, temporary inactivation of POR during extinction of a remote tone fear memory impairs renewal of that extinguished fear cue. Furthermore, temporary inactivation of POR during the renewal test also disrupts renewal of the extinguished fear cue.

Disclosures: N.E. DeAngeli: None. **D.J. Bucci:** None. **T.P. Todd:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

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Topic: H.01. Animal Cognition and Behavior

Support: NSF Grant IOS1353137
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Title: The retrosplenial cortex is necessary for contextual fear memory even when rats are over-trained

Authors: *D. FOURNIER[1], M. EDDY[2], T. TODD[2], D. J. BUCCI[2]
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Abstract: It has been consistently shown that damaging the rodent hippocampus soon *after* Pavlovian fear conditioning (e.g., 24 hr later) produces severe retrograde amnesia for contextual fear memories. In contrast, hippocampal damage that occurs *prior* to conditioning only impacts contextual fear memory when relatively weak fear conditioning procedures are used (e.g., 1-3 trials, weak shock); if rats receive strong conditioning (i.e., over-training) procedures, hippocampal lesions are without effect (Wiltgen et al., 2006). This supports the long-standing view that alternate brain pathways and structures can 'compensate' for the absence of the hippocampus under certain conditions. To date, these alternate regions and systems remain unidentified. Moreover, an important, yet unstudied corollary of this hypothesis is that there may be brain regions that are essential for context fear memory regardless of the training parameters or timing of the damage. One such structure may be the retrosplenial cortex (RSC), based on its position at the interface between hippocampal/parahippocampal memory structures and the sensory cortical regions that provide essential information about the context. Consistent with this idea, we and others have previously shown that RSC lesions or inactivations impair context fear memory regardless of whether damage occurs soon after conditioning, or at distal time points

(e.g., 28 days after conditioning). In addition, damage to RSC prior to conditioning impairs the expression of contextual fear memories. However, most of the pre-training RSC lesion studies to date have used relatively weak conditioning procedures. If RSC is essential for contextual fear memory, we would expect that RSC lesions, unlike hippocampal lesions, would impact context fear memory even when rats are over-trained. To test this, rats were conditioned using the identical overtraining procedures and experimental designed used by Wiltgen et al. (2006) to demonstrate that the effects of pre-training hippocampal lesions could be overcome with strong conditioning. Like hippocampal lesions, neurotoxic lesions of RSC carried out 24 hours after conditioning abolished contextual fear memory. Unlike the hippocampus, however, RSC lesions also impaired context fear memory when damage took place *prior* to strong conditioning. This pattern of results suggests that RSC has an essential role in contextual fear memory regardless of the strength of training or timing of the damage.

Disclosures: D. Fournier: None. **M. Eddy:** None. **T. Todd:** None. **D.J. Bucci:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NSF Grant IOS1353137
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Title: Effects of retrosplenial cortex damage on negative and positive patterning discrimination tasks

Authors: *A. TAVAKKOLI[1], D. I. FOURNIER[2], T. P. TODD[3], D. J. BUCCI[3]
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Abstract: The retrosplenial cortex (RSC) is a polymodal association area that is highly interconnected with hippocampal, parahippocampal and cortical sensory regions. This pattern of connectivity suggests that RSC may contribute to variety of forms of learning and memory, particularly those that involve linking together two more sensory cues. Consistent with this, previous research has demonstrated that lesioning or temporarily inactivating the RSC impairs contextual fear memory, which is thought to involve forming a configural representation of the collection of stimuli that define the environment. Similarly, RSC lesions impair several forms of discrimination learning, including serial and compound feature negative discriminations. As a

result, we predicted that RSC lesions would also impact so-called negative and positive patterning discriminations, which arguably provide a strong test of the hypothesis that RSC is important for forming associations between multiple sensory cues. In this study, we used electrolytic lesions of the RSC specifically to produce extensive damage and to maximize the likelihood of observing an effect on behavior. Rats were trained in one of two discrimination tasks. In the negative patterning procedure, two individual cues (click, C and light, L) were each paired with food reward on separate trials, while on a third type of trial, the cues were presented in simultaneous compound and non-reinforced. Conversely, in the positive patterning procedure, presentation of the compound stimulus was followed by food, but presentations of the individual cues were non-reinforced. We hypothesized that the RSC- lesioned animals would be impaired in both discrimination tasks if the RSC is needed to learn the meaning of the compound stimulus and successfully discriminate between the trial types. To our surprise, the pre-training lesions of RSC did not impair the ability of rats to learn the negative patterning or positive patterning discriminations. Subsequently we tested the efficacy of the lesions by testing rats in a spatial object-in-place task that is known to depend on RSC. Consistent with prior studies, the lesioned rats were impaired in this procedure, suggesting that the lack of effects on negative and positive pattering was not due to insufficient damage to RSC. The implications of these findings for understanding the functional contributions of RSC to learning and memory are discussed.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

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Program #/Poster #: 329.14/HHH2

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH108729

Title: Characteristics and interactions in the local field potential of the perirhinal and postrhinal cortices

Authors: *S. G. TRETTEL[1], I. TOMAS PEREIRA[2], V. R. HEIMER-MCGINN[1], R. D. BURWELL[1]
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Abstract: Local field potential oscillations appear to play an important role in coordinating the activity of ensembles of neurons located in different brain regions. Previous studies have shown that in the hippocampus and its connected cortical regions, theta (6-12 Hz), slow gamma (25-55

Hz), and fast gamma (65-100Hz) oscillations all appear to play a role in temporarily synchronizing cell ensembles to perform computation. In the parahippocampal region, the perirhinal and postrhinal cortices are integrally related to structures in the hippocampal formation and play roles in hippocampal memory functions. What is less understood, however, is how the local field potential correlates across the two regions and how the field potential patterns change across layers and rostral-caudal position within these areas. By examining the pattern of field potential oscillations, we can better understand how perirhinal and postrhinal cortices communicate with each other and other structures of the parahippocampal region. We used local field potential data recorded simultaneously from the perirhinal and postrhinal cortices of Long-Evans rats as they traversed a familiar environment to examine oscillations in the theta and gamma ranges. We compared the oscillations between these two regions, and we investigated how these oscillations changed across cortical layers. We found that the theta oscillation in postrhinal cortex is phase-reversed from the weaker theta oscillations of the perirhinal cortex. We also found that, while transient fast-gamma epochs appear to occur concurrently in perirhinal and postrhinal cortex, slow gamma epochs were not coherent between the two regions. Our findings indicate that, like other regions of the hippocampal memory system, perirhinal and postrhinal oscillations in different frequency bands may be coordinating temporary increases in synchrony between sub-regions of the hippocampal formation. This temporary synchrony allows for a flexible set of sub-circuits to be set up to perform different but related computations.

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Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.15/HHH3

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01MH108729

Title: Neuronal correlates in the rat retrosplenial cortex and the postrhinal cortex during performance on a visuospatial attention task

Authors: *E. HWANG[1], F.-C. YANG[3], T. K. JACOBSON[1], R. D. BURWELL[2]
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Abstract: Recent work in both primates and rodents has addressed the role of the retrosplenial cortex (RSC) in spatial and non-spatial information processing. These studies show that the RSC

is implicated in navigation, spatial memory, processing of contextual information, sensory integration, cross-modal information processing, and the representation of stability or reliability. While most studies of the RSC address hypothesis about the spatial functions, the findings of non-spatial studies provide compelling evidence that cannot be explained by a purely spatial hypothesis. An open question is what core function of the RSC could support this wide variety of functions in both the spatial and non-spatial domains. Rodent studies show that the RSC and the postrhinal cortex (POR) are functionally and anatomically interconnected (Burwell & Amaral, 1998, Burwell et al, 2004, Keene & Bucci, 2008). We have shown that the POR exhibits object-location conjunctive coding (Furtak, Ahmed, & Burwell, 2012). Previous work also shows that the POR plays an important role in spatial information processing. We hypothesize that the RSC integrates information across multiple information processing domains that include both spatial and non-spatial information. Here we report a study in which we compare neuronal activity in the rodent RSC and POR during performance on a visuospatial attention (VSA) task in the Floor Projection Maze (Jacobson et al., 2014). The VSA task is a purely visual task that was adapted from the five choice serial reaction time task (Bari, Dalley, Robbins, 2008) for a double-sided, bowtie shaped enclosure. The VSA task allows assessment of top-down and bottom-up visuospatial attention as well as multiple spatial reference frames. Detailed analyses of neuronal correlates for both RSC and POR will be presented. In addition, the patterns of neuronal activity in RSC and POR will be compared with those of the PPC recorded in rats performing the same VSA task.

Disclosures: E. Hwang: None. **F. Yang:** None. **T.K. Jacobson:** None. **R.D. Burwell:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.16/HHH4

Topic: H.01. Animal Cognition and Behavior

Support: NSF Award 1656488

Title: Control of perirhinal-dependent novelty exploration in rats by optogenetic modulation of prefrontal cortex

Authors: *A. E. IOANNOU[1], D. L. POETA[2], R. D. BURWELL[3]
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Abstract: The perirhinal cortex (PER) has a well-established role in the identification and recognition of individual items and objects (reviewed in Ho and Burwell, 2014). Animals and

humans with perirhinal damage are unable to distinguish familiar from novel objects or images in recognition memory tasks. Our lab previously found that neuronal activity in PER appears to signal novelty and familiarity through synchronous activity at specific frequencies (Ho et al., 2015), with novelty signaled at 30Hz and familiarity signaled at 11Hz. Whereas many animals have a propensity to explore novel objects, it is sometimes necessary to suppress that activity when exploration is not optimal, e.g. a hungry animal may avoid exploring a novel item when navigating toward a food source. Evidence indicates that such cognitive control relies on prefrontal cortex (PFC) (reviewed in Lehky and Tanaka, 2016). Medial prefrontal cortex (mPFC) is known to be involved in processing information about novelty (Dias and Honey, 2002;). The secondary motor cortex (MOs, also known as medial agranular cortex, AGm) in the rodent plays an important role in processing sensory information in order to guide appropriate goal-directed behavior (Sul et al., 2011). Based on this evidence, it is reasonable to suggest that the PER interacts directly with the mPFC and the MOs to provide the necessary cognitive control over this novelty exploration. In this study we employ optogenetics to address the hypotheses that PER-PFC interaction is necessary for novelty guided exploration and that these interactions are modulated by synchronous neuronal activity in specific frequency bands. Rats were bilaterally injected with an adeno-associated viral vector (AAV) containing channelrhodopsin (ChR2) and bilaterally implanted with an optical fiber in either the MOs or in the infralimbic cortex (IL), located in the mPFC. During a Spontaneous Object Recognition (SOR) task, rats underwent optical stimulation in a within subject design. Conditions were 30Hz, 11Hz, 8Hz (theta frequency), and a no-stimulation control (optical fiber was physically blocked). Based on our hypotheses, we expect that pairing a familiar object with a 30Hz stimulation in either the MOs or IL, will increase exploration of that object, as if it were novel. Further, pairing a novel object with 11Hz stimulation in either the MOs or IL, will decrease exploration of that object, as if it were familiar. The 8Hz condition was intended to determine how stimulation in the theta frequency band might impact exploratory behavior.

Disclosures: A.E. Ioannou: None. **D.L. Poeta:** None. **R.D. Burwell:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.17/HHH5

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP 1058262 to VJE
NIMH R01MH108729 to RDB

Title: Characterizing representations in the postrhinal cortex during a location bi-conditional spatial memory task

Authors: *V. J. ESTELA[1], R. D. BURWELL[2]
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Abstract: Episodic memory, or the recollection of events in time and space, requires the ability to fully represent and recall context. Context-dependent cognitive processes are disrupted in a number of neuropsychiatric and neurological disorders such as schizophrenia, depression, PTSD, and Alzheimer's disease. These disruptions are associated with changes to the parahippocampal region of the medial temporal lobe, specifically the parahippocampal cortex (PHC, human homologue of the rodent postrhinal cortex, POR) and the hippocampus (HC). The contribution of each of these areas and the mechanisms underlying the representation of these context-dependent memories is still unknown. My laboratory showed that the POR, situated upstream of the HC, has neurons that respond to a particular item only when it is in a particular location (Furtak, et al., 2012). In the HC, this type of object-location conjunctive coding emerges with the learning of an association (Komorowski, et al., 2009), and is proposed to be a signature of episodic memory. The temporal characteristics of these conjunction cells in the POR have yet to be defined, nor has the relationship between the conjunction cells in the POR and the HC. Further, initial data indicates that oscillations in the theta frequency in the POR might signal error (Furtak, et al., 2012), but this function should be studied further. Finally, the POR appears to have cells that represent both egocentric and allocentric reference frames, indicating another integrative function of the region. Based on this preliminary data, we hypothesize that the POR integrates object information from the PER with spatial information from the posterior parietal and retrosplenial cortices to represent the spatial layout of objects, patterns, and features in the local environmental context. Further, we hypothesize that the HC relies on contextual representations from the POR for associative learning and episodic memory. Based on this, we predict that object-location conjunctions should be present in the POR before they emerge in the HC, and that we will recapitulate the results showing error signaling via theta in the POR. To test these predictions, we will record in the POR and HC during performance on the Location Biconditional Discrimination task in the floor projection maze. In this task, a pair of objects is presented alternatingly on the east or west side of a bowtie-shaped maze. The east-west location determines which of the two objects is correct. Finding object-location conjunctions in the POR prior to the HC would be consistent with the interpretation that object-location conjunctive coding in the HC relies on POR representations of context.

Disclosures: V.J. Estela: None. **R.D. Burwell:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

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Program #/Poster #: 329.18/HHH6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG049090 (AAW)
NSF Grant 1631465 (BLM)
NSERC Grant RGPIN-2017-03857 (BLM)

Title: Impaired spatial reorientation and amyloidosis in the dorsal hippocampus of the 3xTg-AD mouse model of Alzheimer's disease

Authors: *A. C. STIMMELL[1], S. C. MOSELEY[1], V. LAPOINTE[2], L. MESINA[2], L. F. SANTOS-MOLINA[1], B. N. CRAFTON[1], B. L. MCNAUGHTON[2,3], A. A. WILBER[1]
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Abstract: In early Alzheimer’s disease (AD) spatial navigation is impaired; however, the precise cause of this impairment is unclear. Recent evidence suggests that getting lost is one of the first impairments to emerge in AD. It is possible that getting lost represents a failure to use distal cues to get oriented in space. Therefore, we set out to look for impaired use of distal cues for spatial orientation in a mouse model of amyloidosis (3xTg-AD). To do this, we trained male and female mice to shuttle to the end of a track and back to an enclosed start box to receive a water reward. Then, mice were trained to stop in an unmarked reward zone to receive a brain stimulation reward. The time required to remain in the zone for a reward was increased across training, and the track was positioned in a random start location for each trial. Finally, we compared performance on the spatial reorientation task to pathology marker density (e.g., 6e10, M22, M78) measured across the whole brain. We found that 6-month female, but not 6-month male, 3xTg-AD mice were impaired at the spatial reorientation task. However, 3-month female and 13-month male 3xTg-AD mice were not impaired. Male and female mice had only intracellular amyloid pathology and male mice had less pathology, particularly in the dorsal hippocampus. Phosphorylated tau was present but in such a small proportion of neurons that it was not quantified. Thus, AD may cause spatial disorientation early in the disease progression as a result of impaired use of landmarks and this impairment may be a related to intracellular amyloid accumulation in the dorsal hippocampus.

Disclosures: A.C. Stimmell: None. **S.C. Moseley:** None. **V. Lapointe:** None. **L. Mesina:** None. **L.F. Santos-Molina:** None. **B.N. Crafton:** None. **B.L. McNaughton:** None. **A.A. Wilber:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.19/HHH7

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG049090

Title: Parietal contributions to context-dependent spatial sequence learning

Authors: *C. SIMMONS, H. BOWLEY, M. KIRLAN, M. BAIAMONTE, A. A. WILBER
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Abstract: A preponderance of evidence suggests that the internal map of the environment is represented in world-centered (allocentric) coordinates; however, movements and perception of the environment are in body-centered (egocentric) coordinates. Therefore, to navigate in space, it is essential to translate between egocentric and allocentric coordinates. Cell activity in the parietal cortex (PC) and hippocampus suggests a PC-hippocampal network for transforming landmark representations from egocentric to allocentric coordinates (Wilber et al., 2014), consistent with theoretical modeling work (McNaughton et al., 1995). More recent computational modeling studies predict bi-directional coordinate transformation (Byrne et al., 2007; Oess et al., 2017). Finally, PC is organized in a modular fashion with each module tuned to specific action states (Wilber et al., 2017). Thus, PC is uniquely positioned to interface between allocentric spatial location and action. This suggests that PC could be part of a brain network involved in assigning the appropriate action at a redundant spatial location. For example, on the way to the grocery store I turn right at an intersection, but on the way to the library I turn left from the same intersection. We set out to test this hypothesis by training rats to learn complex sequences that require disambiguating a common spatial location associated with two distinct actions. Specifically, rats were trained to run through an 8-zone, complex sequence that contains repeating zones (similar to: Bower et al., 2005). After each pass through the repeated zones, the correct path diverges toward two reward locations (i.e., 1-2-3-**4**-1-2-3-**5**). To receive an immediate reward, the rat needed to go toward zone 4 after the first pass through the repeated zones (1-2-3), and toward zone 5 after the second. To investigate its role in this disambiguation, PC was inactivated using bilateral infusions of muscimol, a $GABA_A$ receptor agonist, during learning and after acquisition of the complex sequence task. Saline infusions were performed either in the session immediately before or after each muscimol infusion session,

and this order was counterbalanced. Performance during inactivation showed an increase in path distance toward the two disambiguation zones (zones 4 and 5) compared to saline controls during learning and after acquisition. However, performance was not impaired for the other items of the complex sequence (1-2-3), or with muscimol infusions for an 8-zone simple sequence that did not contain any repeating segments (i.e., 1-2-3-4-5-6-7-8). Thus, PC may be particularly important for disambiguating place and action.

Disclosures: C. Simmons: None. **H. Bowley:** None. **M. Kirlan:** None. **M. Baiamonte:** None. **A.A. Wilber:** None.

Poster

329. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 329.20/HHH8

Topic: H.01. Animal Cognition and Behavior

Support: NIA Grant AG049090 to AAW
NSF Grant 1631465 to BLM
NSERC Grant RGPIN-2017-03857 to BLM

Title: Impaired spatial orientation and memory reactivation in a mouse model of Alzheimer's disease

Authors: S. C. MOSELEY[1,2], S. D. BENTHEM[1,2], I. SKELIN[3,4], A. MELILLI[1,2], A. C. STIMMELL[1,2], B. L. MCNAUGHTON[5,4], *A. A. WILBER[1,2]
[2]Dept. of Psychology and Program in Neurosci., [1]Florida State Univ., Tallahassee, FL; [3]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [4]Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA; [5]Dept. of Neurosci., The Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: In preclinical Alzheimer's disease (AD), spatial navigation is impaired (Allison et al., 2016). We recently found impaired spatial orientation and increased pathology in the dorsal hippocampus of 6-month female 3xTg-AD mice compared to male 3xTg-AD and non-Tg controls of the same age (Stimmell et al., 2018). This finding suggests that impaired use of landmarks may underlie navigation impairments in AD. Theoretical, computational and recording studies of parietal cortex (PC) and hippocampal activity patterns suggest a PC-hippocampal network for transforming landmarks from egocentric (body-centered) to allocentric (map-like) coordinates for spatial orientation. Thus the spatial orientation deficit in female 3xTg-AD mice could be a consequence of AD related changes to the PC-hippocampal network for coordinate transformation. Recent findings suggest that in preclinical AD a functional deficit

emerges in PC, as a consequence of entorhinal cortex pathology (Kahn et al., 2014). Therefore, to look for evidence of dysfunction in the PC-hippocampal network related to impaired spatial orientation, we assessed modular (multi-unit activity) memory reactivation in 6-month female 3xTg-AD mice that were learning a spatial orientation task. The spatial orientation task requires use of distal cues to locate an unmarked reward zone (Rosenzweig et al., 2003). Mice were implanted with a 16 tetrode recording arrays targeting right PC and hippocampus and then underwent daily recording sessions of rest-task-rest as they learned to locate the unmarked reward zone. To assess memory reactivation we took advantage of a new approach using template matching to compare multi-unit activity patterns from the approach to the reward zone to activity patterns observed during slow-wave sleep (Wilber et al., 2017). Female 6-month 3xTgAD mice had impaired memory reactivation within the PC compared to age-matched non-Tg controls. Further, temporal correlations between markers of memory reactivation in hippocampus (sharp wave ripples) and parietal cortex (delta waves) were reduced in 6-month 3xTg-AD female mice. Thus, AD may cause PC-hippocampal network changes which impair spatial orientation as a consequence of impaired learning related plasticity during sleep.

Disclosures: S.C. Moseley: None. **S.D. Benthem:** None. **I. Skelin:** None. **A. Melilli:** None. **A.C. Stimmell:** None. **B.L. McNaughton:** None. **A.A. Wilber:** None.

Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 330.01/HHH9

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant PO1 AG009973

Title: Head-scan firing cells in hippocampal subregion CA3 of aged rats

Authors: *G. RAO[1], H. LEE[1], N. LUKISH[1], A. TILLEKERATNE[1], M. GALLAGHER[2], J. J. KNIERIM[1]
[1]Zanvyl Krieger Mind/Brain Inst., [2]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: CA3 hippocampal place cells in aged rats fail to rapidly encode spatial changes (Wilson et al., 2005), but this study did not isolate forward locomotion from head-scanning epochs, in which the animal pauses to inspect the environment with head movements (Whishaw et al., 1994). Hippocampal cell firing during scanning is correlated with the formation or potentiation of place fields in adult animals (Monaco et al., 2014). To address how head scanning behavior and hippocampal firing is affected by aging, we examined CA3 cells that fired during

scanning in 8 Long-Evans male rats [3, young (YG, 5-7 mos.), 3 aged-unimpaired (AU, 25-26 mos.), and 2 aged-impaired (AI, 25-26 mos.)] pretested in the Morris water maze to assess their cognitive status. The rats were then trained to run on a circular track, consisting of 4 textured quadrants, located in a curtained room with peripheral objects. Multiple tetrode recordings consisted of 3 sessions with a standard cue configuration identical to training, interleaved with 2 mismatch sessions in which global cues were rotated CW and local cues CCW. All groups exhibited scanning: the mean scanning rate (scans/min) ± s.e for DAY 1, session 1, prior to any cue manipulation, was YG: 6.78 ± 1.89, AU: 8.01 ± 1.00, AI: 5.56 ± 0.04. A significant effect of group on normalized scan rate was observed for the first cue mismatch session [YG: 1.47 ± 0.23; AU: 0.74 ± 0.03; AI: 1.06 ± 0.02; $F(2,5) = 6.2$, $p = .023$], indicating a heightened response to environmental change in the YG group. Spikes were recorded from 110 YG, 152 AU, and 93 AI CA3 pyramidal cells. Cells with at least 30 scanning-related spikes but no place fields in a given session (n = 33 YG, 50 AU, 38 AI) were analyzed. Scan firing rates (number of scan spikes/time spent scanning) showed a significant increase with age [YG: 0.39 ± 0.23; AU: 0.74±.09 ; AI= 1.00 ± 0.17; $F(2,118) = 5.65$, $p < .005$]. The mean vector length of the angular locations around the circular track where scanning spikes occurred (measuring dispersion) was not significantly different across groups [YG: 0.75 ± 0.04; AU: 0.68 ± 0.03, AI: 0.61 ± 0.03; $F(2,118) = 2.61$, $p = .08$], but tended to decrease with age. Significant increases in scan firing rate in the absence of spatially focused firing may explain prior reports of larger CA3 place fields with aging (Wilson et al., 2005). Interestingly, we have observed scan-firing cells in all groups that fire robustly solely during scanning, but not during forward movement, particularly at locations on the track near cues. It is possible that the function of these cells is to punctuate the hippocampal spatial code and segment the representation of space (McKenzie and Buzsaki, 2016; Wang et al., 2017, SFN Abstracts).

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 330.02/HHH10

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIA Grant AG009973

Title: Aged rats with intact memory show additional recruitment in cortical regions relative to young adults in a cue mismatch task

Authors: *R. P. HABERMAN, A. BRANCH, A. MONASTERIO, M. GALLAGHER
Dept Psychol & Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: Functional neuroimaging studies of cognitively normal older adults demonstrate greater activation of cortical regions relative to younger adults during memory tasks. Determining the implications of such enhanced cortical activation is difficult because this cognitively normal older population exhibits variability in long term outcomes and progression to cognitive decline. Here we asked if greater cortical recruitment also occurs in aged memory intact rats, which perform on par with young rats in hippocampal dependent memory tasks and show phenotype stability lasting many months. Using in situ hybridization, we measured a marker of neural activation, Zif268 (Egr1), in the hippocampus and select cortical regions of memory intact aged and young rats in response to a cue mismatch task that engages hippocampal functions critical to memory formation. After being trained to run on a circular track with local and global cues arranged in a fixed position, half the rats experienced a cue rearrangement on test day such that local and global cues were rotated for a 180-degree mismatch. A control group of rats experienced the familiar cue orientation. Behavioral measures assessing recognition of the cue mismatch were similar across. Previously presented work demonstrated similar increases in hippocampal activation in young and aged intact rats in the mismatch group relative to the familiar group. In a new extended analysis, we found elevated Zif268 expression across several cortical regions, including retrosplenial cortex, perirhinal cortex, and lateral entorhinal cortex in the mismatch relative to the familiar group only in aged intact rats. No differences between mismatch and familiar Zif268 expression was found in these regions for young rats, and no differences were found for either age group in the medial entorhinal cortex. Increased expression in parietal association cortex in mismatch relative to familiar occurred in both young and aged rats, demonstrating some consistency across age. These mismatch-induced increases occurred in addition to an overall increase in Zif268 expression in all rats that completed track running (mismatch and familiar combined), relative to home cage rats, for all five cortical regions. These data suggest that, similar to cognitively normal older humans, aged rats with intact memory show greater recruitment of cortical regions than younger rats in a hippocampal activation paradigm. Furthermore, these results are consistent with accumulating data that suggest that aged intact rats recruit adaptive mechanisms, that differ from typical young neurobiological activity, to preserve cognitive function during aging.

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 330.03/HHH11

Topic: H.01. Animal Cognition and Behavior

Support: NIH P01 AG009973

Title: Age does not increase the magnitude of afterhyperpolarization in CA1 pyramidal cells of a behaviorally characterized Long-Evans rat model of aging

Authors: *A. KIRKWOOD[1], D. SEVERIN[2], M. GALLAGHER[3]
[1]Mind Brain Inst., [2]Zanvyl Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD; [3]Dept Psych & Brain Sci., Johns Hopkins Univ. Dept. of Psychological and Brain Sci., Baltimore, MD

Abstract: Recent studies in aging rodents and humans have identified an excess of hippocampal neural activity as an attractive candidate mechanism contributing to age-related cognitive decline. In aged individuals with impaired learning hyperactivity is prominent in the dentate gyrus/CA3 subfields, but not so prominent in the CA1 subfield. This raises the question of how neural activity is maintained in CA1 in the face of excess input from CA3 pyramidal cells. One possible mechanism is a reduced intrinsic excitability of CA1 cells. Indeed, previous studies in Fisher-344 rats, a model of accelerated aging, report an age-related increase in the slow afterhyporlarization (AHP) evoked by a burst of action potentials. This prompted us to test the possible relationship between AHP magnitude and learning performance in a Long-Evans model of cognitive decline. The experiments were conducted in slices prepared from young 6-month adult rats (Y) and ~24-month rats characterized in the Morris water maze as aged impaired (AI) or aged unimpaired (AU). Whole-cell current clamp recordings were made from CA1 pyramidal cells and the AHP was evoked by bursts of somatically induced action potentials (8 AP at 50 Hz) as in previous studies. Our measurements indicate that AHP does not increase with aging in the Long-Evans rat model. Indeed, we found that the peak AHP in the AI group (5.50±0.41 mV; 6 rats, 31 cells) was smaller than the peak AHP measured in the AU group (7.50±0.54mV; 6 rats, 46 cells), which in turn was comparable to the peak AHP measured in the Y group (7.05±0.47; 6 rats, 42 cells). The statistical significance of these findings was confirmed with a Kruskal-Wallis test (KW=6.944) followed by a Dunn's test. These results indicate that reduced intrinsic cellular excitability is not a universal compensatory mechanism to maintain neural activity within optimal ranges. In the CA1 region of Long-Evans rats this function might be accomplished by changes in synaptic inhibition as we have reported previously.

Disclosures: A. Kirkwood: None. **D. Severin:** None. **M. Gallagher:** None.

Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 330.04/HHH12

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant PO1 AG009973

Title: Local-global reference frame control in the CA3 region of aged rats

Authors: *H. LEE[1], N. LUKISH[1], A. TILLEKERATNE[1], M. GALLAGHER[2], J. J. KNIERIM[1,3]
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Abstract: Hippocampus-dependent spatial memory declines with age, and aged rats showed reduced changes in their spatial representations in response to environmental manipulations (Tanila et al., 1997). To address altered hippocampal processing in aging when local and global reference frames are in conflict, young rats and aged rats were trained to run around a circular track containing salient local cues (textures on the track) in a curtained room containing salient global cues (landmarks along the curtains). Three standard sessions were interleaved with two mismatch sessions, in which the local cues were rotated counterclockwise (CCW) and the global cues were rotated clockwise (CW) by an equal amount. Total mismatch angles between the local and the global cue sets varied between 45°, 90°, 135°, or 180°. We recorded neurons from the CA3 region in 3 young, 3 aged-impaired, and 5 aged-unimpaired male, Long-Evans rats. Young (Y) rats were 5-7 months old and aged rats were 25-26 months old at the time of recording. Aged rats were pretested in the Morris water maze and categorized as learning impaired (AI) or learning unimpaired (AU). Comparing the rate maps between a standard and the following mismatch session, cells were classified as "rotating" if their place fields rotated CCW with the local cues or CW if their place fields rotated with the global cues in the mismatch session. They were classified as "remapping" if the place fields appeared or disappeared in either the standard or the mismatch session. Approximately 58% of CA3 neurons (59/101) in young rats and 58% of CA3 neurons (176/301) in AU rats had rotating place fields, while 73% of CA3 neurons (78/107) in AI rats had rotating place fields (X^2=7.4, p = 0.02). All other cells remapped their place fields. Individual cell rotation amounts showed significant angular clustering in all three groups (Rayleigh test, all *p* values < .007). In all combinations of mismatch angles (n = 4) and age groups (n = 3), the mean angle rotated in the CCW direction (binomial test, p < .001), showing control by the local cues. The higher proportion of rotating cells in the AI rats suggests that the spatial representations remained more coherent in the conflict situations than the young and the AU rats. These data are in agreement with the results of Tanila et al. (1997), with the exception that the CA3 cells were more controlled by the local frame of reference compared to the global frame. It is possible that the functional differences observed in the AI rats may be CA3 subregion specific (Lee et al., 2015; Lu et al, 2015). Further analyses will examine the population coherence differences along the CA3 transverse axis (proximal vs distal) in the young and the aged groups.

Disclosures: H. Lee: None. **N. Lukish:** None. **A. Tillekeratne:** None. **M. Gallagher:** None. **J.J. Knierim:** None.

Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC Halls B-H

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Program #/Poster #: 330.05/HHH13

Topic: H.01. Animal Cognition and Behavior

Support: R01 NS039456
NSF Graduate Research Fellowship #DGE1746891

Title: Firing rate modulations may encode surface texture cues within the place cell map of hippocampal CA1 neurons

Authors: *W. HOCKEIMER[1,2], J. J. KNIERIM[1,2]
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Abstract: An influential theory asserts that episodic memories are stored within a framework of the location where they occurred [1]. The hippocampus has been suggested as a neural substrate of this "cognitive map." It has further been proposed that spatial information is encoded in the set of neurons that are active in an environment and nonspatial information in the distribution of those neurons' firing rates [2]. To provide a direct test of this hypothesis, pilot data was collected from a 20-month old, male, Long-Evans rat implanted with a tetrode array in hippocampal CA1. The animal was trained to perform a match-to-sample task on a T-maze using textured floor plates as stimuli. On each trial, the rat traversed a textured plate on the stem and chose the arm of the T-maze that contained a matching copy of that texture, ignoring the nonmatching distractor placed on the opposite arm. Average performance was 64.3% across 11 days of recording, providing single-unit data from 94 pyramidal neurons. To test the hypothesis that texture identity is encoded in rate modulations of place field activity, data was compared across trials from periods during which the animal occupied the same location but different textures were present underneath. This analysis revealed a subset of place cells exhibiting field modulation as a function of texture present. To assess the significance of these findings, we performed a permutation test with a family-wise error rate of 0.05 to identify location bins in which a cell fired more strongly to one of the textures over another. We further required that there be a set of contiguous bins of > 5 cm that pass the 0.05 familywise criterion and that the firing rate of the cell be > 1 Hz in at least one of these bins. These criteria resulted in 18/94 cells displaying firing rate modulations to at least one of the texture pairs. Further, a random forest classifier trained on the population firing rates was able to correctly predict texture identity with 50% accuracy, compared to 33% chance performance, suggesting that the population contains information about texture identity. These preliminary data support the rate-remapping hypothesis that hippocampal

neurons encode specific nonspatial cues present within the cell's place field by modulating the firing rate of the cell when the rat occupies the place field.
[1] O'Keefe, John, and Lynn Nadel. *The hippocampus as a cognitive map*. Oxford: Clarendon Press, 1978.
[2] Leutgeb, Stefan, Jill K. Leutgeb, Carol A. Barnes, Edvard I. Moser, Bruce L. McNaughton, and May-Britt Moser. "Independent codes for spatial and episodic memory in hippocampal neuronal ensembles." *Science* 309, no. 5734 (2005): 619-623.

Disclosures: W. Hockeimer: None. **J.J. Knierim:** None.

Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

Location: SDCC Halls B-H

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Program #/Poster #: 330.06/HHH14

Topic: H.01. Animal Cognition and Behavior

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Title: Spatial firing properties of the lateral entorhinal cortex on a one-dimensional track

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Abstract: Decades of research have established the role of the hippocampus and its neighboring areas in spatial navigation as evidenced by the presence of numerous spatially selective cell types, such as place cells in the hippocampus and grid cells and head direction cells in the medial entorhinal cortex (MEC), one of the primary input areas to the hippocampus. Neurons of the lateral entorhinal cortex (LEC), which is the other major input pathway to the hippocampus, are much less spatially selective, even in cue rich environments. Instead, when objects are present in an environment, LEC neurons fire at the location of the objects and a small proportion develop spatial firing fields away from the objects. Even though many studies of the hippocampus employ tasks in which rats run on one-dimensional tracks (e.g., linear or circular tracks), few studies have examined the responses of LEC cells during goal-oriented tasks on such tracks. We recorded 242 LEC neurons from 4 male Long-Evans rats (5-6 months old) while they performed a shuttling task on a linear track (5 feet long) or a circular track (radius 46 cm) between fixed goal locations. A majority of LEC cells showed weak but significant spatial tuning for at least one running direction (shuffling test, $\alpha = 0.05$, linear track: 131/194; circular track: 134/199), with a small percentage of cells having strong (information score > 0.5) and significant spatial

information (linear track: 28/194; circular track: 24/199). In addition, a significant number of cells showed direction selectivity on the track (88/227 on linear track, 90/231 on circular track), especially around the goal locations (Monte Carlo simulation test against uniform distribution, linear track, $P < 0.001$, circular track, $P = 0.004$). When we recorded the cells in the dark on the circular track, the number of cells that showed significant direction selectivity did not change significantly (dark, 65/140; $\chi 2(1) = 2.00$, $P = 0.16$), although the correlation of spatial firing patterns between light and dark sessions showed a significant difference from the correlation between the two light sessions ($t(243) = 3.92$, $P < 0.001$). Previously we reported that many LEC neurons encode egocentric bearing relative to certain external locations or objects (Wang et al., SFN Abstracts 2017). Thus, the direction-dependent firing of LEC neurons on the 1-D apparatus could be a demonstration of egocentric bearing selectivity relative to the goal locations at the ends of journeys. These results further suggest that under naturalistic behaviors involving behaviorally relevant items or locations, LEC neurons show rich dynamics, which may be related to the encoding of the contents of episodic memory.

Disclosures: C. Wang: None. **H. Lee:** None. **G. Rao:** None. **J.J. Knierim:** None.

Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Topic: H.01. Animal Cognition and Behavior

Support: R01 NS039456
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Johns Hopkins University Brain Science Institute

Title: Responses of granule cells, mossy cells, and proximal CA3 cells to local/global cue mismatch indicate a shared role in pattern separation

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Abstract: The processes of pattern completion and pattern separation are thought to be essential for memory storage and recall. Neunuebel & Knierim (2014) provided evidence for the hypothesis that CA3 and the dentate gyrus (DG) are involved in pattern completion and pattern separation, respectively. In a “double rotation” task, where local texture cues on a circular track and global cues at the perimeter of the room were rotated in opposite directions (for total cue mismatch amounts of 45°, 90°, 135°, or 180°), there was a relatively coherent population

response in CA3, despite disrupted input from the DG. Furthermore, Lee et al. (2015) found that the response of cells in the proximal part of CA3 (pCA3) was similar to the DG response, while more distal regions of CA3 were involved in pattern completion.
Although most cells in the DG are granule cells, mossy cells in the hilus may be recorded on tetrodes located throughout the DG and in pCA3. It is uncertain how the responses of mossy cells compare to granule cells and pCA3 cells. We used a random forests classifier to classify pCA3 recordings from Lee et al. (2015) and DG recordings from Neunuebel & Knierim (2014) to examine the responses of granule cells, mossy cells, and pCA3 cells in the double rotation task.
Out of 272 active cells from 14 Long-Evans rats (male, 4-7-months old), 124 were classified as mossy cells (21/114 from tetrodes in pCA3, 103/158 from tetrodes in DG). For all three cell types, most cells gained or lost place fields (i.e., remapped) following the cue mismatch sessions > 45° (number of remapping cells/total: granule 18/30, mossy 78/140, pCA3 101/126). These proportions were significantly different (chi-square = 18.4, p = .0001), demonstrating that pCA3 cells were less likely to maintain their place fields in the mismatch session compared to the granule and mossy cells. We further investigated whether the subset of cells that maintained place fields between the standard and > 45° mismatch sessions rotated their place fields as a coherent ensemble in the same direction, as has been reported for distal CA3 (Lee et al. 2015). For all 3 areas, ~60% of the rotating place fields followed the local cues and ~40% followed the global cues (local cue cells divided by total number of rotating cells: granule 6/10; mossy 28/49; pCA3: 16/24; chi-square = 0.61, p = .74). Analyses of population vector correlations demonstrated very small correlations between standard and mismatch sessions in all 3 classes of cells. These data show that mossy cells resembled the pattern observed previously in the DG and pCA3 regions and suggest that all components of the DG/pCA3 circuit may work together as a computational unit to support pattern separation.

Disclosures: D. Goodsmith: None. **H. Lee:** None. **J.P. Neunuebel:** None. **J.J. Knierim:** None.

Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Support: NIH Grant R01 NS102537
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Title: Hippocampal place fields from modular and distorted entorhinal grid inputs via synaptic plasticity in environments of varying size: A model

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[1]Zanvyl Krieger Mind/Brain Inst., [2]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: How entorhinal grid cells contribute to the generation of stable place fields in the hippocampus is poorly understood. Hippocampal cells can produce place fields in the absence of these inputs, but several studies indicate that this ability may be limited to place fields expressed by CA1 neurons near environmental boundaries. These studies thus suggest that grid inputs become increasingly relevant in the earlier stages of the trisynaptic loop, or while the animal ventures farther into open space. We previously described a spiking model of place-field formation based on a Hebbian plasticity rule applied to grid inputs, which were simulated from real animals' trajectories recorded during foraging sessions. The momentary firing rate of the inputs determined the direction of synaptic weight changes, which were gated postsynaptically by the place cell activation—consistent with later experimental observations that intrinsic excitability is correlated with a cell's propensity to form a place field. Very high learning rates were necessary for place fields to form, sometimes causing their abrupt emergence, also consistent with experimental observations. Here, we updated this model by (A) revising some of the original assumptions in light of the richer experimental characterization of grid cell properties currently available and (B) testing the model in larger environments, where grid inputs may become increasingly important to the expression of place fields. (A) We modeled grid distortions (elliptical compressions and shearing); clustered grid orientation and scale following a modular organization; and varied peak firing rates across different vertices of the grid. These modifications to the inputs did not compromise the model's ability to produce spatially selective and stable place fields. (B) As larger environments were tested (and more grid modules could be accommodated), we found that more place fields were typically produced per place cell, consistent with experimental observations. Some of these fields, however, were the result of remapping episodes that could occur after tens of minutes from the beginning of the session. In sum, our theoretical proposal that place fields can form autonomously from grid cell inputs via a fast, postynaptically gated, Hebbian plasticity rule holds up to observed deviations of the grid representation from a continuum of purely periodic patterns. Moreover, our simulations highlight the need for experiments characterizing how place field properties may change in large 2D environments away from their boundaries.

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Title: Robust tracking of neuronal spatial dynamics enables discovery of recalibration of the path integrator in hippocampal place cells

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Abstract: Path integration, the ability to update an internal estimate of position by integrating over time a movement vector representing speed and direction, is critical for survival across taxa. This computation requires a finely tuned gain factor that relates the animal's self-motion to the update of position in the internal representation. We investigated how visual landmarks can calibrate this gain factor using a novel, augmented reality system that puts these landmarks in continuous conflict with nonvisual self-motion cues. An estimator of spatial coding was required to determine the effect of these manipulations on hippocampal place cells. Standard Bayesian decoding techniques can estimate a rodent's position from a population of place cells. However, visual cue manipulations can trigger extensive reorganization (remapping) of place cells, causing these population decoders to become less accurate or fail entirely. Using an experimental paradigm where the animal traverses a closed 1D curve, we took advantage of the periodicity of place fields as the animal runs laps to develop a spectral algorithm to track the hippocampal gain by estimating the spatial frequency of a place cell's firing pattern. Each cell's gain was tracked independently, allowing detection of subpopulations that might have different spatial tuning characteristics. The gain of interneurons could also be tracked. This technique is robust to remapping: such events cause phase shifts in a cell's spatial tuning which only induce a localized effect on the gain estimate. In a coherent population of cells, the estimated gain trajectory can be integrated to estimate the animal's position. We used this novel spectral estimation technique to analyze CA1 place cell ensembles recorded from 5 male, Long-Evans rats (5-9 months old) as the rats ran circular laps while an array of visual landmarks under feedback control was rotated in directions the same as, or opposite to, the rats' movement. In all 5 rats, the gain of the hippocampal path integration system could be recalibrated quickly (30 laps or less) and the recalibrated gain was sustained over extended periods. Thus, the path integration gain is a plastic variable that is fine-tuned through experience. This fine-tuning may be required to (a) maintain accuracy of the path integration signal under different behavioral conditions; (b) synchronize the different types of self-motion signals (e.g., vestibular, optic flow, motor copy, or proprioception)

thought to underlie path integration; and (c) coordinate the discrete set of different path integration gains thought to underlie the different scales of grid cell modules in the medial entorhinal cortex.

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Topic: H.01. Animal Cognition and Behavior

Support: Whitehall Research Grant 2017-12-114

Title: Is theta a traveling wave in the medial entorhinal cortex?

Authors: *J. HERNÁNDEZ, K. COOPER, E. NEWMAN
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Abstract: Though it is well known that the entorhinal-hippocampal system supports spatial navigation and memory, how these circuits interact to support adaptive behavior remains poorly understood. Both regions exhibit prominent 6-12 Hz rhythmic fluctuations in the LFP (i.e., theta activity) during exploratory behaviors and REM sleep. In the hippocampus, theta activity is not synchronous. Rather, it precesses steadily across the long axis to span a total of 180 degrees phase offset. At dorsal sites, it is well known that the entorhinal activity is phase locked to the hippocampal theta rhythm. For these areas to communicate in a similar fashion across their long-axes, theta activity in the entorhinal cortex must also precess across the long-axis. Whether this is the case remains unknown. To understand how the hippocampus and entorhinal cortex functionally interact, it is essential to know whether theta also precesses along the long axis of the medial entorhinal cortex. To resolve this, we built custom electrode arrays designed to simultaneously record across the entire long axis of the rat medial entorhinal cortex (spanning >4.5 mm) at regular fixed intervals (~580 um). We then recorded theta activity as rats performed a variety of tasks. We found a systematic theta phase shift along the length of medial entorhinal cortex. As previously reported for the hippocampus we found that there is a 180-degree total shift indicating that the two areas are likely to be synchronized across the long axis. The phase shift is attributable, in part, to a shift in the theta waveform across the axis. The theta wave recorded from dorsal sites was a leftward shifted asymmetric wave while the theta wave recorded ventrally was largely symmetric. This shift, however, did not account for the full phase precession across the axis. To understand if the phase shift across the axis reflects a traveling

wave, we computed the temporal cross-correlation of theta power across electrodes with the rationale that changes in power should propagate along with phase if it is a traveling wave. Notably, however, across all electrodes, the peak correlation occurred at zero-lag indicating that theta activity in the entorhinal cortex is a phase-shifted standing wave, increasing in power synchronously across the axis rather than propagating along the axis. These results suggest that the entorhinal cortex and hippocampus are likely synchronized across the long-axis and provide new insights into the nature of theta phase shifts along the long-axis constraining our understanding of how these areas work together to support spatial navigation and memory.

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Topic: H.01. Animal Cognition and Behavior

Support: Whitehall Research Grant 2017-12-114

Title: Dorsal hippocampus not necessary in a delayed spatial win-shift radial arm maze task

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Abstract: Effective foraging and navigation depend upon spatial working memory. However, spatial working memory is not well understood at a systems level. The hippocampus is well known for its role in spatial coding and involvement in spatial memory (Buzsaki & Moser., 2013) and prior inactivation studies in rodents have suggest that the dorsal hippocampus is necessary to perform spatial working memory tasks as the temporal delay increases from seconds to minutes (Lee & Kesner., 2003; Churchwell & Kesner., 2011). This dependency is widely understood to persist independently of the amount of training animals receive. Here we describe data which demonstrates that the dorsal hippocampus is not always necessary for spatial working memory at intermediate delays, particularly when animals become overtrained. Procedurally, rats were trained to visit all arms of an 8-arm radial maze in a delayed spatial win-shift task across two trials. In the first trial (i.e., study trial), only four arms were open. In the second trial (i.e., test trial), run 8 minutes later, the rat was challenged to remember which four arms they had not yet visited when all arms were opened. A unique configuration of arms was used for each study-test trial pairing. Rats received bilateral infusions of either 4 % w/v lidocaine or phosphate buffered saline prior to the test phase such that with the lidocaine, the dorsal hippocampus could

be expected to be inactivated throughout the test trial. Compared to saline infusions, lidocaine infusions produced no difference in the number of correct arm entries or the number of total arm entries in the test trial. These results indicate that spatial working memory was largely preserved despite the 8-min delay between trials. Importantly, these rats were overtrained on the task before infusions began. Thus, the role of the dorsal hippocampus in spatial working memory may be attenuated in contexts with extensive training. The discrepancy of these result with prior literature and the roles of the dorsal and ventral hippocampus are discussed.

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Topic: H.01. Animal Cognition and Behavior

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Title: Decoding the elements of neural computation

Authors: *S. P. FABER[1], N. M. TIMME[2], J. M. BEGGS[1], E. L. NEWMAN[1]
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Abstract: Understanding how networks of neurons process information is a major objective of systems neuroscience. In particular, the determinants of how information is modified through successive interactions between neurons is poorly understood. Information theoretic analyses are useful for quantifying information propagation and modification in networks of spiking neurons and have revealed important new insights into how cortical networks process information. Yet, the results of information theoretic analyses do not address what types of propagation (e.g., excitatory vs. inhibitory) or modification (e.g., ‘and-gate,’ ‘x-or,’ etc.) occur between neurons. The goal of this project was to reveal the types of information propagation and modification that take place in cortex. To do this, we recorded the spiking activity of 98 - 594 well isolated neurons simultaneously from organotypic cultures of mouse somatosensory cortex using a high-density 512-channel microelectrode array. We then identified functionally connected pairs of neurons using an information theoretic approach (i.e., those with significant transfer entropy in the 1.6–14 ms range), across which we could evaluate the types of information propagation. We further identified triads, sets of three neurons, where the output of two transmitting neurons

converged on a third receiving neuron and, for each triad, used partial information decomposition to quantify neural computation within that triad. We then asked: how does neural computation depend on the spiking patterns of interacting neurons? The analyses revealed three clear patterns. First, information modification by a receiving neuron is greatest when there is greater information transfer between the upstream neurons. Second, information modification is greatest when the information transfer from the upstream neurons to the downstream neurons is unidirectional (i.e., the receiving neuron does not transfer information back upstream). Third, excitatory interactions lead to increased amounts of information transfer and neural computation relative to inhibitory interactions. These findings inform our understanding of how network topology and neural activity shape neural computation. We discuss these results in the context of learning and memory by considering the role of neural computation in memory encoding and retrieval.

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Whitehall Foundation 2010-05-84
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National Science Foundation Graduate Research Fellowship DGE-1321846

Title: A nonspatial auditory task to investigate the memory for sequences of events across timescales

Authors: *S. M. GIL[1], G. A. ELIAS[2], S. MESA[3], R. METHERATE[4], N. J. FORTIN[5]
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Abstract: The ability to temporally organize information is fundamental to many perceptual, cognitive, and motor processes. To investigate the neural basis of this capacity, we previously

developed a cross-species sequence memory task, using olfactory stimuli in rodents and visual stimuli in humans, in which sequences of stimuli are presented over a timescale of seconds. Importantly, we found that the two versions show strong behavioral parallels and depend on similar circuits across species, including the hippocampus and prefrontal cortex. Here we developed an auditory version of the task, which involves repeated presentations of pure tones of different frequencies and requires subjects to correctly identify each tone as presented "in sequence" (e.g., ABC···) or "out of sequence" (e.g., ABD···). Since the auditory modality allows for greater control over the timing of stimuli, this approach will allow us to more systematically investigate the neural mechanisms underlying the memory for sequences of events across timescales. In addition, this approach may help determine how this capacity relates to other forms of temporal integration performed by the auditory system.
Keywords: sequence memory, temporal order, temporal context, timing, temporal integration, auditory processing, episodic memory

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Whitehall Foundation 2010-05-84
NIMH R01 MH115697

Title: Prefrontal neurons represent task-relevant information about upcoming events

Authors: *G. A. ELIAS, S. MESA, M. GIRCZYC, M. MCDERMOTT, A. T. GUDMUNDSON, J. D. LUONG, G. G. K. GOLLA, N. J. FORTIN
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Abstract: A defining feature of episodic memory is its sequential organization. The hippocampus and prefrontal cortex have been identified as key regions in a network supporting memory for sequences of events. In a recent study, we recorded neural activity in hippocampal region CA1 as rats performed a nonspatial odor sequence memory task. A significant proportion of CA1 neurons fired differentially to odors based on their temporal context, i.e. whether the

odor was presented “in sequence” or “out of sequence” (Allen et al., 2016, *JNeurosci*). Here, we recorded prefrontal neurons (prelimbic region) in rats performing the same task to determine how task-relevant coding differs in prefrontal cortex. Briefly, rats were trained to identify whether each delivered odor was presented in or out of sequence. Preliminary results show the activity of prefrontal neurons is influenced by the ordinal position of a trial (odor presentation) within the sequence. This modulation was observed prior to the start of a trial, suggesting it might serve to track the current sequence position or store a short-term memory trace of the previously presented odor. To distinguish these alternatives, we determined the degree to which the pre-trial activity of each neuron was explained by the identity of the *previous* odor or the *upcoming* sequence position. Pre-trial activity was significantly explained by both the previous odor and the upcoming position on trials identified correctly, but not on errors. Notably, activity explained by the previous odor was present only ~200ms prior to trial start whereas activity explained by upcoming position was present during the entire pre-trial period. Interestingly, on trials following an odor presented out of sequence (when the identity of the previous odor is not informative about the upcoming odor), pre-trial activity was significantly explained only by the upcoming position, not the preceding odor. These results suggest the prefrontal cortex plays a key role by representing different forms of task-relevant information, but can also selectively activate the correct, task-critical representation when necessary.

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Poster

330. Animal Cognition and Behavior: Learning and Memory: Cortical-Hippocampal Interactions II

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Title: Sequential activation of upcoming nonspatial item representations in hippocampal activity

Authors: *N. J. FORTIN[1], G. A. ELIAS[1], L. LI[2], F. AGOSTINELLI[3], P. BALDI[3], B. SHAHBABA[2]
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Abstract: The hippocampus plays a key role in the memory for sequence of events. Considerable research suggests this applies to both spatial and nonspatial memories; however, our understanding of the fundamental neuronal mechanisms is limited by the fact that electrophysiological studies almost exclusively focus on spatial information. It therefore remains to be determined whether sequence coding properties observed in hippocampal neurons, including the reactivation of experienced or predicted sequences of locations, extend to nonspatial information. To address this important issue, we recorded CA1 activity in rats performing a nonspatial sequence memory task. Briefly, the task involves repeated presentations of sequences of odors at a single port and requires rats to identify each item as "in sequence" or "out of sequence". We then used statistical machine learning methods to quantify the information represented in CA1 ensemble activity during odor presentations. First, we used an unsupervised deep learning model to identify the structure in population activity vectors at different moments within trials. As expected, the model did not clearly differentiate among population vectors before trial-specific information was present (i.e., immediately after the rat enters the port; 0-50ms time period). However, during the same odor presentations, the model then strongly differentiated among the different odors (200-250ms time period) and whether odors were presented in or out of sequence (400-450ms time period). Second, we used the output of this model to quantify the degree to which each odor representation was decoded (predicted) during individual trials. As expected, we found that the representation of the currently presented odor could be accurately decoded when the animal is sampling the odors (~250ms). Importantly, within the same odor presentation, we also found that the representations of upcoming odors were then activated in the correct sequence, and that this coding property was linked with performance. These results provide compelling evidence that reactivation of experienced sequences of events in hippocampal neurons extends beyond the domain of spatial trajectories, and thus represent a fundamental role of the hippocampus in memory.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.01/HHH24

Topic: H.01. Animal Cognition and Behavior

Support: Dart NeuroScience LLC

Title: Optimising a behavioural protocol for an animal model of everyday memory

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Abstract: Aim: Better animal models of 'everyday memory' are required beyond tests of novelty-recognition or spatial memory. A behavioural protocol in the 'event arena' in rats (Bast et al., J. Neurosci., 2005) was recently revised (Nonaka et al., Eur. J. Neurosci., 2017); it shows overnight forgetting, retention sensitive to novelty and other relevant properties. We have recently found, however, that a subset of animals use ideothetic path integration rather than allocentric representations. Our aim was to optimise the protocol whereby rats demonstrably use allocentric representations.
Methods and results: The core concept is that regular training takes place over weeks or even months, with new memory traces encoded each day. During encoding, rats find a rewarded food pellet hidden in a different daily location. Instead of carrying the rewarded pellet back to the startbox (permissive for path integration), they are trained to always carry it to a specific goal box (in the north). Memory retrieval after a delay consists of the rats being released from the different startbox (East, South or West) either (a) to find more food at the same place from a choice of 6 locations (choice test), or (b) to dig freely in these 6 locations with no accessible food available (probe test). We found that rats initially prefer to return to their start location (Whishaw et al., Behav. Brain. Res., 2001) but soon overcome this, thereby abandoning path-integration, and display good performance with the properties of everyday memory.
Conclusion: The protocol is reliable and absolutely requires use of allocentric cues. Current work is checking beneficial effects of novelty and optogenetic manipulations in the locus coeruleus that was shown in mice (Takeuchi et al., Nature, 2016).

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.02/HHH25

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIMH 4R00H099153
NIH/NINDS 1R01NS104828

Title: Biphasic hippocampal activation by unconditional stimulus shapes contextual memory and memory generalization

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Abstract: To apply what has been learned from experience to new situations, memories need to be generalized based on the similarity among circumstances. Failing to generalize can lead to failure to recognize danger. On the other hand, over-generalization leads to ambiguity in memory retrieval and is implicated in neuropsychiatric disorders such as post-traumatic stress disorder, depression and schizophrenia. To understand how the level of generalization is determined, we conducted functional imaging of neuronal activity at the CA1 region of the hippocampus, a brain region critical for encoding and generalizing contextual memories, during contextual fear conditioning training and tests. We found that CA1 neurons showed specific activities in reaction to the contexts and unconditional stimulation - the electric foot-shocks. Interestingly, the responses to foot-shocks were biphasic, consisting of an early phasic phase and a delayed tonic phase. The neurons active in the delayed phase showed high activity when the mice were learning the context and when the contextual memory was retrieved, suggesting that they encoded contextual information. Moreover, their activity during context exploration predicted the level of memory generalization. The results indicate that the hippocampus, in contrast to what has been described in the traditional models of conditioning, reacts to unconditional stimulation and this reaction may determine the precision and generalization level of memories. Future work will focus on using temporal-specific optogenetic silencing to examine the causal roles of foot-shock-related neuronal activity in memory generalization and on elucidating the neuronal mechanisms underlying the biphasic activation.

Disclosures: J. Guo: None. **D. Truong:** None. **A. Samuel:** None. **A. Barreiro:** None. **E. Kavalali:** None. **D. Lin:** None. **W. Xu:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.03/HHH26

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NINDS grant #R37 NS-071785-07

Title: Effect of time and speed on hippocampal theta rhythm in freely behaving mice

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Francisco, San Francisco, CA; [3]Dept Neurolog Surgery, Univ. California San Francisco, San Francisco, CA

Abstract: Hippocampal theta (6-12 Hz) oscillations are implicated in different aspects of behavior and are correlated with running speeds. Recent research has highlighted the effect of time on hippocampal processing (Colgin et al 2018), however it is unknown how speed and time interact to modulate theta rhythm within the hippocampal sub-regions (CA1, CA3, DG) when the animal is exposed to the same environment. We hypothesized that hippocampal theta is affected by both speed and time independently, and, depending on the cognitive state of the animal, observed theta will be disproportionally affected by one process more than the other. To test this hypothesis, we studied hippocampal theta oscillations in mice while performing open field navigation. Specifically, we used 32-channel silicone probes with recording electrodes distributed across different regions of the hippocampus (area CA1, CA3 and DG) to record *in vivo* local field potential signals in wild-type mice (n = 6) while freely moving in an open field task. Mice were exposed to three different environments for two 25-min sessions per day. We analyzed how time and running speed effected theta power within each hippocampal sub-region across sessions. In general, we present two major findings: (1) the previously reported positive correlation of running speed on hippocampal theta power is present only in the first exposure trial, and habituates across both time and session, and (2) there is an overall tendency for theta power to decrease in amplitude across time and sessions (holding speed constant). These results suggest that speed effects theta power in the earlier stages of encoding. However, after the environment is well known, time plays a larger role in theta modulation.

Disclosures: R. Paterno: None. **T. Li:** None. **S.C. Baraban:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.04/HHH27

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH100318

Title: Oscillatory and single-unit activity in the amygdala-hippocampus circuit in response to optogenetic stimulation of the amygdala

Authors: *N. S. AHLGRIM[1,2], D. S. REIS[1], S. A. SWARNA[3], J. R. MANNS[1]
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Abstract: Activation of the basolateral amygdala (BLA) by both arousal and direct brain stimulation can modulate hippocampal activity. Prior work has assessed the impact of direct BLA stimulation on memory performance, plasticity, and oscillatory activity in the hippocampus. Here, we optogenetically stimulated the BLA in awake rats over a large parameter space to determine the extent of and the quality of effect that stimulation has within and between those brain regions. Specifically, we recorded local field potentials and single units in the BLA and in the CA1 and CA3 subregions of the dorsal and intermediate hippocampus. The design allowed us to record the changes in neural activity during and after BLA stimulation, with focus on oscillatory power and coherence between regions. Given the ability of the BLA to induce remapping of place cells in the hippocampus, we also stimulated the BLA while rats ran on a fixed path to investigate the effect of stimulation on place cell dynamics. We recorded activity before, during, and after stimulation throughout a continuous block of activity. We hypothesized that hippocampal ensembles that were active concurrently with BLA stimulation would be disproportionately represented in subsequent activity. Finally, we repeated the running task after 24 hours to assess the stability of any changes to place cell properties. Our results demonstrate the effects of optogenetic stimulation on the communication between the BLA, CA1, and CA3.

Disclosures: N.S. Ahlgrim: None. **D.S. Reis:** None. **S.A. Swarna:** None. **J.R. Manns:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

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Title: Intracellular dynamics of hippocampal CA3 pyramidal cells in relation to brain state in awake head-fixed mice

Authors: *A. L. KEES, M. MALÉZIEUX, C. MULLE
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Abstract: Different behavioral states are associated with distinct brain states. Each brain state is associated with characteristic oscillatory patterns in the local field potential (LFP), which reflects different patterns of coordinated neuronal activity. Studies from several brain areas show that changes in single cell properties correlate with and possibly result in these changes in brain state. While much work has characterized different brain states and their LFP signatures, the underlying cellular mechanisms are less known.

Area CA3 of the hippocampus, important in rapid encoding of one-trial memory, is of particular interest for this line of research because of its unique function and network structure. CA3 is the site where information from the entorhinal cortex, dentate gyrus, and CA3 itself (via extensive recurrent connections and local inhibition) is compared and integrated before output to CA1. During quiet wakefulness, the hippocampal LFP displays large irregular activity punctuated by short oscillations known as sharp-wave ripples, which play a role in memory consolidation. During exploratory behaviors, hippocampal LFP oscillates at both theta and gamma frequencies. CA3 pyramidal cells play an important role in each of these brain states; they are involved in the generation of both sharp waves during quiet wakefulness, and gamma during exploratory behavior.

To explore the changes that occur in the intracellular dynamics of CA3 pyramidal cells during changes in brain state, we made whole-cell patch-clamp recordings from CA3 pyramidal cells in awake head-fixed mice. In order to characterize brain states, we combined those recordings with measurements of pupil diameter and CA3 LFP.

We find that during running, CA3 pyramidal cells reduce their firing rate. Additionally, as the mouse transitions between resting and running, there is an overall change in the membrane potential, either a hyperpolarization or a depolarization, which can be partially explained by the membrane potential of the cell before the start of the run. Finally, the variance of the membrane potential is different during running and rest, which may have ramifications on the integration of synaptic inputs as well as indicate changes in the function of the CA3 network as a whole. Taken together, these findings indicate that changes in behavioral state are accompanied by changes on the single-cell and network levels in area CA3 of the hippocampus; these changes may underlie the ability of this area to switch between different stages of memory processing.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.06/HHH29

Topic: H.01. Animal Cognition and Behavior

Support: R01-MH101198

Title: Stability and disruption of hippocampal spiking sequences encoding odors and time during working-memory

Authors: *J. TAXIDIS[1], A. L. MYLAVARAPU[1], E. PNEVMATIKAKIS[2], P. GOLSHANI[3]
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Abstract: Working memory (WM) allows for active retention of information during a short period of time. Even though its neurophysiological hallmark is persistent neuronal firing across a delay period in prefrontal cortical areas, WM is thought to incorporate a larger network, including the hippocampus (Sreenivasan et al. 2014). Instead of persistent firing, hippocampal ensembles typically fire in sequences during delayed-response tasks (Pastalkova et al. 2008, MacDonald et al. 2011). These sequences may be critical for task performance, but their link to WM is not understood. Are they associated with the memory of the stimulus? Are they causally linked with learning the task? How do they evolve over time? To gain more insight in these questions, we applied two-photon calcium imaging *in vivo* in the dorsal CA1 pyramidal layer of head-fixed mice while they performed an olfactory delayed non-match-to-sample task (DNMS) requiring WM activation (Liu et al. 2014). We recorded activity from hundreds of neurons over multiple days and a variety of delay periods (5-10 seconds). We observed two distinct classes of pyramidal cells: (i) neurons that were active during the presentation of specific odor stimuli ('odor-cells') and (ii) neurons that were active during given time points in the delay following specific odor stimuli ('delay- cells'). These collectively formed odor-specific spiking sequences that covered the entire odor presentation and delay period and encoded odor identity and delay time. When extending the delay, odor-cells remained stable whereas delay-cells shifted their fields. Similarly, by tracking the same neurons over multiple days, we observed that odor-cells retained their representation for multiple days, whereas delay-cells remapped their activity, yielding overall unstable sequences. Moreover, we conducted optogenetic manipulation experiments, disrupting these sequences during (i) learning the task, (ii) in the well-trained phase and (iii) when extending the delay, but found no significant effects in any of these conditions. However, performing the same manipulation in the medial entorhinal cortex (MEC), resulted in slower learning curves and adaptation to extended delay duration. This work indicates that two distinct neural codes coexist in CA1. A stable stimulus-driven and an internally-generated unstable one encoding task-relevant time. Activation of MEC, plausibly shaping these dynamics, is required for efficient learning of the task or adapting to increased memory load. Untangling the mechanisms that generate these representations is crucial for understanding population encoding in the hippocampus and its role in memory formation.

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331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.07/HHH30

Topic: H.01. Animal Cognition and Behavior

Title: Phase decoding of replay events in the rodent hippocampus

Authors: *S. MACKESEY[1], F. T. SOMMER[2]
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Abstract: Over the last decade, the local field potential (LFP) has been shown to encode high-fidelity behavioral information. In particular, the phase structure of theta-filtered recordings from rat hippocampal area CA1 robustly encodes the position of a navigating rat. Application of dictionary learning to a demodulated version of this signal reveals the presence of place-tuned phase-distortion signal components distributed across a broad swath of CA1. One possible explanation for this phenomenon is that upstream spiking place cells generate a downstream distributed field potential signature due to postsynaptic EPSPs. Here we investigate hippocampal replay events to test this hypothesis. Replay events are temporally compressed "replays" of earlier sequential place cell activity. They take place both during sleep and during periods of rest (i.e. non-locomotion) during activity. While the spiking activity during replay corresponds closely to that during navigation, the extracellular environment is markedly different in that theta-band power is low but higher-frequency "sharp-wave ripple events" are common. Our hypothesis predicts that spiking place cells should produce field potential phase distortions during replay just as they do during navigation. We test this hypothesis by comparing phase-decoding performance of replay events (during momentary pauses) and location during locomotion) from the same linear-track recording sessions in rodent CA1.

Disclosures: S. Mackesey: None. **F.T. Sommer:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.08/HHH31

Topic: H.01. Animal Cognition and Behavior

Title: Structurally and functionally dissociable hippocampal outputs via distinct classes of subiculum neurons

Authors: *M. S. CEMBROWSKI[1], M. G. PHILLIPS[3], S. F. DILISIO[2], B. C. SHIELDS[4], J. WINNUBST[5], J. V. CHANDRASHEKAR[7], E. BAS[8], N. P. SPRUSTON[6]
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Abstract: The mammalian hippocampus participates in a variety of behavioral and cognitive functions. It has been postulated that parallel circuitry, embedded within the serial architecture of

the hippocampus, may give rise to such functional diversity. We aimed to identify, delineate, and manipulate such putative parallel architecture in the dorsal subiculum, the primary output subfield of the dorsal hippocampus. Population and single-cell RNA-seq revealed that the subiculum could be divided into two spatially adjacent subregions that exhibited prominent differences in pyramidal cell gene expression. We found that these two regions varied in their long range inputs, local wiring, projection targets, and electrophysiology. Leveraging the gene-expression differences between these regions, we used region-specific neuronal silencing to show that they provide distinct contributions to spatial working memory. This work provides a coherent molecular-, cellular-, circuit-, and behavioral-level illustration that the hippocampus embeds structurally and functionally dissociable streams within its serial architecture.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

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Program #/Poster #: 331.09/HHH32

Topic: H.01. Animal Cognition and Behavior

Support: NIH U19NS104590

Title: GABAergic inhibition coincident with sharp wave-ripples broadcasts within and beyond the hippocampal formation

Authors: *G. G. SZABO[1], I. GULSEVER[1], B. DUDOK[1], C. VARGA[3], M. OIJALA[1], I. SOLTESZ[2]
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Abstract: Information processing in the hippocampal formation involves the reception and transmittance of activity patterns of ensembles of excitatory neurons in the dentate gyrus, CA3 and CA1 subfields. At each of these subfields, the information flow is efficiently regulated by GABAergic inhibition in a spatio-temporal manner by specific subsets of GABAergic cells that fire at preferred time windows during ongoing network oscillations. For example, during the hippocampal theta rhythm, a prominent oscillatory pattern that occurs during running, GABAergic cells typically increase their firing rates and show preferential spiking activity at distinct theta phases. During sharp wave-ripples, another prominent hippocampal oscillatory activity pattern that occurs during rest, the discharges of most GABAergic cells in the hippocampal formation are also modulated in distinct cell type-specific manners in terms of

frequency and phase of firing. Here we introduce a special population of GABAergic cells that markedly differ from the known GABAergic neurons in the hippocampal formation. Unlike other GABAergic neurons, these cells reduce their firing rates during running, and show drastically increased spiking activity during sharp wave-ripples such that the action potentials are not phase-locked to the individual ripple cycles. This GABAergic cell population is comprised of cells located in the CA3 and CA1 subfields and their targets are neurons within the hippocampal formation as well as in remote brain areas. Our findings suggest the existence of a particular subtype of GABAergic cells that preferentially discharge during sharp wave-ripples and broadcast this information within the hippocampal formation and beyond.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

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Title: Task specific roles of distinct hypothalamic-hippocampal circuits

Authors: *L. HE[1,3], S. CHEN[1], A. J. Y. HUANG[1], X. WANG[1], R. BOEHRINGER[1], D. POLYGALOV[1], M. E. WINTZER[1], Y. TAO[1], M. GU[1], H. HAMA[2], K. NAMIKI[2], A. MIYAWAKI[2], V. ROBERT[4], L. THERREAU[5], R. A. PISKOROWSKI[6], T. J. MCHUGH[1,3]
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Abstract: Episodic memory, consisting of social, contextual and temporal information, is dependent on the integrity of the hippocampus. While these different types of information are thought to preferentially engage distinct subcircuits within the structure, the mechanisms of this specialization remains poorly understood. We found that the anatomically and physiologically

distinct parallel projections from the supramammillary nucleus (SuM) of the hypothalamus to the CA2 and dentate gyrus (DG) hippocampal regions differentially modulate cognition in a task specific manner. Employing immediate-early gene expression labeling, optogenetics and *in vivo* recordings in a newly developed SuM-Cre transgenic mouse line we find that the SuM to DG circuit is preferentially engaged by spatial novelty while the neurons targeting CA2 are activated by social novelty. As a result, photoinhibition of the SuM-DG projections leads to deficits in recognizing contextual change while photostimulation of the SuM-CA2 circuit impairs the expression of social memory. These data demonstrate that the hypothalamus can play a task-specific role in the encoding and expression of hippocampal memory.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

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Title: Experience-dependent changes in CA1 place cell spatial information and CA1 network activity are disrupted in Fmr1 KO rats

Authors: *A. ASIMINAS[1,3,4], E. A. M. A. ALLISON[2], P. C. KIND[2,3,4,5], E. R. WOOD[2,3,4,5]
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Abstract: Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability and Autism Spectrum Disorder. It is caused by epigenetic silencing of the fragile X mental retardation gene (*Fmr1*), causing a loss of Fragile-X Mental Retardation Protein (FMRP).

Abnormal neuronal function has been reported in many animal models of FXS, but most studies have used an in vitro approach.Using in-vivo electrophysiology in behaving mice, two recent studies reported reduced spatial specificity (Arbab et al. bioRxiv 2017) and discoordinated place cell discharge (Talbot et al. Neuron 2018) of hippocampal place cells in *Fmr1* KO mice. Building upon our previously reported deficits in hippocampal plasticity and episodic memory in a rat model of FXS (Till et al. Hum Mol Genet 2015), we used in-vivo electrophysiology to examine how loss of FMRP affects hippocampal spatial information processing.We recorded from the CA1 in *Fmr1* KO and WT littermates over six 10 min exploration sessions in a novel environment - three sessions per day (ITI 10 min). Our recordings yielded 332 and 276 putative pyramidal cells from 7 WT and 8 *Fmr1* KO rats respectively. Overall, we found no significant differences between WT and *Fmr1* KO pyramidal cells in firing rate, or in the number, size or in-field firing rate of their place fields. Comparison of firing rate maps yielded similar correlations between sessions for both groups, suggesting no reduction in place cell stability in the *Fmr1* KO rats. However, we found that while on Day 1 the spatial information of place cell activity was similar in *Fmr1* KO and WT littermates, on Day 2 *Fmr1* KO rats showed significant less spatial information than WT, suggesting that the place cells of KO rats fail to show normal experience-dependent increase in spatial tuning over 24 hours. We also examined the temporal firing pattern of simultaneously recorded place cells in each session, and the recurrence of patterns between sessions. Our analyses indicate that the recurrence of the network states between sessions within each day was similar between groups. However, *Fmr1* KO rats exhibited significantly higher recurrence between days than WT rats (who showed significantly less recurrence between days than within days). In conclusion, we found that hippocampal place cells from *Fmr1* KO rats show similar spatial firing properties as those from WT rats but do not show the same experience-dependent increase in spatial specificity or the experience-dependent changes in network coordination. The present study furthers our understanding of the cellular and network processes which are affected by the lack of FMRP, which may contribute to the cognitive impairments observed in FXS.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.12/HHH35

Topic: H.01. Animal Cognition and Behavior

Title: The effects of the inducible transcription factor, Npas4, on place cell characteristics in CA1 of freely behaving mice

Authors: *A. PAYNE, A. HARTZELL BRIGIDI, C. QUIRK, S. LEUTGEB, B. BLOODGOOD
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Abstract: In order to form a memory, an animal must be capable of transforming a transient experience into long-lasting changes in cell function. One potential method for capturing such transitory moments is through the action of inducible transcription factors such as Npas4. In hippocampal CA1 pyramidal neurons (PNs), Npas4 is expressed rapidly and transiently following neuronal depolarization and results in a long-lasting and sophisticated reorganization of inhibition along the somato-dendritic axis - simultaneously recruiting inhibitory synapses to the soma while destabilizing those in the apical dendrites. Moreover, we have recently discovered that Npas4 selectively increases the number of somatic inhibitory synapses made by CCK basket cells (CCKBCs). Synapses made by these inhibitory interneurons undergo a unique form of short-term presynaptic plasticity termed depolarization-induced suppression of inhibition (DSI). During DSI, depolarization of the postsynaptic PN results in the production and release of endocannabinoids. These endocannabinoids bind to CB1 receptors on the presynaptic CCKBC and initiate a downstream cascade resulting in the suppression of GABA release. This mechanism allows PNs with increased inhibition from CCKBCs to enter a temporary state of increased activity reminiscent of place cell activity as an animal traverses the receptive field. Since PNs in CA1 are known to be involved in spatial encoding and novelty detection, we propose two potential outcomes following Npas4 expression: First, recruitment of inhibitory synapses to the soma of the PN will alter firing characteristics of these place cells, thus changing their receptive fields. Second, the loss of inhibitory synapses at the dendrites will create an environment that is more conducive to plasticity, allowing these cells to readily encode new environments. Here we compare the spike timing characteristics, receptive field properties, and network dynamics between wild-type and Npas4 knockout neurons to better elucidate how transient expression of Npas4 might contribute to long-lasting changes in place cell characteristics.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

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MEXT/AMED SRPBS

Title: Altered hippocampal replay is associated with memory impairment in mice heterozygous for the SCN2A gene

Authors: *S. J. MIDDLETON[1], E. M. KNELLER[2], S. CHEN[2], I. OGIWARA[2], M. MONTAL[4], K. YAMAKAWA[5], T. J. MCHUGH[3]
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Abstract: Experimental evidence has implicated hippocampal replay occurring within sharp wave ripples (SPW-Rs) as crucial for learning and memory in healthy subjects. This raises speculation that neurological disorders impairing memory disrupt either SPW-Rs or their underlying neuronal activity. Here, we demonstrate that mice heterozygous for the gene *SCN2A*, a site of frequent de novo mutations in patients with intellectual disability, displayed impaired spatial memory. While no changes were observed during encoding, to either single place cells or cell assemblies, we identified abnormalities restricted to SPW-R episodes which manifest as decreased cell assembly reactivation strengths and truncated hippocampal replay sequences.

Disclosures: S.J. Middleton: None. **E.M. Kneller:** None. **S. Chen:** None. **I. Ogiwara:** None. **M. Montal:** None. **K. Yamakawa:** None. **T.J. McHugh:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.14/HHH37

Topic: H.01. Animal Cognition and Behavior

Support: MOST 104-2410-H-006-025-MY3
MOST 105-2410-H-006-019-MY2

Title: Differential effects of rottlerin and MK-801 on aversive memory: Involvement of different signaling molecules in the hippocampus

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Abstract: Rottlerin is a multifunctional drug that has been used to treat cancer cells in the preclinical trials. It inhibits eukaryotic elongation factor 2 kinase (eEF2K), which increases the brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus. The eEF2K, which phosphorylates eukaryotic elongation factor 2 (eEF2), is one of the downstream signaling molecules of the *N*-methyl-D-aspartic acid receptor (NMDAR). Moreover, rottlerin is a mitochondrial uncoupler that affects many protein kinases, such as PKC, Akt/PKB, and extracellular-signal-related kinases 1/2 (ERK1/2). Likewise, MK-801, a non-competitive antagonist of NMDAR, exerts a fast-acting antidepressant-like effect through the eEF2K inhibition-mediated increase of BDNF protein in the hippocampus. Both the NMDA receptor and PKC have long been implicated in the normal function of learning and memory. Blockade of NMDA receptor prevents long-term potentiation (LTP), a cellular mechanism underlying learning and memory. Furthermore, the NMDA receptors in the dorsal hippocampus are involved in the establishment of long-term memory of inhibitory avoidance (IA) task.
IA is widely used in the preclinical research to measure avoidance or aversive behavior, which is one of the symptom clusters in the posttraumatic stress disorder (PTSD). We sought to examine the effect of two putative antidepressants, rottlerin and MK801, on memory acquisition, consolidation, reconsolidation, and retrieval of the IA task. Since both rottlerin and MK-801 increase BDNF protein in the hippocampus, which plays an essential role in enhancing long-term memory, we next examined whether the effects of rottlerin and MK-801 on IA is *via* changes in BDNF and other signaling molecules in the hippocampus.
Our results indicate that systemic rottlerin impaired memory acquisition and consolidation of IA, but had no effect on memory retrieval. Systemic MK-801 impaired acquisition of the same aversive memory, which may be confounded by drug-induced change of shock sensitivity. Intriguingly, MK-801 facilitated memory consolidation and retrieval of IA. We also found that the intra-hippocampal infusion of rottlerin significantly impaired memory acquisition and consolidation of IA, indicating the effects of rottlerin are *via* the hippocampus. However, the intra-hippocampal infusion of MK-801 significantly facilitated memory consolidation and retrieval of IA, indicating the effects of MK-801 are also *via* the hippocampus. Finally, the signaling molecules in the hippocampus underlying the opposite modulatory effects of rottlerin and MK-801 on IA memory are currently under intense investigation.

Disclosures: S. Hu: None. **M. Hsiung:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.15/HHH38

Topic: H.01. Animal Cognition and Behavior

Support: Pilot funds from the Mays Cancer Center, UT Health San Antonio

Title: Vortioxetine reverses the cognitive impairments associated with hippocampal-dependent visuospatial memory induced in a rodent model of androgen deprivation therapy for prostate cancer

Authors: *A. SHARP[1,2], S. LERTPHINYOWONG[1,2], J. GELFOND[3], T. JOHNSON-PAIS[3], R. LEACH[3], M. LISS[3], A. SULLIVAN[2,3], I. THOMPSON[3], D. A. MORILAK[1,2,3]
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Abstract: Androgen deprivation therapy (ADT) is the primary treatment for prostate cancer. However, it is also associated with several serious side effects, including profound cognitive impairment that is observed in more than half of patients treated with ADT. This significantly reduces quality of life for cancer survivors and their families. Typically, the deficits occur in visuospatial cognition and executive function, cognitive domains associated with function of the hippocampus (Hipp) and medial prefrontal cortex (mPFC), respectively. Further, cognitive impairment has been found to increase in severity with duration of ADT treatment, suggesting that it may be possible to slow or reverse the impairment. Vortioxetine (VTX) is a novel multi-modal antidepressant that has been shown to improve cognitive impairment in depressed patients, Thus, we hypothesized that vortioxetine may also reverse the cognitive impairment induced by ADT. Our lab has established a rodent model of ADT by surgically castrating male Sprague-Dawley rats. Castrated animals display deficits in cognitive flexibility on the Attentional Set-Shifting Test (AST), a measure of prefrontal executive function ($p<0.001$, n=6-12), as well as reduced afferent-evoked field potential response recorded in the mPFC after stimulation of the ventral Hipp ($p<0.01$, n=8-9). Chronic dietary VTX (28mg/kg/day) was able to reverse the deficits on AST ($p<0.001$) and normalized response in the ventral Hipp to mPFC pathway ($p<0.05$). These results suggested possible mechanisms for the deficits of executive function after ADT, mediated by changes in mPFC function. The purpose of the present study was to investigate potential changes in behavior measuring visuospatial cognition, and in electrophysiogical afferent response of the dorsal Hipp, which is involved in visuospatial memory, after ADT, and whether VTX was also able to reverse these deficits. Preliminary data (n=8-9) suggest that surgical castration induced a deficit on the Novel Object Location task, and chronic dietary VTX reversed this impairment (both $p<0.05$, n=10-12). Experiments are currently underway to examine changes in local field potentials evoked in the dorsal Hipp. Future experiments will assess changes in dendritic morphology in the Hipp after ADT and VTX. These results suggest that ADT induces cognitive impairment in visuospatial cognition mediated in the Hipp and chronic treatment with the novel antidepressant drug, VTX, may be effective in reversing these deficits.

Disclosures: A. Sharp: None. **S. Lertphinyowong:** None. **J. Gelfond:** None. **T. Johnson-Pais:** None. **R. Leach:** None. **M. Liss:** None. **A. Sullivan:** None. **I. Thompson:** None. **D.A. Morilak:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.17/HHH40

Topic: H.01. Animal Cognition and Behavior

Support: DFG Grant ON 151/1 -1

Title: Avian sharp wave-ripples reveal link to ancestral sleep circuits

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Abstract: Sleep in birds and mammals involves two alternating phases of brain activity. While rapid eye movement (REM) sleep resembles activity in the awake brain (desynchronized, high frequency oscillations of low voltage), slow wave sleep (SWS) consists of synchronized and slow high-voltage activity.
Embedded within SWS and REM sleep are local field potential (LFP) events that occur within distinct areas of the mammalian brain. In the hippocampus, sharp wave-ripples (ShWRs), characterized by large amplitude negative deflections that are associated with a fast oscillation, or “ripple”, occur preferentially during phases of SWS [1].
ShWRs are important largely due to their functional role in memory consolidation [2], and the network activity underlying mammalian ShWRs is well understood. However, the recent finding of ShWRs during SWS in a reptile [3] gives rise to the question of whether ShWRs (and their corresponding memory functions) might also arise from other neuroarchitectures.
In this regard, birds represent an important link. Birds, like reptiles, belong to the class of sauropsids and share a (now extinct) stem amniote ancestor with mammals [4]. We chose to investigate ShWRs in the brain structure associated with reptilian ShWRs - the dorsal ventricular ridge (DVR). Although avian and reptilian brains are different with regard to cellular lamination, the DVR in both reptiles and birds is largely similar with regard to its pallial origin.
Here I show the first evidence of ShWR events in the avian DVR. To investigate sleep-related electrical activity in the avian brain, I recorded LFP from the anesthetized DVR of two avian species (Gallus gallus and Taeniopygia guttata). LFP data show clear evidence of ShWR events that are highly similar to those observed in reptiles: repeated occurrence of large negative deflections of LFP (100-300 ms duration). High-pass (HP) filtering of these sharp waves revealed that they contained short bursts of >70-Hz ripple activity locked to the deflection’s descending phase.
These results suggest that although mammalian, reptilian, and avian brains are organized differently, brain activity patterns - and specifically ShWR events - are remarkably similar during sleep. Functional similarities between sauropsid DVR and mammalian hippocampus

suggest that the memory functions of sleep may be invariant to the overall neuroanatomical organization of the brain, and highlight the potential that these ancestral circuits developed over 300 million years ago in a common amniote ancestor.
[1] Buzsáki 2015. [2] Roux et al., 2017 [3] Shein-Idelson et al., 2016 [4] Naumann et al., 2015

Disclosures: J.M. Ondracek: None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.18/HHH41

Topic: H.01. Animal Cognition and Behavior

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NIH R00 NS087110
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McKnight Land-Grant Fund

Title: HippoBellum: Cerebellar modulation of hippocampal functioning

Authors: *Z. ZEIDLER[1], M. BRANDT-FONTAINE[2], Z. MONTES[2], E. I. KROOK-MAGNUSON[3]
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Abstract: The cerebellum is being increasingly recognized for its roles and relationships to non-motor functions and structures. In particular, the cerebellum has been shown to influence hippocampal functioning in both healthy and disease states. Yet important questions about the cerebello-hippocampal relationship remain answered, such as how the local hippocampal network responds to cerebellar stimulation, which populations of hippocampal neurons are sensitive to cerebellar activation, and whether acute modulation of the cerebellum interferes with hippocampal-dependent behavior. Using transgenic mice to optogenetically modulate the cerebellar cortex, we provide evidence that specific populations of hippocampal neurons are active following cerebellar stimulation. Furthermore, we show that cerebellar stimulation can modulate hippocampal population response in vivo. Additionally, acute open-loop optogenetic activation of the cerebellum during memory tasks produced a selective impairment on a hippocampal-dependent spatial memory task. These data point to important components of the

hippocampus' response to cerebellar activation and emphasize the power and specificity of the hippocampo-cerebellar relationship.

Disclosures: Z. Zeidler: None. **M. Brandt-Fontaine:** None. **Z. Montes:** None. **E.I. Krook-Magnuson:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.19/HHH42

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI 16H02061

Title: Functional left/right asymmetry of rat hippocampus depending on short/long-term memory

Authors: *Y. SAKAGUCHI, Y. SAKURAI
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Abstract: Functional asymmetry in the left/right hemisphere is a well-known feature in human, e.g., the left-sided function of the language area and the right-sided spacial cognitive function. Especially in the human hippocampus, the right hippocampal volume of the taxi driver is larger than the left one. However, such asymmetrical function is not specific in human but also in the various animals. For example, the hippocampus of rodents have a difference in volume between the left and right hemisphere, and the left hippocampus is more important than the right for forming long-term memory. These evidences suggest the functional asymmetry of the hippocampus, but its details are now not well known. Therefore, we investigated the hippocampal lateralization focusing on the long-term memory (LTM) and the short-term memory (STM). Before starting the behavioral tests, the rats underwent the surgery and one of the left or right hippocampus was electrically destroyed. We used these three tests as the behavioral experiment models; Spontaneous alternation test (SAT) for STM, Spatial preference test (SPT) for STM and Plus maze test (PMT) for LTM. As a result, SAT and SPT showed significantly lower performance in the right lesion group compared with the sham operation and the left lesion group, whereas PMT showed significantly higher performance in the right lesion group compared with the two groups. Therefore, 1. STM is responsible only for the right hippocampus, 2. Both the left and right hippocampus contribute to LTM, and either hippocampus is sufficient for LTM formation, but the right hippocampus might inhibit the left one. We concluded that the rodent hippocampus may be performing complementarily or competitively through interhemispheric interactions for the learning and memory.

Disclosures: Y. Sakaguchi: None. **Y. Sakurai:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.20/HHH43

Topic: H.01. Animal Cognition and Behavior

Support: CUNY DSRG
PSC-CUNY 68159-00 46

Title: Learning and memory in split-brain mice

Authors: *J. JORDAN[1], Y. TONG[2], C. L. PYTTE[3]
[1]Biol., Grad. Center, The City Univ. of New York, New York, NY; [2]Psychology, [3]Queens Col., Flushing, NY

Abstract: Lateralization is an organizing principle of nervous systems across taxa. The hippocampus is essential for the formation of new declarative memories and spatial navigation and is known to be lateralized in many forms of anatomy, physiology, and cognitive function. In the rodent brain, the left and right hippocampi are strongly interconnected via the hippocampal commissure (HC). Despite a number of recent studies examining the role of the left or right hippocampus in memory, very little attention has been paid to the role of interhippocampal communication in memory. Here, we adapted a protocol for rodent split-brain surgery to sever either the corpus callosum (CC) or the CC and HC to test contributions of these interhemispheric pathways to hippocampus-dependent memory. Three groups of mice were operated on: 1) transection of both the HC and CC (HC+CC); 2) transection of just the CC (CC); 3) transection of cortical areas lying above the CC (SHAM). We then tested these mice on a short-term spatial memory version of the Y-Maze in which mice were allowed to explore a start arm and a familiar arm with the third arm blocked off. On a retrieval trial one minute later, all arms were open and preference for the novel arm was measured. We found that both CC and Sham mice exhibited a preference for spatial novelty, whereas the HC+CC mice did not. These results indicate impaired short-term spatial memory in the absence of a functional HC pathway and may contribute to our understanding of the role of interhippocampal communication and learning and memory.

Disclosures: J. Jordan: None. **Y. Tong:** None. **C.L. Pytte:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.21/HHH44

Topic: H.01. Animal Cognition and Behavior

Support: NHMRC (Morris) APP1126929

Title: The effects of continuous versus intermittent access to a western style diet on short-term object and place recognition memory in rats

Authors: *M. D. KENDIG[1], R. F. WESTBROOK[2], M. J. MORRIS[1]
[1]Pharmacol., [2]Psychology, Univ. of New South Wales, Sydney, Australia

Abstract: The so-called western diet is rich in saturated fat and refined carbohydrates. Excessive intake of this diet promotes weight gain and may result in deficits in hippocampal-dependent forms of learning and memory. Many people do not eat such diets continuously but instead alternate between periods of healthy and unhealthy eating as part of efforts to maintain healthy body weight. Animal models can systematically vary access to these diets (days per week) and study cognitive and molecular outcomes over time. The present study compared the effects of continuous versus intermittent exposure to a western diet on object and place recognition memory in an established rat model. Adult male Sprague-Dawley rats received 25 days of access to a western-style, cafeteria diet (CAF) for either 7 days per week (continuous group); 5 consecutive days followed by 2 days of chow each week (5:2 group); 3 consecutive days followed by 4 days of chow each week (3:4 group), while a fourth group received chow (control). In an initial test conducted after 16-18 days of CAF, place recognition memory was impaired only in the continuous group relative to controls ($p < 0.05$), but fat mass (assessed via EchoMRI) was elevated in the three CAF-fed groups. In a second test conducted after 23-25 days of CAF, place recognition was impaired in both the 5:2 and continuous CAF groups. Consistent with previous research, there were no between-group differences in object recognition on either test. Groups exposed to CAF did not differ in their daily energy intake of CAF nor in self-selected macronutrient distribution. These results demonstrate that, when matched for total cumulative exposure to the western style diet, the pattern of access to CAF diet determines cognitive and metabolic effects in a graded fashion. Thus, the same total duration of exposure to an unhealthy diet impaired spatial recognition memory when the diet was available 7 or 5 days, but not 3 days per week. Current work is aimed at isolating whether the partial protection in the 3:4 group relates to the length of the CAF or the chow portion of the cycle.

Disclosures: M.D. Kendig: None. **R.F. Westbrook:** None. **M.J. Morris:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.22/HHH45

Topic: H.01. Animal Cognition and Behavior

Title: Effects of paternal obesity on behavior and hippocampus CB1-R in offspring

Authors: *G. SINDI[1], Y. SLYVKA[2], Y. ZHANG[2], F. V. NOWAK[2]
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Abstract: Paternal and maternal diet-induced obesity strongly impact subsequent generations. While the center of the mammalian reward circuit is the dopaminergic neurons of the ventral striatum and substantia nigra, the endocannabinoid system (ECS) modulates reward processing, including food intake and physical activity. Cannabinoid receptor type-1 (CB1-R) is the major ECS receptor in the CNS and is highly expressed in the hippocampus and hypothalamus. Previous studies have focused on the direct effect of CB1-R in mice eating high fat diet (HFD), but not their offspring. In HFD-fed mice, CB1-R expression is increased in hippocampus due to overeating. Our team hypothesized that HFD-induced paternal obesity would also affect offspring appetite and activity. Measures done at 1.5, 6, and 12 months of age demonstrated that voluntary physical activity occurred more in male offspring of HFD-fed fathers (Gr2) at 1.5 months of age than offspring of low fat diet (LFD)-fed fathers (Gr1). Female offspring ran more than males in three groups: HFD-fed father offspring at 6 and 12 months, and LFD-fed father offspring at 1.5 months. Offspring from Gr2 showed higher food consumption at 1.5 months than Gr1 offspring. We hypothesized that alterations within the CNS reward circuitry are related to different levels of physical activity and food preference in offspring of obese HFD-fed fathers versus non-obese LFD-fed fathers. Brain slices from offspring at 1.5, 6, and 12 months of age were used for immunohistochemistry. Sections were incubated in primary polyclonal rabbit anti-CB1-R antibody against the C-terminus of the receptor, and Horseradish Peroxidase (HRP)-conjugated goat anti-rabbit secondary antibody. CB1-R were detected using DAB substrate, which generates a brown to black product when cleaved by HRP, and quantified using ImagePro. All results are reported as mean ± S.E.M. and differences accepted as significant at $p \leq 0.05$. Our results demonstrate that at 12 months of age, CNS reward circuitry is altered with an increase in CB1-R in the CA3 region of the hippocampus in offspring of sires fed a HFD compared to offspring of fathers fed a LFD. At 6 months of age, CB1-R is higher in the CA1 and CA2 regions of Gr2 females than Gr2 males. Currently, we are investigating CB1-R quantification in hypothalamus, a major target region of ECS. This study further clarifies the relationship between paternal obesity, voluntary exercise, and CB1-R expression alterations in the brain which may lead to new strategies for prevention of obesity in offspring of obese parents.

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Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Program #/Poster #: 331.23/HHH46

Topic: H.01. Animal Cognition and Behavior

Support: National Natural Science Foundation of China (31500865)
Tianjin Municipal Natural Science Foundation (17JCQNJC10500)

Title: Modulation of low-frequency pulsed magnetic field on hippocampal neural oscillation in depression rats

Authors: *J. YANG, L. WANG, D. MING
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Abstract: Transcranial magnetic stimulation (TMS), as a non-invasive brain stimulation technique, has been approved for some medication-resistant depression by the United States Food and Drug Administration. However, the majority of these studies have focused on the effects of high-frequency TMS, and little is known about low-frequency TMS in depression treatment. Unlike high frequency TMS inducing evoked potentials, low-frequency (<1Hz) magnetic field could modulate the neuronal spike times and spiking frequency, which is considered to constitute the neural oscillations. Accordingly, in the present study we aimed to examine whether LFPMF (1Hz) can modulate hippocampal neural oscillations in a model of depression induced by chronic unpredictable stress (CUS), which can mimic the development and progress of clinical depression. To address this, a depression rat model was established by chronic unpredictable stress (CUS). Rats were exposed to low-frequency pulsed magnetic field (LFPMF) (1Hz, 20mT) for 14 days, one hour per day, then sucrose preference test (SPT) and plus-maze test were assessed to evaluate depression-relevant behaviors. Local field potentials (LFPs) from the hippocampal Schaffer collaterals (CA3) and CA1 region were recorded respectively to explore the neurodynamic alternations, including the degree of synchronization in an identical-frequency rhythm and the strength of coupling between theta-gamma cross bands. In order to analyze LFPs, sample entropy was calculated to make complexity analysis, while phase locked value and phase-amplitude coupling modulation index were used to figure out the correlation of oscillations. Our data showed that LFPMF significantly relieved CUS-induced depression-behaviors and improved the undesirable changes of the identical-frequency synchronization and theta-gamma phase-amplitude coupling in CUS rats. Our study elucidated that LFPMF stimulation (1Hz) can ameliorate the depressive behaviors on the rat model of CUS, suggesting that LFPMF may serve as a potential treatment in depression. Meanwhile the potential electroneurophysiology mechanisms may be the improvement of neural

synchronization and cross- coupling in hippocampal CA3 and CA1 regions.
Research Supported by the National Natural Science Foundation of China (31500865), and Tianjin Municipal Natural Science Foundation (17JCQNJC10500).

Disclosures: J. Yang: None. **L. Wang:** None. **D. Ming:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.24/HHH47

Topic: H.01. Animal Cognition and Behavior

Support: JSPS Grants in Aid

Title: Serotonergic neuromodulation in dorsal CA1 shapes reward receiving behavior

Authors: *A. LUCHETTI[1,2], A. BOTA[3,4,5], T. ISLAM[3], A. TASHIRO[6], Y. HAYASHI[7,3,8,9]
[1]NTU, Singapore, Singapore; [2]RIKEN Brain Sci. Inst., Wako, 351-0198 Japan, Japan, Japan; [3]RIKEN Brain Sci. Inst., Wako, 351-0198 Japan, Japan; [4]Kyoto University, Grad. Sch. of Med., Kyoto, 606-8501 Japan, Japan; [5]Grad. Sch. of Sci. and Engin., Saitama University, Saitama 338-8570, Japan, Japan; [6]Nanyang Technological Univ., Singapore, Singapore; [7]Dept. of Pharmacol., Kyoto Univ. Grad. Sch. of Med., Kyoto-Shi, Japan; [8]Brain and Body Syst. Sci. Inst., Saitama University, Saitama 338-8570, Japan, Japan; [9]Sch. of Life Sci., South China Normal University, Guangzhou 510631, China

Abstract: The hippocampus integrates subcortical reward signals into representations of space and memory. Among candidate sources, serotonergic fibers from the raphe nucleus are known to exert tight control over hippocampal physiology. However, the input architecture and behavioral functions of serotonin in the hippocampus remain unknown. Here we report transmission of reward and locomotion information from the raphe to hippocampal CA1. Using 2-photon calcium imaging during exploration in a virtual reality task, we recorded 5HT fibers in CA1 and identified stereotypical patterns of activity. Consistent with the reward related activity, optogenetic activation of CA1 5HT fibers increased reward acquisition in the VR task. These results suggest that serotonergic long range subcortical inputs from the raphe define a subcortical pathway for the representation of rewarded events to the hippocampal network.

Disclosures: A. Luchetti: None. **A. Bota:** None. **T. Islam:** None. **A. Tashiro:** None. **Y. Hayashi:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1R21NS101694-01A1
NSF GRFP DGE-1650042

Title: Functional segregation along the proximo-distal axis of CA1

Authors: *Y. OTA[1,2], B. J. WILTGEN[1,2,3]
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Abstract: Recent evidence suggests that some functions of the hippocampus (HPC) may be segregated along its transverse axis. For instance, the HPC receives spatial input from the medial entorhinal cortex (MEC) and postrhinal cortex while it receives odor/object-related information from the lateral entorhinal cortex (LEC) and perirhinal cortex. Although these inputs are mixed in dentate gyrus and CA3, they remain segregated in the entorhinal cortex projections to CA1. The proximal (next to CA2) and distal (next to subiculum) segments of CA1 receive direct projections from MEC and LEC, respectively. This suggests that information processing may be functionally distinct along the proximo-distal axis of CA1. To test this idea, we quantified c-fos expression in proximal and distal CA1 of mice that were either exposed to a novel context, novel objects in a familiar context, or a familiar context without objects. Consistent with previous reports, we found that novel context exposure increased c-fos activity in proximal CA1 while exposure to novel objects resulted in higher c-fos levels in distal CA1 compared to control mice. Using targeted infusions of halorhodopsin, we are currently in the process of silencing distinct regions during testing of spatial and object recognition tasks. We predict that silencing proximal CA1 will impair contextual memory retrieval of a familiar environment. In contrast, we predict that silencing distal CA1 will impair performance on object recognition tasks. Our experiments will further improve the current framework of how the hippocampus forms and retrieves different types of memories.

Disclosures: Y. Ota: None. **B.J. Wiltgen:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01NS088053-03
NIH Grant T32MH112507-01

Title: Altered immediate early gene expression in fos-tTA transgenic mice

Authors: *J. H. WILMOT[1,2], J. A. GRAHAM[2], M. M. LAFRENIERE[2], K. PUHGER[1,2], B. J. WILTGEN[1,2]
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Abstract: Memory retrieval is thought to occur when neurons that were engaged during learning are later reactivated. Until recently, testing this prediction has been difficult due to technical limitations. However, newly developed molecular and genetic techniques now allow researchers to test this idea by selectively tagging and manipulating cells that were active during learning. One popular approach to labeling these cells is to use the *fos-tTA* transgenic mouse. In these mice, active (*c-fos*+) neurons express the tetracycline transactivator (tTA), which can be used to drive the expression of other proteins under the *tetO* promoter in order to identify (fluorescent proteins) and/or control (opsins, DREADDS) these cells. Importantly, tagging is restricted to periods when there is no doxycycline present in the animals' diet, allowing temporal control over the tagging window for selective tagging of neurons activated during a specific experience. In addition to tagging cells active during learning, it is common to examine the reactivation of these cells using the immediate early gene *c-fos* as an index of neural activity. However, *c-fos* expression has never been thoroughly characterized in these mice. Here, we demonstrate that *fos-tTA* mice express increased levels of *c-fos* in the hippocampus compared to wild type animals. This difference is observed in mice that undergo different types of behavioral training and can also be seen in home cage control mice. Interestingly, this effect appears to be strain specific, as *fos-tTA* mice maintained on a C57BL/6J background show heightened *c-fos* expression, while F1 hybrids generated by breeding *fos-tTA* mice with wild type 129S6 mice do not. Ongoing experiments are examining the regulation of *tetO-H2B-GFP* in these animals and the use of an AAV to drive *tTA* expression. These results illustrate some of the limitations inherent in the use of *fos-tTA* transgenic mice and provide potential solutions to these issues.

Disclosures: J.H. Wilmot: None. **J.A. Graham:** None. **M.M. Lafreniere:** None. **K. Puhger:** None. **B.J. Wiltgen:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 331.27/HHH50

Topic: H.01. Animal Cognition and Behavior

Support: National Institutes of Health (RO1 NS088053 to B.J.W.)

Title: Increases in hippocampal activity are more detrimental to memory retrieval than decreases

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Abstract: The hippocampus (HPC) is important for spatial and contextual memory retrieval. This was initially demonstrated using lesions or pharmacological inactivation prior to memory testing. Modern tools like optogenetics and designer receptors exclusively activated by designer drugs (DREADDs) are now being used to manipulate HPC activity in a more targeted manner. The goal of the current experiments was to examine the effects of several of these manipulations on neural activity and memory retrieval. To do so, we used contextual fear conditioning and examined c-Fos expression following testing as a measure of neuronal activity. To decrease activity we used CaMKII-hM4di, ArchT and Halo. To increase activity we used CaMKII-ChR2, CaMKII-hM3Dq and Syn1-hM4Di. Syn1-hM4Di was recently shown to silence inhibitory neurons and increase overall activity. Preliminary results indicate that manipulations that reduce activity (eg CaMKII-hM4Di) have minor effects on retrieval, while manipulations that increase activity (eg CaMKII-ChR2) severely impair retrieval. Interestingly, manipulations that decrease activity in some neurons while increasing activity in many others, also robustly impair memory. Taken together, the data thus far indicate that decreases in HPC activity are often less effective at producing behavioral impairments than increases in HPC activity. The results are discussed in terms of the magnitude of change (net excitation vs. inhibition) vs. the direction of change (increase vs. decrease in activity).

Disclosures: J.N. Krueger: None. **J.H. Wilmot:** None. **K.R. Puhger:** None. **S.E. Nemes:** None. **B.J. Wiltgen:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R01NS088053-03

Title: Mechanisms of memory impairment following optogenetic disruption of the ventral hippocampus

Authors: *J. A. GRAHAM[1], N. VISHWAKARMA[1], B. J. WILTGEN[2]
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Abstract: The hippocampus(HPC) is known to be important for spatial and contextual memories. It is also necessary for acquisition and retrieval of memories wherein a previously neutral context or location becomes associated with fear. The ventral portion of the hippocampus(VHC) contains projections to many areas of the brain that are associated with fear memories including the Basal Amygdala(BA), where it is thought that the association between contextual information provided by the hippocampus and information about the fear inducing stimulus from nuclei of the brainstem are stored. Consistent with previous reports(Jimenez et al., 2018), we find that disrupting activity in the VHC via fast acting channel rhodopsin variant ChETA impairs fear memory. This was true regardless of whether we non-selectively stimulated excitatory pyramidal neurons or only VHC-BA projection neurons. Surprisingly, we found optogenetic stimulation did not significantly increase expression of the immediate early gene c-fos beneath the optic fiber tip. This contrasts with what we find in dorsal HPC where large increases in fos expression are visible after stimulation(Krueger et al/Pugher et al, SfN 2018). It is possible that the VHC requires stronger stimulation protocols to initiate c-fos expression due to differential activation of NMDAR receptors in the VHC(Babiec, Jami, Guglietta, Chen, & O'Dell, 2017). We plan to record from neurons expressing ChETA in the VHC slices in order to verify that our stimulation protocol produces robust activity. Finally, we plan to examine the nature of the memory impairment we saw during optogenetic stimulation. Memory retrieval typically requires reactivation of the neural ensemble active during learning. We hypothesize that memory is impaired during optogenetic stimulation because brain activity during stimulation does not match that occurring during acquisition. To test this idea, we plan to artificially match training and testing activation in the VHC with optogenetic stimulation.

Disclosures: J.A. Graham: None. **N. Vishwakarma:** None. **B.J. Wiltgen:** None.

Poster

331. Animal Cognition and Behavior: Learning and Memory: Hippocampal Circuits III

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Topic: H.01. Animal Cognition and Behavior

Support: 5R01NS088053

Title: Neural circuits underlying trace fear conditioning

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Abstract: In Pavlovian trace fear conditioning, a temporal delay (the trace interval) is inserted between the CS and US presentation. Pavlov theorized that a 'memory trace' or representation of the CS must be maintained during this interval in order for the association to be formed. Recent neurobiological studies indicate that certain brain regions such as the hippocampus (HPC) and medial prefrontal cortex (mPFC) play a distinct role in this task. Lesions and pharmacological inactivation of both the hippocampus or mPFC impair trace fear conditioning. Multi-unit recordings from the HPC show learning-related activity changes, and CA1 single-unit activity increases in response to the CS and exhibit population-level encoding of the trace interval. Recording studies have also found that the mPFC exhibits learning-related increases in activity to the CS and US. Interestingly, a subpopulation of cells in the mPFC showed sustained firing during the trace interval. Recent optogenetic studies have shown that inactivating CA1 or the mPFC selectively during the trace interval impairs learning in trace fear conditioning, suggesting that CA1 and mPFC process information during the trace interval necessary for learning this association. However, there are no strong, direct projections between the mPFC and dorsal hippocampus. They are bidirectionally connected via the midline thalamic nucleus reuniens (NR) which receives dense inputs from both the mPFC and HPC, and projects back to these areas. The NR is important for facilitating communication between the hippocampus and mPFC, and is also critical for spatial working memory and contextual fear memory. In the current study, we utilized ChR2 and eNpHR3.0 for optogenetic stimulation and inhibition to disrupt activity in CA1 and impair trace fear conditioning. Present and future experiments will characterize the neural circuits underlying trace fear conditioning by examining the role of the NR. Next, we will use projection-specific optogenetics to target projections between CA1 and the reuniens. We predict that selective disruption during the trace interval will impair the formation of trace fear memories. To test this idea we will compare manipulations during the trace interval to manipulations during the CS or intertrial interval periods.

Disclosures: K. Puhger: None. **J. Wilmot:** None. **B. Wiltgen:** None.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 332.01/HHH53

Topic: H.01. Animal Cognition and Behavior

Support: Coinside project
BPI France
Grenoble-Alpes METROPOLE

Title: The use of EEG evoked responses for the identification of cognitive enhancers in rodents

Authors: *V. DUVEAU, A. WOźNIAK-KWAśNIEWSKA, A. EVRARD, C. RUGGIERO, C. ROUCARD, Y. ROCHE
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Abstract: Electroencephalography (EEG) and related methodologies have emerged as powerful tools in both, clinical and preclinical research programs, for the identification of physiological and pathological biomarkers. Nowadays, EEG endpoints are commonly used in the clinic to identify and evaluate a pathological state and/or as surrogate biomarkers for clinical trials (Alzheimer's disease, schizophrenia, autism, epilepsy, etc.). EEG biomarkers are easily translatable from humans to rodents, thus offering a unique opportunity to develop more efficient drug discovery programs. In rodents, EEG responses evoked by auditory stimulation can be recorded in various brain areas. They underlie the integration and processing of sensory information, which are altered in many neurological and psychiatric disorders. We distinguish two main types of auditory evoked responses: auditory evoked related potentials (AERP) and auditory steady state response (ASSR). AERPs are composed of successive positive and negative deflections, which differ from their latencies and amplitudes and are well conserved throughout the evolution. ASSRs consist in cortical electrophysiological oscillations entrained to the frequency of a periodic auditory stimulus presented at a gamma rhythm range (that is, 30-80Hz). In this study we investigated the effect of a cognitive enhancer, donepezil, on AERP and 40Hz-ASSR in mice. Our AERP protocol consisted in 250 pairs of white noise clicks at 85dB with an interval of 0.5 sec between paired clicks. The 40Hz-ASSR protocol was composed of 360 trains of stimulation at 85dB. First, we evaluated the effect of donepezil on the total power elicited by the auditory stimulation at 40Hz in mice. Donepezil dose-dependently increased the 40Hz total power with a significant effect observed at the dose of 1 or 1.5 mg/kg, depending on the recorded structure. When tested on AERP alone, donepezil did not modify the amplitudes and latencies of different AERPs' deflections. Then, we tested the effect of donepezil against the modifications induced by scopolamine, a molecule known to provoke cognitive impairments. Scopolamine alone dose-dependently reduced the N1 gating in our AERP paradigm. The administration of

donepezil before scopolamine dose-dependently reversed the modifications induced by scopolamine. This effect was significant at the dose of 1 mg/kg of donepezil. We identified functional biomarkers in mice using EEG and related methodologies. These specific biomarkers could represent a crucial tool for the identification, selection and validation of new innovative therapeutics and more specifically, for the identification of new cognitive enhancers.

Disclosures: V. Duveau: A. Employment/Salary (full or part-time):; SynapCell SAS. **A. Woźniak-Kwaśniewska:** A. Employment/Salary (full or part-time):; SynapCell SAS. **A. Evrard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Ruggiero:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Roucard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **Y. Roche:** A. Employment/Salary (full or part-time):; SynapCell SAS.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 332.02/HHH54

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH104589

Title: Control of fear and extinction memory retrieval via manipulation of BLA-PFC oscillatory network state

Authors: *M. OZAWA[1], P. DAVIS[2], T. PAPOUIN[1], J. MAGUIRE[1], L. REIJMERS[2]
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Abstract: The formation and retrieval of a memory is mediated by experience-dependent changes in the brain. Yet, the exact nature of these changes is not fully understood. Contextual fear conditioning (FC) combined with subsequent extinction is a learning paradigm that allows investigation of memory retrieval mechanisms. It leads to the formation of two distinct memories, a fear and extinction memory, both associated with the same context. The basolateral amygdala (BLA) is critical for forming both types of memories. We previously showed that PV-interneurons in the BLA regulate the expression of a conditioned fear response after extinction. We found that after extinction, PV interneurons also control the relationship between a 3-6Hz and 6-12Hz oscillation, the relative balance of which correlated with behavioral expression of conditioned fear. To test whether the two oscillations are causally involved in the retrieval of fear and extinction memories, we used an optogenetic approach to exogenously induce the two oscillatory states in the BLA and tested the effect on memory retrieval. We found that mimicking the two oscillations has opposite effects on fear and extinction memory retrieval. We propose

that the effect of stimulation on behavior is mediated by changes in phase coherence between BLA and prefrontal cortex (PFC).

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Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

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Program #/Poster #: 332.03/HHH55

Topic: H.01. Animal Cognition and Behavior

Support: NINDS NS088567

Title: Amygdala central nucleus inactivation impairs learning-related spike activity and local field potentials in the basilar pontine nucleus

Authors: *J. KIM[1,2], S. J. FARLEY[1,2], J. H. FREEMAN[1,2]
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Abstract: Accumulating evidence shows that amygdala central nucleus (CeA) output to the basilar pontine nucleus (BPN) may function as a modulator of sensory information to the cerebellum (Farley 2016, 2018; Pochiro 2015; Siegel 2015; Taub 2010). Additionally, pharmacological inactivation of the CeA during eyeblink conditioning reveals that conditioned responses (CRs) are strongly attenuated and only modest levels of acquisition occur without CeA input (Farley 2018). In this study, we recorded single unit and local field potential (LFP) activity in the BPN of adult rats as they were trained in the cerebellum-dependent task, delay eyeblink conditioning. In this task, a neutral conditioned stimulus (CS; 2 kHz tone, 400ms duration) is paired with an unconditioned stimulus (US; 2.5 mA periorbital stimulus). We first analyzed pontine baseline LFP activity with and without bilateral CeA inactivation using the $GABA_A$ agonist, muscimol (2mM). A stable recording was acquired, muscimol infused, and then recording continued following a brief diffusion period. After 48 hours, rats were subsequently exposed to a counter-balanced order of saline or muscimol CS-alone sessions (50-trials) while recording BPN spike and LPF activity. Following CS alone sessions, rats were then randomly divided into muscimol or saline groups for training in delay eyeblink conditioning. Bilateral infusions to the CeA occurred before each of the first 5 eyeblink sessions (100-trials/session). Training continued without infusions from session 6 until reaching an 80% CR criterion. After criterion, rats completed counter-balanced muscimol or saline retention sessions. CeA inactivation modulated behavioral CRs and neural activity in the BPN. Accompanying the impairment in CRs, BPN spike activity, which was CS-responsive under the vehicle control sessions, was significantly decreased when CeA was inactivated by muscimol. BPN LFP signals

also showed the notable modulation by CeA activation/inactivation. Specifically, CeA inactivation resulted in the most significant decreases in the alpha (12 - 18 Hz) and beta (20 - 30 Hz) bands. To a lesser extent, LFP power also decreased in the theta (4-8 Hz) band. The results suggest that the CeA modulation of learning and neural activity in BPN might occur via higher frequency bands.

Disclosures: J. Kim: None. **S.J. Farley:** None. **J.H. Freeman:** None.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

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Program #/Poster #: 332.04/HHH56

Topic: H.01. Animal Cognition and Behavior

Title: Interplay of resonant and synchronizing generators in a hippocampal theta model

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Abstract: Rhythmic activity characterizes neuronal processing in multiple brain areas. Study of rhythms indicate the involvement of a multitude of rhythm generators, likely through a variety of mechanisms. Considering the multitude of involved mechanisms in rhythm generation, inactivation of circuit components can produce complex and unpredictable results.
We use computational modeling to examine interaction between circuit components that participate in rhythm generation. We distinguish between resonant components and synchronizing components and demonstrate that this categorization permits predicting the rules of which components can interfere with one another and which can substitute for one another. Resonant mechanisms inherently produce rhythmic signals as a product of their dynamics and include spike-frequency adaptation, slow inhibition, rhythmic external input, and slow neuronal currents. Synchronizing mechanisms promote coordinated activity and include inhibitory feedback, non-rhythmic external input, and recurrent excitatory connections. Some circuit components can provide both resonance and synchronization.
We found the most robust rhythm generation to require at least one resonant component and one synchronizing component. We found that pyramidal cells adaptation can interfere with theta produced by slow inhibition, and fast inhibition can either substitute for or interfere with rhythm generation by slow inhibition, depending on the cholinergic state. These results begin to shed light on the conflicting evidence produced by studies inactivating circuit components, and also predicts circuit states where inactivating a component known to participate in rhythm generation might paradoxically enhance rhythmic activity. We conclude that effects of component inactivation can only be predicted in the context of what other components are present and on the neuromodulatory state of the circuit.

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Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

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Program #/Poster #: 332.05/HHH57

Topic: H.01. Animal Cognition and Behavior

Support: ERC
Wellcome

Title: Do ethological differences between species shape neural mechanisms in the hippocampus?

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Abstract: The hippocampus is a brain region with important roles in memory and spatial navigation, which is positioned at the confluence of many streams of multimodal sensory processing. In rodents, this information is used to create a representation of the current environment. The hippocampal local field potential (LFP) gives insight into how the hippocampus processes information to create this representation. For example, theta oscillations (5-12Hz in the rat), represent a well-defined network state during which sensory information is thought to enter the hippocampus. Oscillations such as theta play a critical role in many hippocampal models of memory and spatial navigation. However, these models are based almost exclusively on rodent studies, and it remains an open question whether the specific ethological constraints of the rodent shape these neural mechanisms. Rodents primarily rely on the proximal sensing strategies of sniffing and whisking, so their sensory world is closely tied to their current location. In species where distal sensing is more dominant, activity in the hippocampus is not always consistent with the rodent data. We have recorded hippocampal LFP in the rat and the ferret (*Mustela putorius*), a predatory carnivore that relies predominantly on distal senses, to investigate the impact of ethological differences on hippocampal processing. We have identified theta oscillations in the ferret hippocampus which occur at a 3.5-7.5 Hz, a lower frequency band than commonly observed in the rat. Ferret hippocampal theta showed a positive correlation with the animals' speed, however the gradient of this relationship was roughly half that found in the rat over the same speed range. Rats and ferrets were trained on comparable auditory/visual localisation tasks designed to manipulate sensory attention. While theta activity was greatly diminished in rodents during immobility, we observed robust theta activity in ferrets during the entire behavioural task, including periods of immobility.

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Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

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Topic: H.01. Animal Cognition and Behavior

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Title: Discrete structure of the brain rhythms

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Abstract: Neurons in the brain are submerged into oscillating extracellular potential—Local Field Potential (LFP), which is one of the principal determinants of the brain activity and a key component of many neurophysiological mechanisms. Our understanding of the LFP's structure and of its physiological functions depend on the mathematical approaches used for its analysis. Most current signal decomposition methods are based on formal decompositions (sinusoids, wavelets, etc.), and the goal of the subsequent analysis reduces to identifying the combination that reproduces the original signal as closely as possible. Since all decompositions are mathematically complete and useful in their own way, it may appear that the question about the "actual" structure of the signal is of little importance if not at all meaningless. However, this is not the case: for as long as the physiological mechanisms of the LFP oscillations remain unknown, the search of a physically adequate description of their structure remains a matter of fundamental importance.
We propose a novel approach to analyzing biological signals, in which the signal's prime components are not *a priori* presumed, but discovered empirically. By applying this method to the analysis of the hippocampal "brain waves" we demonstrate that these signals decompose into a superposition of a few phase modulated oscillatory processes, which we call the oscillons. Since oscillons emerged as a result of *empirical* data analysis, we hypothesize that they represent the actual, physical structure of synchronized neuronal oscillations, whereas Fourier-defined brain waves are nothing but poorly resolved oscillons. In particular, there is a single discrete θ-oscillon that corresponds to the standard θ-rhythm and a couple of γ-oscillons that correspond to slow and fast γ-rhythms, and so forth. Proving this hypothesis will advance our principal

understanding of the biological oscillations and help to connect the experimental data with computational models of the neuronal synchronization.

Disclosures: Y.A. Dabaghian: None. **L. Perotti:** None.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NIH #1-ZIA-AG000340

Title: Cortico-hippocampal gene expression following rTMS in rats is dependent on age and cognitive status

Authors: M. WEILER[1], K. C. STIEGER[2], *J. M. LONG[2], E. LEHRMANN[2], Y. ZHANG[2], K. G. BECKER[2], P. R. RAPP[2]
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is FDA-approved for the treatment of pharmacologically refractory depression, and there is increasing interest in potential application for neurodegenerative disease, substance abuse, and other conditions. Although the molecular basis is largely unknown, considerable evidence indicates that the effects of TMS are 'state-dependent', raising the possibility that age and cognitive status might differentially affect the neurobiological response to rTMS. Using genome-wide microarray, we investigated the effects of rTMS on hippocampal and neocortical gene expression in young and behaviorally characterized aged Long-Evans rats. Spatial memory was assessed in a standardized Morris water maze protocol and aged rats were classified as Aged-Impaired (AI) or Aged-Unimpaired (AU). A total of 24 animals were examined: 4 Young/stimulated, 4 Young/sham, 5 AU/stimulated, 4 AU/sham, 3 AI/stimulated and 4 AI/sham. rTMS was implemented using a "MagStim rapid" stimulator and a 70mm figure-of-eight coil (MagStim Company Ltd.). Rats were anesthetized (dexmedetomidine, 0.03 and 0.035 $mg.kg^{-1}$ aged and young animals, respectively) and received intermittent theta burst stimulation (iTBS; 600 pulses applied as bursts of 3 pulses, 50Hz, repeated at 5Hz as 20 trains of 2s repeated at intervals of 10s). This pattern was repeated 5 times at 15 min intervals. Stimulus intensity was individually adjusted, just below the threshold for evoking visible neck muscle activity (11-20% machine power). Forty-eight hours after rTMS or sham treatment, cortical and hippocampal samples were microdissected and subsequently analyzed using Agilent rat whole genome microarrays. iTBS significantly altered cortico-hippocampal gene expression, with almost no overlap in the profile of specific genes affected in Y, AU and AI brains. In addition, the number of genes affected was far greater in the

Y group (cortex: 56 genes upregulated and 58 downregulated; hippocampus: 72 genes upregulated and 28 downregulated), followed by the AU (cortex: 6 genes upregulated and 22 downregulated; hippocampus: 1 gene upregulated) and AI (cortex: 1 gene upregulated and 6 downregulated; hippocampus: 6 genes upregulated and 6 downregulated). Our results highlight not only the divergent effects of TMS as a function of chronological age, but also that age-related cognitive impairment represents a distinct condition differentially affected by TMS. The neurobiological mechanisms responsible for the therapeutic effects reported in the growing clinical application of rTMS, including Alzheimer's disease, merit careful investigation.

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Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

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Topic: H.01. Animal Cognition and Behavior

Support: BSB Research Enhancement Funding
ATA

Title: D-cycloserine enhances location specificity of CA1 place cells by enhancing signal-to-noise ratios and transiently increasing theta cell activity

Authors: *P. J. NGUYEN-LEE[1], C. HACKER[2], L. T. THOMPSON[2]
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Abstract: Place cells exhibit stable location-specific firing in discrete locations in an environment, and fire at lower (often zero) rates in other locations and environments, forming a cognitive map linking locations and events in space. Hippocampal theta cells provide feedback and feedforward inhibition to CA1 place cells, helping regulate their excitability. Previous studies from our lab have demonstrated that D-cycloserine (DCS), an NR1 partial agonist, has nootropic effects, facilitating both spatial maze learning and rabbit trace eyeblink conditioning at a dose of 6 mg/kg in young animals. Our objectives here were to 1) investigate the effects of DCS on in-field and out-field firing rates of hippocampal place cells, and 2) investigate the effects of DCS on theta cell firing in rats actively exploring a radial-arm maze.
Young male and female FBN hybrid rats were trained to sample all maze arms within 5 min sessions using droplets of chocolate milk as incentives. Trained rats were stereotaxically implanted with chronic implants consisting of 4 microdrivable tetrode bundles over dorsal CA1. Baseline recordings were used to evaluate stability of place cell and theta cell waveforms and firing. In a blind fashion, rats were given either DCS (6 mg/kg) or equivolume PBS. Immediately

post-injection, recording sessions on the maze assessed unit activity every 15 min for the first 2 h, every 30 min up to 4th h, and then at the 6th, 12th, and 24th h post-injection. To classify place and theta cells, activity was sampled using a Plexon MAP system, and clustered with an agglomerative sorting algorithm verified by visual inspection. Spatial location histograms for aggregate spike counts and firing rates were then computed to quantify in- and out-of-place-field firing and theta cell firing over time.
Our results show that DCS decreased place cell firing, with out-of-field firing rates decreased more than in-field, and theta cells showed increased firing rates. DCS effects on unit activity persisted less than 4 h in behaving rats. The net effect was a sharpening of place fields, with enhanced signal-to-noise ratios, the converse of the impact of advanced age on place cell firing characterized by broader poorly tuned place fields. The net effect of DCS is consistent with nootropic effects in spatial memory tasks.

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Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

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Title: Hippocampal slow and fast gamma rhythms correlate differentially with successful memory performance in a goal-directed spatial memory task

Authors: *C. ZHENG[1,2,3,4], L. L. COLGIN[3,4,5]
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Abstract: Hippocampal gamma rhythms are thought to play a role in memory processing by coordinating the activity of distributed neurons that code related information. Increasing evidence in behaving rats suggests that slow (~25-55 Hz) and fast (~60-100 Hz) gamma rhythms reflect functionally distinct states of the hippocampal network. We have previously shown that place cell ensembles code spatial information differently during slow and fast gamma, with relatively long paths represented in a temporally compressed manner during slow gamma and ongoing trajectories accurately followed in real-time during fast gamma. However, the relevance of these different firing modes to memory performance remains unclear. In this study, we used a delayed match-to-sample circular track task to test whether different place cell representations

during slow and fast gamma are related to goal-directed spatial memory. Place cell ensemble activity and local field potentials were recorded in hippocampal subfield CA1 in 4 rats. Behavioral trials consisted of a sample phase in which a reward location was indicated by cues and a test phase in which rats were required to recall the reward location from memory. A Bayesian decoding approach was used to continuously decode place cell ensemble activity in each trial and showed that predictive firing representing paths toward the reward location by place cell ensembles developed with learning. Also, in later trials, place cell ensemble activity predicted locations where rats stopped for both correct and error trials. Furthermore, across correct trials, fast gamma power was significantly increased during the sample phase, and slow gamma power was significantly enhanced during the test phase. On the other hand, slow gamma power in the sample phase of error trials was significantly higher than slow gamma power in the sample phase of correct trials. These results suggest that slow and fast gamma support memory retrieval and memory encoding, respectively, and raise the possibility that slow gamma interference with fast gamma-associated memory encoding relates to errors in memory performance.

Disclosures: C. Zheng: None. **L.L. Colgin:** None.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 332.10/III1

Topic: H.01. Animal Cognition and Behavior

Support: National Science Foundation CAREER Award #1453756.
UT Center for Learning and Memory Training Grant #5T32MH106454-03

Title: Preferential reactivation of CA3 place cells representing a novel experience during post-learning sleep

Authors: *E. HWAUN, L. L. COLGIN
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Abstract: A popular model of memory consolidation posits that recent memories stored in the hippocampus are reactivated during sleep and thereby transferred to neocortex for long-term storage. This process is thought to take place specifically during sharp wave-ripples (SWRs) in non-rapid eye movement (NREM) sleep. To reduce redundancy in memory storage, one would expect that recent memories containing novel information are preferentially reactivated and consolidated. Indeed, a previous study has shown enhanced reactivation of neurons in hippocampal subregion CA1 during awake SWRs in novel environments (Cheng and Frank 2008). But whether this enhanced reactivation persists into subsequent sleep and manifests as

replay of novel experiences remains unknown. In addition, hippocampal memories are thought to be stored in the recurrent collateral system of CA3, yet it remains unclear whether novelty-selective reactivation occurs in CA3. To address these questions, we recorded place cells in CA3 as rats were exposed to a familiar and a novel environment and during the subsequent night's sleep. At the individual cell level, our data suggest that CA3 firing rates during SWRs in NREM sleep increased in a novelty-dependent manner. Moreover, we observed novelty-dependent decreases in CA3 place cell firing rates during REM sleep, potentially supporting a homeostatic role for REM sleep. At the population level, ensembles of CA3 place cells during NREM sleep replayed trajectories from the novel environment with higher fidelity than trajectories from the familiar environment. Together, these results support the hypothesis that CA3 representations of novel experiences are selectively reactivated during post-learning sleep.

Disclosures: E. Hwaun: None. **L.L. Colgin:** None.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 332.11/III2

Topic: H.01. Animal Cognition and Behavior

Support: NIH 1R01MH102450-01A1

Title: CA2 place cells remap in response to social olfactory stimuli

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Abstract: Several reports have implicated hippocampal subfield CA2 in social memory. A recent study showed that place cells in CA2, but not CA1, change their spatial firing patterns ("remap") during social interactions (Alexander et al., 2016). However, it was unclear whether these effects were specifically caused by social interactions or by associated sensory stimuli such as social olfactory stimuli. Here we show that CA2 place cells remap in rats interacting with a familiar rat's empty homecage. Such remapping did not occur in response to interactions with an identical cage containing clean bedding and no rat-associated odors. Our results suggest that CA2 place cells respond to the olfactory content of social experiences. Control experiments testing responses to odors unrelated to social stimuli will also be discussed.

Disclosures: A.J. Mably: None. **L.T. Hewitt:** None. **L.L. Colgin:** None.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

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Support: National Science Foundation CAREER Award #1453756
Whitehall Foundation #2014-05-102
UT Center for Learning and Memory Training Grant #5T32MH106454-03 (to EH)

Title: Persistent co-activity patterns of neurons in the medial entorhinal cortex across waking and sleep states are not explained by similar patterns of place cell co-activity

Authors: *J. B. TRIMPER[1], S. G. TRETTEL[2], E. HWAUN[3], I. R. FIETE[4], L. L. COLGIN[5]
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Abstract: Multiple spatially selective subtypes of neurons, including head direction cells and grid cells, are found within the medial entorhinal cortex of rats and other species. The question of which mechanisms drive these neurons' activity patterns remains an area of active study. Continuous attractor network models posit that recurrent connectivity between grid cells controls their patterns of co-activation, whereas alternative models point to correlated inputs from sensory cortex or hippocampus. To clarify this issue, we recorded single units from the superficial layers (II/III) of the medial entorhinal cortex in six rats performing active exploratory behaviors and throughout subsequent overnight sleep. We found that the degree of spatial overlap between neurons' firing patterns observed during active waking behaviors predicted neuronal co-activity patterns during REM and non-REM sleep, when sensory inputs are absent. This relationship was observed for grid cell pairs from the same module, but not for grid cell pairs from different modules, further supporting recurrent connectivity as the mechanism for grid field formation. Through analyses of place cell recordings, along with modeling and simulations, we also found that medial entorhinal cell co-activity patterns were not explained by similar place cell activity patterns. These results suggest that, barring grid-like structured input from other cortical areas, local recurrent connectivity drives the co-activity of spatially selective cells in the superficial layers of medial entorhinal cortex across behavioral states.

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Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

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Program #/Poster #: 332.13/III4

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1R15AG045820-01A1

Title: Maturation of hippocampal oscillatory activities during Barnes maze navigation in the juvenile rat

Authors: *D. G. MCHAIL[1], R. H. OGOE[2], C. KIMBALL[1], T. C. DUMAS[2]
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Abstract: Spatial navigation is a critical cognitive ability, yet the supporting neural mechanisms are not well understood. The hippocampus is a forebrain structure in mammals that is necessary for spatial cognition. One emerging approach to better understand how the hippocampus subserves spatial navigation is neurodevelopmental, relating changes in neuron function to changes in spatial behavior. In rodents, spatial navigation ability first emerges around three weeks of age. Also around three weeks of age in rodents, hippocampal excitatory synapses undergo changes in composition and function that facilitate the ability to induce long lasting changes in synaptic strength (Blair et al., J. Neuroscience, 2013; Stoneham et al., Biological Bulletin, 2013). It is not known how these synaptic changes relate to the development of hippocampal circuit processes, such as activity oscillations in the local field potential at the population level (e.g. theta, gamma, sharp-wave ripples) known to define functional states and coordinate activity of spatially tuned cells. Therefore, we used lightweight tetrode hyperdrives to record population neural activity from hippocampal area CA1 of rats younger and older than three weeks during performance in an adapted Barnes maze (McHail et al., Learning and Memory, 2018). Preliminary results suggest that theta, gamma, and SWRs are prominent during maze behaviors in both age groups, but their relationships to maze performance might differ with increasing age and accuracy of navigation to goal. Our findings suggest that alterations in population oscillatory activities mediate the postnatal development of hippocampal networks and maturation of spatial cognition and support this approach as a valuable tool to relate neural network operations to cognitive states.

Disclosures: D.G. McHail: None. **R.H. Ogoe:** None. **C. Kimball:** None. **T.C. Dumas:** None.

Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 332.14/III5

Topic: H.01. Animal Cognition and Behavior

Title: Thalamic reticular nucleus controls the gain of the head-direction signal

Authors: *A. J. DUSZKIEWICZ[1], E. BROWN[1], M. YAMASAKI[3], M. WATANABE[4], A. PEYRACHE[2]
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Abstract: As we navigate the world, it is crucial to maintain a robust sense of where we are. Head-direction (HD) cells serve as the brain's internal 'compass' and each of them is tuned to the specific direction the animal is facing, independently of its location and ongoing behavior. The anterodorsal thalamic nucleus (AD) is a key relay of the HD signal. AD neurons seem to be reciprocally connected with the reticular nucleus (TRN) - an inhibitory thalamic nucleus believed to control the routing of sensory information. Recurrent inhibition is important in shaping attractor network dynamics and it may select subsets of neurons coding for the same direction. Therefore, although the HD signal itself may originate from subthalamic nuclei, the AD-TRN system may play a central role in its processing. Still, connectivity and functional importance of the AD-TRN circuit remain elusive. In order to characterize the functional significance of the AD-TRN circuit, we used a combination of high-density single unit recordings and optogenetic interrogation in freely moving mice, as well as anatomical tract tracing. We observed that TRN sends dense projections to AD and that the vast majority of AD neurons project to back to TRN. Preliminary electrophysiological-optogenetic analysis of this reciprocal connectivity indicates that TRN inhibition leads to global increase in peak firing rates of thalamic HD cells. Further studies will examine whether this gain control mechanism is dependent on the feedback from AD neurons to TRN.

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Poster

332. Animal Cognition and Behavior: Learning and Memory: Gamma and Theta Rhythms

Location: SDCC Halls B-H

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Program #/Poster #: 332.15/III6

Topic: H.01. Animal Cognition and Behavior

Support: A.P. was supported by a Canada Research Chair Tier 2 (154808)

Title: Thalamic nuclei are specifically entrained to hippocampal oscillatory dynamics

Authors: *G. VIEJO[1], G. BUZSAKI[2], A. PEYRACHE[3]
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Abstract: The brain is organized in parallel and interacting loops that coordinate large-scale neuronal assemblies and support cognitive functions. The thalamus, a collection of anatomically separated nuclei, acts as an essential component of large-scale brain circuits, relaying sensory inputs to the cortex and mediating cortico-cortical interactions. Although thalamic nuclei have been intensively characterized at the anatomical and genetical levels, their in-vivo dynamics remain poorly described. Here, we provide an electrophysiological characterization of the anterior thalamus, a critical "hub" of the limbic system playing a central role in memory and spatial navigation. We demonstrate that neurons of different anterior nuclei, including the antero-dorsal (AD), antero-ventral (AV), and antero-medial (AM), are characterized by specific spike train dynamics. In addition, the entrainment of thalamic neurons to the two dominant oscillatory patterns of the hippocampus, sharp-wave ripples (SWRs) and theta oscillations are unique to each thalamic nucleus. Finally, we show how the response to SWRs and theta oscillations are intrinsically related and invariant, indicating that the responses result from specific anatomical pathway rather than different brain-state dynamics. Our results provide an essential description of the dynamical organization of the hippocampo-thalamic network, a critical step towards the understanding of how neuronal populations are coordinated in the limbic system.

Disclosures: G. Viejo: None. **G. Buzsaki:** None. **A. Peyrache:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.01/III7

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant F4301

Title: Psychophysics of political preferences mediated by information

Authors: *B. LU, J. ZIMMERMANN, P. W. GLIMCHER
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Abstract: Unlike value-based decision-making, it is not immediately obvious that political decisions are made using some principled evaluation of alternatives that can be operationalized in the lab. Many scholars consider politics to be a privileged class of decision-making, much like religious beliefs, that defy logical thought processes. Since the mid-20th century, political science has tried to make sense of this behavior, first using normative economic and later decision theoretic models that have been of great use in neuroscience. One school of thought holds political awareness and exposure to new information as the key mediators to political preference change, whereas others emphasize the role of partisanship. Here, we developed a novel psychophysics task that orthogonalizes partisanship and information flow to evaluate the optimal conditions for preference change—one which renders political decision-making tractable to neuroeconomic-style analysis. Over 500 Amazon Mechanical Turk subjects and 100 traditional lab participants engaged in this task, which consists of making preference ratings on real proposed laws that have appeared before US Congress. Subjects first reported their preferences based solely on a synopsis of the proposal—subsequently they must reevaluate those preferences after learning about the true percent of Congressmen of each party that voted in favor of the proposed law. Proposals uniformly tiled the space of Democratic and Republican support and were controlled for their intrinsic perceived partisanship, i.e., the true levels of support for each bill were completely uncorrelated with participants' estimates of that support. Behavioral results among both study populations dichotomized the pool: roughly 50% of subjects exhibited robust preference changes (to one or both partisan signals) while the remainder did not. Neither trait-level political awareness nor partisanship alone account for this divide, which casts doubt on the established awareness model for political preference shifts. This result, persistent across repetitions, is key to ongoing functional imaging work that examines political preference representation in the brain. Previous studies report a common currency among neural correlates of economic value and this work will assess whether political preferences lie in this same axis.

Disclosures: B. Lu: None. **J. Zimmermann:** None. **P.W. Glimcher:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.02/III8

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DA043676
NIH Grant DA039648

Title: Psychosocial stressors promote opioid use by sharpening the neural representation of subjective value

Authors: *A. B. KONOVA[1], S. LOPEZ-GUZMAN[2,3], C. IFRAH[4], N. BANAVAR[2], K. LOUIE[2], J. ROTROSEN[5], P. W. GLIMCHER[2]
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Abstract: Stress is a major impediment to recovery in mental illness. Treatment-seeking opioid users, for example, experience frequent and intense psychosocial stress that limits their capacity to abstain from drug use, leading to relapse, treatment dropout, and even death. However, how psychosocial stressors bias behavior toward rewarding but overall less adaptive alternatives (e.g., opioid use) and away from an individual's health goals is poorly understood. Here we test the hypothesis that underlying this bias is a stressor- and anxiety-related adaptation of the brain's subjective valuation (SV) system. Method: We studied 87 chronic opioid users seeking medication-assisted treatment. Patients completed up to 15 sessions (762 in total). At each, we probed recent notable life events via interview, state anxiety, and opioid use (by self-report and urine drug screens). Text analysis of all interview reports was used to determine the relevant psychosocial domains in which our sample reported life events, and the presence/absence of recent positive/negative events in each domain was coded for each session. A subset of 17 patients (7 scanned 2x) additionally completed 1 h fMRI scans during which they made financial decisions in two economic tasks. We modeled choice behavior on the tasks to extract estimates of trial-by-trial SV for each patient. To quantify how recent psychosocial stressors and state anxiety affect the neural representation of SV, we examined their effect on SV coding in striatum, VMPFC, and amygdala, defined based on meta-analytic data on value and stress. Results & Conclusions: Patients reported having experienced a recent negative event in the psychosocial domains of housing/financial or social/interpersonal in 26% of sessions and a positive event in 19% of sessions. The two event types, positive vs. negative, occurred independently of each other (P=0.77) and had differential effects on prospective opioid use, conferring either risk or resilience (adj. R^2=0.43, DF=744; negative events β=0.32, positive events β=-0.30). An increase/decrease in state anxiety mediated these effects (adj. R^2=0.67, DF=734; negative events β=2.52, positive events β=-1.67). Initial fMRI analyses showed that the higher state anxiety following recent negative events correlated with stronger SV coding in the amygdala (P=0.015) and VMPFC (P=0.12), revealing a potential mechanism through which psychosocial stressors can bias behavior toward rewards and consistent with the known effect of stress/arousal on neuromodulator systems. Current efforts focus on increasing our MRI sample size and testing how SV representations adapt over the hour long scans.

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Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.03/III9

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01DA038063 to PG
F32MH110135 to CMR
F32DA039648 to AK
Brain & Behavior Research Foundation

Title: Stress causes distinct time-dependent increases in reward valuation in the presence versus absence of explicit temptation

Authors: *C. M. RAIO, A. B. KONOVA, N. V. BANAVAR, P. W. GLIMCHER
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: States of stress and craving are both thought to play a critical role in driving reward pursuit in ways that are important in addiction. However, it is unclear whether these constructs influence reward valuation in similar ways (e.g., by both increasing the subjective value of rewards), or a distinct manner (e.g., by stress rendering individuals more susceptible to cues that induce craving without affecting reward valuation via a second mechanism). The goal of this study was to identify the specificity and independence of stress and craving effects on the valuation of primary rewards, and to characterize how these effects evolve over time. Healthy, hungry non-dieters were randomly assigned to a Control (n=30), Stress (n=30), or Stress+Craving (n=37) group. All participants completed an economic decision-making task in which they reported their willingness to pay ($0-$10) for the opportunity to purchase food items. These 'bids' were placed continuously for different quantities of each snack, allowing us to capture dynamic changes in participants' subjective value of food rewards over time. Bids were realized using a standard economic (Becker-Degroot-Marschak) auction procedure at a fixed low hazard rate. After baseline bids were acquired, participants either underwent a physiological stressor (Stress and Stress+Craving group) or a control task (Control group), before completing the bidding task. After the stress task, the Stress+Craving group additionally completed a cue-induced craving manipulation with one of the foods based on previous work (Konova et al., 2018). Saliva samples were collected to assess neuroendocrine markers of stress. Perceived stress and salivary cortisol were greater in both stress groups compared to controls. Bids did not differ between groups at baseline, however, after their respective manipulations, the stress groups demonstrated a marked increase in bids relative to controls. Interestingly, these effects unfolded

differently over time: whereas the Stress+Craving group showed an immediate increase in bids, the Stress group showed an increase in bids progressively over time, peaking only toward the end of the task. In contrast, bids in the Control group consistently decreased over time. Our results suggest that both acute stress exposure and cue-induced craving enhance the subjective value of food rewards, but that these effects emerge with distinct temporal profiles. These findings provide important insight into maladaptive choice behavior spanning addiction, anxiety and health behavior more generally.

Disclosures: C.M. Raio: None. **A.B. Konova:** None. **N.V. Banavar:** None. **P.W. Glimcher:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.04/III10

Topic: H.02. Human Cognition and Behavior

Title: Collaboration and optimization in the personality game

Authors: *K. MOGI
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Abstract: Personality (Digman 1990, Shrout and Fiske 1995) is an important aspect of the robustness of human cognition, as it represents traits not optimized by simple evaluation function. In assessing human intelligence, the g-factor (Spearman 1904) provides the founding model, where it represents qualities and quantities of resources generically used in various different cognitive functions. Personality, on the other hand, cannot be accounted for as a single scheme of generic resource management. Personality is rather a complex scheme of context-dependent resource allocation in such diverse areas as academic performance (Poropat 2009), work achievements (Mount and Barrick 1998), and the tendency to innovate (Fairweather 2012), subserved by brain circuits correlated with the “big five” factors of personality (Kennis et al. 2013, Wei-Yin et al. 2013). Personality is a social construct formed through interaction among agents, where the self-evaluation of personality often contradicts with the perception of others. A personality game can be formulated, where there is a trade-off between adherence to one’s own assessments of personality and those by others, with the emergence of the Nash equilibrium (Nash 1950). Here I describe a game theoretic analysis of collaboration and optimization in the personality game. An interactive game of personality evaluation is introduced, within a group where there is a connected graph of acquaintances. Analysis of the data suggests that subjects are able to significantly predict how others would evaluate the personality of themselves, as distinct from their own perception of their personality ($p<0.001$). Subjects feel anxiety when there is a significant dissociation between own perception and evaluation by others in agreeableness

($p<0.01$). There are behavioral changes induced by the cognitive dissonance (Festinger 1957), where subjects tend to behave according to others' expectations on openness ($p<0.001$), conscientiousness ($p<0.05$), and neuroticism ($0<0.01$). These data suggest that personality is a social construct formed through collaboration and optimization in interpersonal contexts, leading to a Nash equilibrium.

Disclosures: K. Mogi: None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.05/III11

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI 26120732
JSPS KAKENHI 16H06570

Title: Neural mechanism underlying value conversion of others' reward to decision

Authors: *H. FUKUDA[1,3], N. MA[1], S. SUZUKI[4,5], N. HARASAWA[1], K. UENO[6], J. L. GARDNER[7], N. ICHINOHE[8,9], M. HARUNO[10], K. CHENG[8], H. NAKAHARA[2,11]
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Abstract: In social setting, social signals such as reward to others often modulate one's own reward valuation and decisions. However, the core computations of this process is still poorly understood: how social signal is converted into the self-oriented decision value. Here, we demonstrate the social value conversion process, using behavioral analysis, modeling and human fMRI. Our behavioral task involves three types of trials. Standard trials assess a basic decision process, in which the subject chooses between two options, each of which is associated with one's own probabilistic outcome (standard reward). Other-bonus trials examine social value conversion, in which a number in an option additional to standard reward indicates a bonus reward to others, while self-bonus trial is a control in which an additional number indicates a bonus to the self. Using logistic regression in the choice behavior, we quantified self- and others-bonus value and final decision value difference. These quantifications enabled us to analyze neural correlates of these bonus and decision values. Here, we show three-stage processing of

social value conversion from the offer to the effective value and then to the final decision value. First, a value of others' bonus on offer, called offered value, was encoded uniquely in the right temporoparietal junction (rTPJ), and also in the left dorsolateral prefrontal cortex (ldlPFC), commonly activated by offered self-bonus value. The effective value, an intermediate value representing the effective influence of the offer on the decision, was reprsented in right anterior insula (rAI), and the final decision value was encoded in ventromedial prefrontal cortex (vmPFC). Second, using psychophysiological interaction (PPI) and dynamic causal modeling (DCM) analyses, we demonstrated the three-staged feedforward processing; from the rTPJ and ldPFC to the rAI, and the rAI to the vmPFC. Further, we showed that these characteristics of social conversion underlie distinct socio-behavioral phenotypes. We demonstrate that the variability in the conversion underlie difference between prosocial and selfish subjects, differential emphasis of the rAI and ldlPFC coupling to the vmPFC responses, respectively. Together, these findings identified fundamental neural computation processes for social value conversion, which underlies more complex social decision-making behaviors.

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Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.06/III12

Topic: H.02. Human Cognition and Behavior

Support: Alberta Gambling Research Institute
NSERC
CIFAR

Title: A model of reaching movements as a reflection of ongoing decision making

Authors: *N. J. WISPINSKI[1], C. S. CHAPMAN[2]
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Abstract: Decision making is often conceptualized as a discrete stage in a serial process, occurring after perception but before movement planning. In contrast with this view, studies have shown that decision making can continue into movement to influence how we move in physical space. Perhaps the most notable example of the interaction between decision making and movement are "changes of mind", where participants initially begin moving toward one option before switching their movement in-flight toward an alternative option in light of new information. Previous models explain changes of mind as a discrete switching between straight

reaches toward each available option. However, these models cannot account for results such as intermediate reach trajectories when participants are indecisive. Here, we propose a new computational model and argue that decision making is better conceptualized as an ongoing and graded competition between parallel movement plans, gated by a decision about when to begin moving. This model builds on a conventional evidence accumulation process, adding a second set of mutually inhibited “motor” accumulators. These “motor” accumulators weight competing direction vectors (or reach angles) toward or away from each available option, and result in a single, prepared reach angle at every time step. When the conventional accumulation process crosses a decision threshold, a movement is initiated and prepared reach angles, which have been continuously updating, now guide actual movement. This model is able to explain reaction times, choices, changes of mind, and individual reach trajectories in a simple value-based decision making task. Further, as a result of its core mechanism—approach or avoid movement directions proportional to their current desirability—this model can generalize to account for many movement trajectories in go-before-you-know and obstacle avoidance tasks. These findings provide a simple formalization for the powerful idea that decisions are the result of ongoing, graded competition between multiple motor plans from stimuli onset to movement completion.

Disclosures: N.J. Wispinski: None. **C.S. Chapman:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.07/III13

Topic: H.02. Human Cognition and Behavior

Support: John Templeton Foundation

Title: Estimating the costs of cognitive control: Theoretical validation and potential pitfalls

Authors: *S. MUSSLICK[1], J. D. COHEN[1], A. SHENHAV[2]
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Abstract: Cognitive control is critical for accomplishing daily tasks and yet we experience it as costly/effortful. Researchers have been increasingly interested in estimating just how costly cognitive control is for a given individual, in order to better understand underlying mechanisms and predict motivational impairments outside the lab. Here we leverage an economic model of control allocation to (a) demonstrate how an individual's control cost function can be estimated from task performance and (b) highlight the conditions under which such costs will be confounded with other motivational variables (e.g. sensitivity to reward). We show that poorly calibrated estimates of these other variables can lead to cost estimates that are quantitatively or even qualitatively different than their true values.

We simulated agents performing cognitive control tasks while trying to maximize expected returns and minimize control costs (Musslick, Shenhav, Botvinick & Cohen, 2015, RLDM). We then tested our ability to recover the agent's (known) control cost function based on observed task behavior, as we varied other internal variables describing how the agent processes their environment: task automaticity (quality of task performance in the absence of cognitive control), control efficacy (degree to which increased control increases the likelihood of reaching one's goal), reward sensitivity (utility of monetary rewards), and accuracy bias (intrinsic reward for performing accurately). We then tested our ability to accurately recover an agent's true control costs as our assumptions about these other parameters deviated from their actual values.
When assuming perfect knowledge of the other internal variables (task automaticity, etc.), our estimation procedure successfully recovered the control cost function for the agents. However, if we assumed imperfect knowledge of these variables, the inferred control cost estimates rapidly deviated from their true values. Critically, they could even produce a cost profile for the individual opposite to the ground truth. For instance, an agent with a high cost of control appeared to instead have a low cost of control if the agent was high in task automaticity.
Our findings show that individual differences in the costs of control can be inferred from an individual's behavior, but the validity of those estimates depends heavily on an experimenter's ability to estimate other cognitive/motivational variables. More generally, they provide a method for quantifying limits on the validity of a given measure of task performance (e.g., Stroop interference) as an individual difference measure for a given cognitive variable.

Disclosures: S. Musslick: None. **J.D. Cohen:** None. **A. Shenhav:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

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Topic: H.02. Human Cognition and Behavior

Support: Centre National pour la Recherche Scientifique (France), PICS Grant "APPVIS" to Anna Montagnini
Canada Natural Sciences and Engineering Research Council Discovery and Accelerator Grant to Miriam Spering

Title: Smooth pursuit eye movements as dynamic readout of reward-based target selection in healthy and Parkinson’s disease participants

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Abstract: The efficient selection of one out of several options relies on the estimate of the consequences of this selection, such as a reward or a punishment. The Iowa Gambling Task (IGT, Bechara et al., 1994) has been widely used to test reward-based decision-making performance, when the selection of each particular target was associated to a stochastic reward schedule with varying global payoffs. The IGT has allowed unveiling specific deficits in Parkinson's Disease (PD) patients. Voluntary eye movements efficiently adapt to the contextual requirements in humans, including reward contingencies, under several experimental conditions. Work from our group and others demonstrates that when tracking a visual moving target, smooth pursuit eye movements are dynamically modulated by reward in the very early phases, including prediction-driven anticipation (Damasse et al., 2018). Here we designed a novel smooth pursuit task inspired by the IGT where participants had to track one of two moving targets associated with different schedules of monetary gains or losses. In the main experiment, each target's direction was associated either with a globally advantageous (yielding an overall gain across trials), or disadvantageous (yielding an overall loss) schedule. In the baseline condition, the target to be tracked was explicitly instructed (e.g. "Follow the black target") and the overall monetary gain did not depend on the oculomotor performance. Participants were patients diagnosed with Parkinson's disease (PD), tested both ON and OFF Dopamine medication. We also tested age-matched and young healthy controls. We analyzed reward-based pursuit behavior during different epochs, namely the anticipation phase preceding target motion onset, the visually-guided initiation (which typically follows the vector-average of the two motion signals - Joshua and Lisberger, 2011), and the steady-state tracking phase. In young controls, but not in the other groups, smooth eye movements were dramatically biased, in the main experiment, toward the selected direction, both during the anticipatory epoch and the vector-averaging initiation. PD patients' and age-matched controls' eye movements did not express target selection until after the vector-average phase, about 300ms after target motion onset. Finally, during the late pursuit epoch, PD patients showed larger instability and more frequent *changes of mind* about which target to be tracked. Overall our results point to significant differences across experimental groups in target selection during different time epoch of a reward-based choice-pursuit task.

Disclosures: A. Montagnini: None. **J. Damasse:** None. **G.K. Mann:** None. **C.B. Jones:** None. **M.J. McKeown:** None. **M. Spering:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.09/III15

Topic: H.02. Human Cognition and Behavior

Title: learning from reward feedback in high-dimensional environments

Authors: *S. FARASHAHI, V. NOMOF, Z. ASLAMI, A. SOLTANI
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Abstract: Learning from reward feedback can become extremely challenging in high-dimensional environments with myriad choice options each with many features (curse of dimensionality), as it is the case in the real world. One solution for the curse of dimensionality is to learn reward values of individual features and combine these values to estimate reward values for each option (feature-based learning) instead of learning the value of individual options directly (object-based learning). We have hypothesized that this feature-based learning occurs not just because it can reduce dimensionality, but more importantly because it is faster and therefore more adaptable. Based on this hypothesis, we have recently proposed a framework for learning in high-dimensional environments for which we provided some experimental evidence (Farashahi et al., 2017). This framework also predicts that if the environment is stable (reward values associated with different options do not change very often), the decision maker may gradually learn the reward values of conjunctions of features as a compromise between fast but less accurate feature-based learning and slow but more accurate object-based learning. Here, we tested this prediction in an experiment in which human subjects selected between pairs of visual targets (27 objects defined by three visual features: color, pattern, and shape) and received binary reward feedback on every trial. The reward probability on a given option was determined by the combination of all features whereas one "informative" feature and the conjunctions of the other two "uninformative" features could predict reward probabilities to some extent. We found that majority of subjects learned the informative feature first before learning about the conjunctions of the uninformative features. This was reflected in choice behavior (as revealed by fitting of subject's choices) as well as estimates of reward probabilities. Interestingly, we also found that subjects who only learned individual feature values attributed reward outcomes to the informative feature at the expense of non-informative features. Specifically, these subjects increased (decreased) their tendency to choose objects that shared the same informative features as the rewarded (unrewarded) objects on the previous trial but did the opposite for the non-informative features. Overall, these results suggest that learning about conjunctions of features and competitive associations of reward to individual features (e.g. via attentional selection) can provide plausible mechanisms for adaptive learning in high-dimensional environments.

Disclosures: S. Farashahi: None. **V. Nomof:** None. **Z. Aslami:** None. **A. Soltani:** None.

Poster

333. Decision Making I

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Program #/Poster #: 333.10/III16

Topic: H.02. Human Cognition and Behavior

Support: R01MH116026

Title: Towards a neurometric-based construct validity of trust

Authors: *P.-H. A. CHEN[1], D. S. FARERI[3], B. GÜROğLU[4], M. R. DELGADO[5], L. J. CHANG[2]
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Abstract: Trust is a nebulous construct central to successful cooperative exchanges and interpersonal relationships. In this study, we introduce a new approach to establishing construct validity of trust using "neurometrics". In study 1, we combine data from two studies (n=40) to develop a whole-brain multivariate pattern that can classify whether new participants will trust a relationship partner using a linear support vector machine combined with leave-one-subject-out cross-validation. Our trust signature was able to successfully discriminate decisions to invest compared to keep money with 74% accuracy ($p < 0.001$). In study 2, we find that the pattern can accurately discriminate trust decisions with an accuracy of 68% ($p < 0.001$) in participants collected in a separate country (n=17) demonstrating generalizability of the pattern. In study 3, we establish construct validity by testing the pattern on ten separate datasets measuring distinct psychological processes. We find that our trust signature can successfully discriminate safe compared to risky decisions (accuracy = 93%, $p < 0.001$) and viewing neutral images from those depicting negative arousing scenes (accuracy = 65%, $p < 0.001$). This is consistent with the notion that trust involves an expectation of reciprocation by a relationship partner to avoid negative betrayal experiences. Moreover, we find that the signature does not generalize to reward, social closeness, facial familiarity, cognitive control, self-referential processing, and language processing indicating that the pattern is highly specific. These results provide strong support for the use of "neurometrics" in identifying the psychological processes associated with a brain-based multivariate representation.

Disclosures: P.A. Chen: None. **D.S. Fareri:** None. **B. Güroğlu:** None. **M.R. Delgado:** None. **L.J. Chang:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

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Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China (31230032, 31471071, 31171083, 31500917)
National Key Basic Research Program (2016YFA0400900)
China Postdoctoral Science Foundation (2016M592051)

Title: Behavioral and neural evidence for quantum reinforcement learning during decision making

Authors: J.-A. LI, Z. WEI, *X. ZHANG
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Abstract: Our daily decision making and judgement might obey quantum-like mechanisms. However, little is known about quantum characteristics of value-based decision (VBD) making. In the present study, we applied quantum reinforcement learning (QRL) to determine whether VBDs can be properly explained by quantum framework and how this framework is implemented in the brain. We compared several QRL models (Quantum-Superposition-state-Learning , QSL; Quantum-Superposition-state-Plus- Perseverance, QSPP) and classical reinforcement learning (CRL) models (Value-Plus-Perseverance with decay learning rule, VPPDecay; VPPDelta; etc.) based on behavioral and functional magnetic resonance imaging data from healthy and smoking subjects performing the Iowa Gambling Task (Fig. 1a). We executed the model comparisons based on Akaike and Bayesian information criterion (AIC and BIC) and simulation method and analyzed the entropy and the interaction of entropy and loss predicted by VPPDelta and QSPP based on the blood oxygen level dependent data in both groups. In the behavioral analysis, QRL models provided post hoc fits (Fig. 1b) and simulation better than or comparable to CRL models in both groups. In the fMRI analysis, for the interaction of entropy and loss, we found that the left medial frontal gyrus (MFG) was activated in QSPP but not in VPPDelta in both groups (Fig. 1c), and a set of regions, notably the left anterior cingulate cortex (ACC) and the left orbital frontal cortex (OFC) (Fig. 1d), were activated in QSPP in control group but not in VPPDelta or in smoking group. The behavioral results indicate the QRL method is a powerful quantum framework to describe behavior sequences. These regions which related to the interaction of entropy and loss, including the MFG, the ACC and the OFC, might work as a network in a quantum-like manner, integrating outcomes and learning from experience. In addition, these results provided the first fMRI evidence for quantum

cognition. We anticipate this study will lend support to the fields of quantum cognition and open up a new direction termed as quantum neuroeconomics.

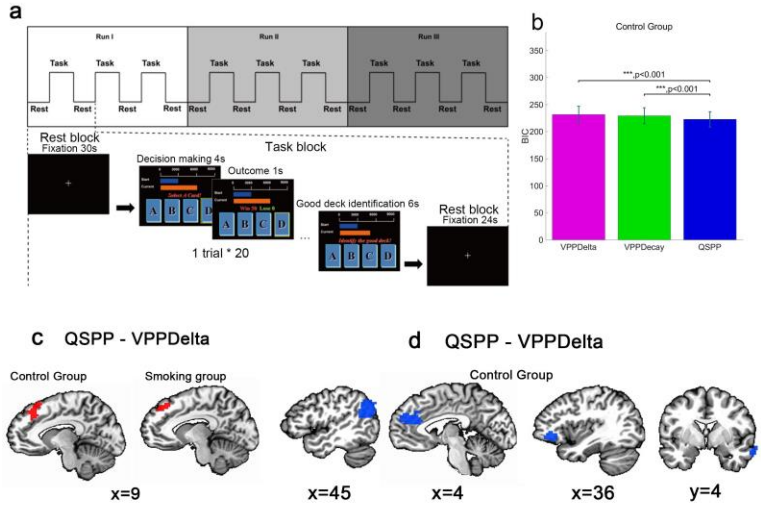

Figure 1: a, a diagram of the IGT and fMRI scan processes. There were three fMRI scan runs of 7 min. Between every two scans, an interval occurred about 1 min. Each scan consisted of one 30s rest block and three 106s-task-and-24s-rest cycles. The last 6s part of task block was designed for good deck identification, which was not analyzed in current paper. The former 100s part contains 20 trials and each trial was divided into two events: (1) during the decision making phase, 4s were provided for card selection and the program would make a random selection if no decision was made during the period, (2) during the outcome phase, the gain and loss were presented on the screen for 1s. There was no inter-trial intervals(ITIs). The blue bar above the decks showed the initial 3000 points throughout the task, and the orange one showed the current accumulated points. b, model BIC results of VPPDelta, VPPDecay and QSPP in control group. QSPP had better fits than other models. All error bars indicate the SEM. c-d, fMRI results of the entropy × loss interaction. c, the interaction positively related to the left medial frontal gyrus (MFG)/superior frontal gyrus in both control group (control QSPP - control VPPDelta) and smoking group (smoking QSPP - smoking VPPDelta). d, the interaction positively related to the left middle temporal gyrus/superior temporal gyrus/angular gyrus, the left anterior cingulate cortex (ACC), the left orbital frontal cortex (OFC) and the right middle temporal gyrus/superior temporal gyrus only in control group (control QSPP - control VPPDelta). All coordinates are plotted in RAI (DICOM) order (-right +left, -anterior +posterior, -inferior +superior).

Disclosures: J. Li: None. **Z. Wei:** None. **X. Zhang:** None.

Poster

333. Decision Making I

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01DC009209
NDSEG Fellowship

Title: Dynamic modulation of brain network integration and arousal during exploration and exploitation

Authors: *N. TARDIFF, S. L. THOMPSON-SCHILL
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Successful learning and decision-making require a balance between the stability necessary to support ongoing behavior and the flexibility necessary to adapt to new exigencies. Theories of norepinephrine (NE) function have ascribed it a key role in adjusting this balance. In particular, NE has been proposed to mediate the tradeoff between exploration and exploitation (Aston-Jones & Cohen, 2005). Alterations of cognitive state, in turn, appear to be supported by large-scale, dynamic changes in functional brain connectivity. For example, a number of studies have demonstrated that demanding tasks requiring stability are associated with increased integration among functional brain networks. Notably, recent neuroimaging studies provide evidence that NE influences the level of integration between functional brain networks, suggesting one route by which NE may alter the balance between stability and flexibility.
Here we utilized an exploration/exploitation task to probe the relationships between flexibility, NE-linked arousal—as measured indirectly via pupil diameter—and network dynamics. We predicted that network integration and pupil diameter would show opposing profiles around exploration, with pupil diameter increasing with exploratory choice and network integration decreasing. Subjects ($N = 19$, $M_{age} = 23$, 9 female) underwent concurrent fMRI and pupillometry while completing a bandit task, a type of task known to induce changes in NE activity as measured by pupil diameter. We parcellated the brain into 234 regions, estimated functional connectivity via wavelet coherence, and used a dynamic community detection algorithm to track changes in network architecture over time. At each time point, we calculated a measure of network integration, indexing the extent to which nodes from different resting-state networks were placed into the same community.
Supporting our predictions, we found that pupil dilation was larger following trials on which subjects explored, and this rise in pupil diameter was accompanied by a decrease in global brain network integration. Follow-up analyses of between-system integration revealed that frontoparietal-somatomotor, dorsal attention-somatomotor, and ventral attention-default integration showed the most reliable decreases. These data provide preliminary evidence that while task-focused states are facilitated by increased integration, exploratory states may be facilitated by less integration between functional networks.

Disclosures: N. Tardiff: None. **S.L. Thompson-Schill:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

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Topic: H.02. Human Cognition and Behavior

Support: NIH K99 AG054732
NIH F32MH102009

Title: Expectations about the source of surprise dictate the relationship between feedback-related eeg signals and learning

Authors: *M. R. NASSAR[1], R. BRUCKNER[2], M. J. FRANK[3]
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Abstract: Successful decision-making requires learning expectations based on experience. This learning should be calibrated according to the surprise associated with each outcome, but also to the most likely source of surprise. For example, when occasional change points are expected, surprising outcomes render past information irrelevant and demand increased learning. In contrast, when signal corruption is expected to occur occasionally, surprising outcomes can suggest a corrupt signal that should be ignored by learning systems. To explore whether and how the brain contextualizes surprise signals to optimize learning, we collected EEG and behavioral data in a task that required subjects to make inferences based on noisy observations of a process that included either change points or signal corruption. In change point blocks participants increased learning from surprising outcomes, whereas in the signal corruption blocks participants decreased learning from surprising outcomes. Thus the effects of surprise on learning depended on subjective expectations about the source of the surprise. Despite this behavioral interaction, feedback-related EEG signals related to surprise were agnostic to its source. A large positive medial prefrontal deflection peaking ~400 ms after outcome presentation was enhanced for surprising outcomes in both conditions equally. Computational fits to behavior showed that the impact of this signal on learning differed across conditions: larger EEG deflections predicted more learning in change point blocks but less learning in signal corruption blocks. Taken together these findings suggest that medial prefrontal surprise signals do not naively reflect increased behavioral updating, but may be used adaptively to modulate learning in either direction.

Disclosures: M.R. Nassar: None. **R. Bruckner:** None. **M.J. Frank:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.14/III20

Topic: H.02. Human Cognition and Behavior

Title: A visual bandit task in mice reveals a female-specific strategy associated with enhanced acquisition of the optimal choice

Authors: *S. CHEN[1], B. EBITZ[2], J. JEONG[3], M. CHU[3], Z. MAHAMED[2], S. BINDAS[4], B. HAYDEN[2], N. GRISSOM[3]
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Abstract: Neurodevelopmental disorders, such as autism spectrum disorders (ASD), have a strong male bias in diagnosis, and are associated with challenges in learning to predict positive outcomes of behavior. Do sex-specific mechanisms of goal-directed learning contribute to the male-specific vulnerability to ASD? One commonly used task, the multi-armed bandit, examines the dynamics of reinforcement learning and decision making, requiring a person or animal to choose each trial between exploitation of a previously experienced option, versus exploration of other options with unknown, but potentially more rewarding, outcomes. Visually cued bandit tasks have been widely employed in humans and nonhuman primates, but are largely unused in rodents. This has limited the ability to understand the neural mechanisms of complex reward environments in rodent models. We used a two-arm bandit task in thirty-two 129/B6 F1 mice (16 male and 16 female) to examine whether there are baseline sex differences in the ability to learning the reward probabilities associated with two visual cues presented on a touchscreen (80% chance of payoff versus 20%). Female mice learned to choose the cue associated with the higher probability of reward faster. A multiple linear regression analysis revealed that female mice relied more on spatial repetition in decision making at the early stage of learning, but switched from this strategy to using information of reward outcome of cues more rapidly than did male mice. We wished to examine neural mechanisms that might support these sex differences in strategy selection. Animals were sacrificed immediately following behavior on their final test day, and c-fos gene expression was used as a proxy for neural activity. In the nucleus accumbens, fos expression was more lateralized in females, while in males, fos expression was equal between left and right accumbens. This suggests that more lateralized activation of the brain in females may drive female-specific decision-making strategies that result in faster learning, and shed light on sex-specific mechanisms in neurodevelopmental disorders.

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Poster

333. Decision Making I

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Program #/Poster #: 333.15/III21

Topic: H.02. Human Cognition and Behavior

Title: Leaky-integrating dynamics, approximating Bayesian assumption of environmental non-stationarity (change points), outperform Q-learning (delta rule) in accounting for human prediction and choice behavior

Authors: *C. K. RYALI[1], A. J. YU[2]
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Abstract: Understanding how humans and animals learn about statistical regularities in stable and volatile environments and utilize these regularities to make predictions and decisions is an important problem in neuroscience and psychology. Using a Bayesian modeling framework, specifically the Dynamic Belief Model (DBM), we previously showed that in many task contexts, human prediction and choice behavior reflects a default tendency to assume the environmental statistics to undergo abrupt, unsignaled changes from time to time, known as change points, even when the environmental statistics are actually stable. Here, we show that near-Bayes-optimal learning and prediction in the DBM setting can be implemented in a computationally inexpensive and neurally plausible manner by a special case of leaky integration dynamics, also known as exponential filtering (Exp). We show that Exp can predict human choice and prediction behavior in a 2-alternative choice task and a visual search task as well as DBM, and significantly better than either Q-learning (equivalent to the Rescorla-Wagner learning rule), or an alternative Bayesian model, the Fixed Belief Model (FBM), which assumes environmental statistics to be stable over time. Using the theoretical relationship we derive between DBM and Exp, we show that the advantage Exp enjoys over Q-learning and FBM is due to the "persistent" influence of the prior assumed by DBM/Exp, which is absent in Q-learning and FBM. Furthermore, we show that the theoretical equivalence between DBM and Exp breaks down when change points are rare, but this seems to be irrelevant in most behavioral tasks where observations are quite noisy since humans appear to assume frequent change points by default even when they are rare or even non-existent.

Disclosures: C.K. Ryali: None. **A.J. Yu:** None.

Poster

333. Decision Making I

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NIMH RC2 MH089983 (REG)
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NIMH RC2 MH089924 (REG)
NIMH R01MH107703 (TS)
NIMH R21MH106799

Title: Effective learning is accompanied by high dimensional and efficient representations of neural activity

Authors: *E. TANG[1], M. G. MATTAR[3], C. GIUSTI[4], S. L. THOMPSON-SCHILL[2], D. S. BASSETT[1]
[1]Bioengineering, [2]Psychology, Univ. of Pennsylvania, Philadelphia, PA; [3]Neurosci. Inst., Princeton Univ., New Jersey, NJ; [4]Mathematics, Univ. of Delaware, Newark, DE

Abstract: A fundamental cognitive process is the ability to map objects into meaningful categories depending on the task at hand. Exactly how such mental constructs emerge and what kind of space best embeds this mapping remains incompletely understood. Here we develop tools to quantify the space and organization of such a mapping, thereby providing a framework for studying the geometric representations of neural responses as reflected in functional MRI. Considering how human subjects learn the values of novel objects, we show that quick learners have a higher dimensional geometric representation than slow learners, and hence more easily distinguishable whole-brain responses to objects of different value. Furthermore, we find that quick learners display a more compact embedding of the task-relevant information, where the ratio of task-relevant dimension to embedding dimension is consistent with a greater efficiency of cognitive coding. Lastly, we investigate the neurophysiological drivers of high dimensional patterns at both regional and voxel levels, and complete our study with a complementary test of the distinguishability of associated whole-brain responses. Our results demonstrate a spatial organization of neural responses characteristic of learning, and offer a suite of geometric measures applicable to the study of efficient coding in higher-order cognitive processes more broadly.

Disclosures: E. Tang: None. **M.G. Mattar:** None. **C. Giusti:** None. **S.L. Thompson-Schill:** None. **D.S. Bassett:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.17/III23

Topic: H.02. Human Cognition and Behavior

Title: Reaction time in speeded decision processing: How stimulus predictability affects the emergence of 1/f noise

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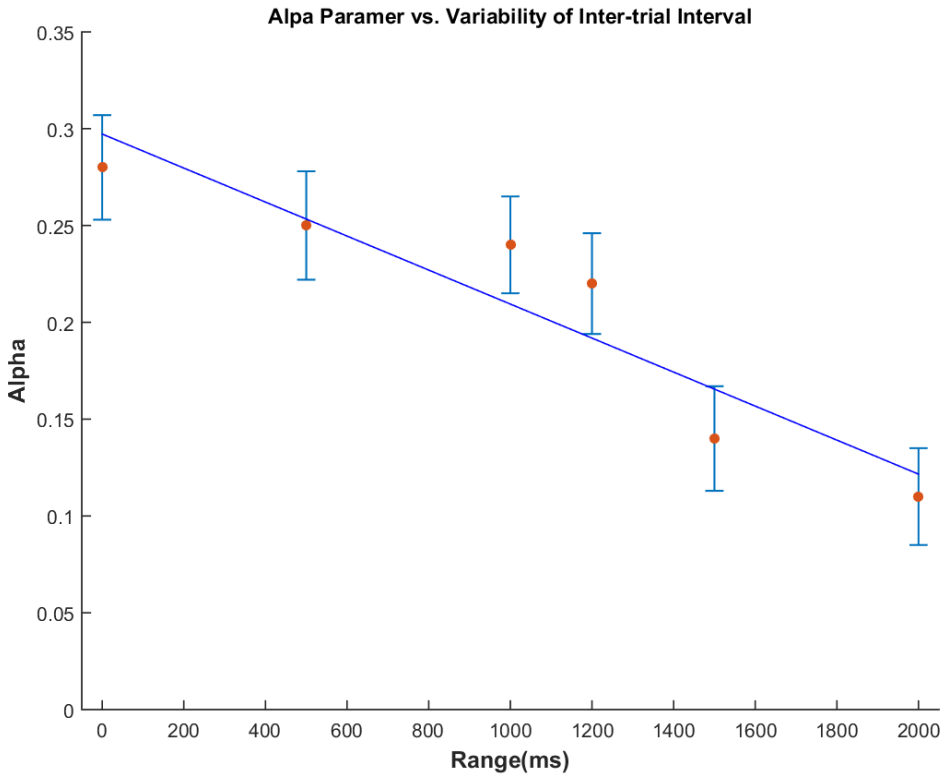
Abstract: Measurement of Reaction Time (RT) in speeded decision processing tasks has shown a large intra-subject variability of RT (ISV-RT). Decomposing the frequency spectrum of the underlying time series of the RT have shown that ISV-RT may be rooted at a long memory process called 1/f noise. 1/f noise is theorized to be a characteristic signature for system complexity and has been associated with the most elementary aspect of cognitive process, the formation of representations. In this study we investigate how the 1/f noise measured using an 1-Back working memory task is affected by stimulus predictability. We used 6 different task conditions in which the inter-trial interval (ITI) was either fixed at 1s, or varied in a uniform distribution of ITI with a mean of 1s and range of .5, 1, 1.2 , 1.5, 2s respectively. The spectrum density of RT confirmed the presence of 1/f noise measured as a decreasing linear trend a in the log-log scale indicating higher power at long frequencies that was reduced in higher frequencies. More importantly this 1/f noise pattern (Alpha parameter) decreased significantly with increasing variability of ITI (see figure 1). These results suggest that the cognitive process of formation of stable representations over time during task performance implied by the presence of 1/f noise in RT is sensitive to stimulus predictability and is drastically reduced when the time of stimulus presentation becomes highly unpredictable. Alternatively the formation of stable cognitive representations seems to be facilitated by the rhythmic presentation of stimuli.



Disclosures: P. Alefantis: None. **C. Siettos:** None. **N.P. Smyrnis:** None.

Poster

333. Decision Making I

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Program #/Poster #: 333.18/III24

Topic: H.02. Human Cognition and Behavior

Support: MEXT/JSPS KAKENHI JP17K13083
MEXT/JSPS KAKENHI JP15H05311

Title: Data-driven mapping of over 100 naturalistic tasks in the human brain

Authors: *T. NAKAI[1,2], S. NISHIMOTO[1,2,3]
[1]Ctr. for Information and Neural Networks (cinet), NICT, Osaka, Japan; [2]Grad. Sch. of Frontier Biosciences, Osaka Univ., Osaka, Japan; [3]Grad. Sch. of Medicine, Osaka Univ., Osaka, Japan

Abstract: The central issue in neuroimaging is to reveal how our daily cognitive processes are represented in the brain. The tasks generally used in standard neuroimaging studies have been far

from our daily activity, and may have not efficiently evoked cognitive processes in the naturalistic situation. It has also been unknown how cognitive processes underlying various daily activities are mutually related. To tackle these issues, we performed fMRI experiments for each subject with over 100 naturalistic tasks. By combining a data-driven mapping and interpretation based on the meta-data, we examined cortical organization of multiple naturalistic tasks.We prepared 103 naturalistic tasks, which can be performed without any pre-experimental training. Six participants (ages 22-33, 2 female) performed tasks while we recorded the evoked brain activity using a 3T MRI scanner (Siemens Trio TIM; TR = 2000 ms, voxel size = 2 mm isotropic, multiband factor = 3). The experiment was composed of 18 runs. Each run contained 77-83 tasks with duration of 6-12 s. We built a voxel-wise encoding model (R=FW), where R was brain activity, F represented 103-dimensional task-feature vectors (1/0 for each time point), and the weight matrix W was estimated using an L2-regularized linear regression. Model accuracy was calculated using Pearson's correlation coefficient between predicted and measured activity in the hold-out test dataset. To examine the dominant cognitive factors that underlie the activity patterns, we performed principal-component analysis (PCA) with the estimated weight matrix. The top PCs contrasted the tasks regarding their sensory factors such as auditory features (e.g., Music category judgment), and cognitive factor such as language features (e.g., Metaphor comprehension). Projections of the PC coefficients into the cortical space revealed that the auditory PC showed large weight in the bilateral temporal regions, while the language PC showed large weight in the bilateral fronto-temporal regions.To assess cognitive factors related to each PC, we calculated Pearson’s correlation coefficients between each PC map and the reference terms in Neurosynth (Yarkoni et al., 2011). The language PC map had higher correlation with the term ‘semantic’, and ‘sentence’, while the auditory PC map had higher correlation with the term ‘listening’, and ’sounds’.Using t-distributed stochastic neighbor embedding, we further found a distinct task distribution in the cognitive map, such that Shopping task was closely positioned to Money counting task. Our data-driven method provides a new insight into the cortical implementation of the cognitive map in the naturalistic situation.

Disclosures: T. Nakai: None. **S. Nishimoto:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.19/III25

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI 16H06570

Title: Neuro-computational mechanisms for deciding with predicting others

Authors: *N. MA[1], N. HARASAWA[1], K. UENO[2], N. ICHINOHE[4], M. HARUNO[5], K. CHENG[3,2], H. NAKAHARA[1]
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Abstract: In social environments, expectation of reward for ourselves and associated decision-making often depend on others' behavior. Thus, our decision processes should include consideration about others' decisions. However, a fundamental of the computational process is still poorly understood: how humans integrate the prediction of others' behavior into self-oriented decisions. To address this issue, we devised a novel behavioral task in human fMRI, combined with computational modeling. In our task, there is a main trial together with two types of control trial, self and other trials. Main trial required the subject to choose an option, using the prediction of others' choice, because a set of options to choose depended upon the others' choice. Self and other trials examined each component in the main trial, which is making probabilistic self-value-based decisions and predicting others' decisions, respectively. Probing the behavior, we first confirmed that the subject's behavior followed self-value difference and predicted-others' value difference in the self and other trials, respectively. In the main trials, the subject's decision followed the self-value difference generated by predictions of others' choices. That is, the subject's choice was governed by a balance of the two possible self-value differences that corresponded to two different predictions of others' choices. The relative contribution of the two self-value differences varied along with the uncertainty in predicting others' choices. We then examined the BOLD signals, using model-based analysis. First, we found that activations in right temporoparietal junction (rTPJ) and medial prefrontal cortex (mPFC) were significantly correlated to prediction uncertainty of others' decision, so that at the group level, the individuals' higher activations in these regions are related to efficiency in using the prediction of others to guide their decisions. The activations in these regions are also significantly correlated to the predictions in both main and other trials. Second, we found that the mPFC responses are significantly activated by self-decisions in both self and main trials. Third, using psychophysiological interaction analysis, we found that the rTPJ activations had impact on the mPFC responses, only mediated through the responses in right inferior frontal gyrus. Taken together, these findings suggest that predicting about others' behavior recruits additional neuro-computational process for using the uncertainty in the prediction to integrate the prediction to generating self-oriented decisions.

Disclosures: N. Ma: None. **N. Harasawa:** None. **K. Ueno:** None. **N. Ichinohe:** None. **M. Haruno:** None. **K. Cheng:** None. **H. Nakahara:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.21/III27

Topic: H.02. Human Cognition and Behavior

Support: MR/P008747/1

Title: Dissociating conflict and uncertainty- An evidence accumulation model

Authors: *A. MANDALI, V. VOON
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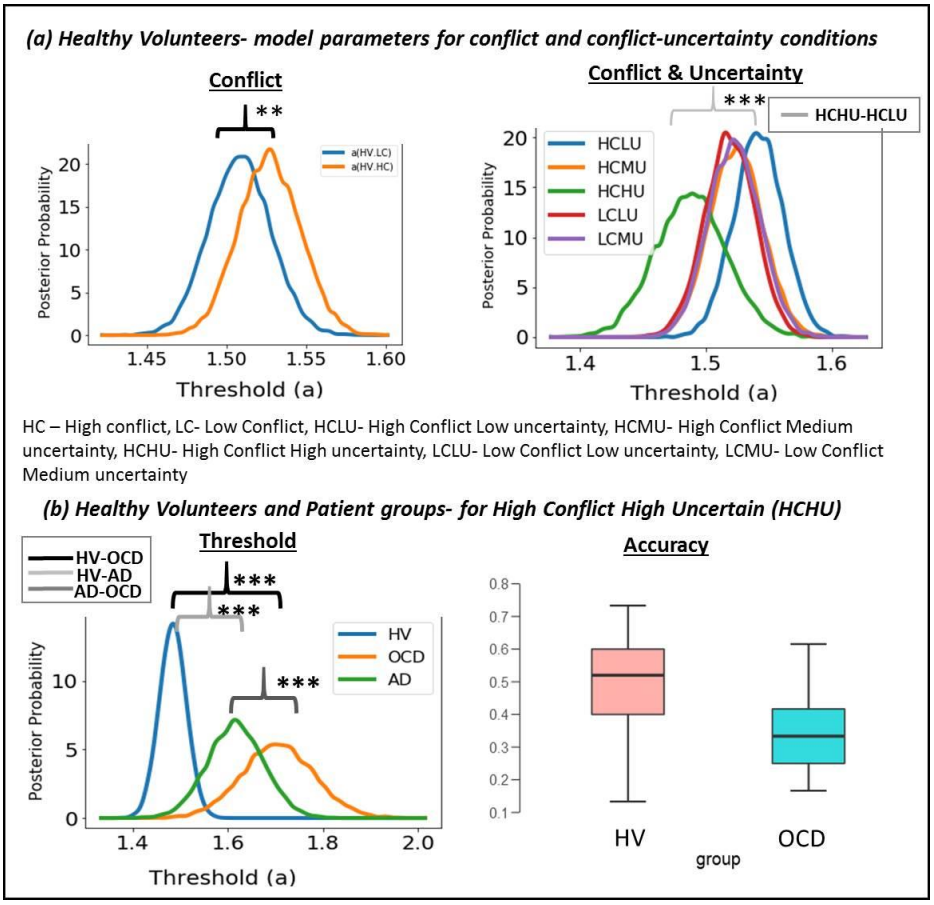
Abstract: Introduction: The likelihood of obtaining a reward (*uncertainty*) and the similarity between choices (*conflict*) critically influence decision making. Conflict and uncertainty are commonly confounded but can be dissociated. Here we study their interaction using a sequential learning task in healthy volunteers (HV) and patients (obsessive-compulsive disorder: OCD, alcohol dependent-AD), by posing it as an evidence accumulation problem.
Method: We defined 2 variables i.e., *Conflict*- high or low (difference between reward probabilities of the stimuli) and *Uncertainty*- low, medium or high (inverse U-shaped probability-uncertainty function). The above variables were used as inputs along with the behavioural data in a hierarchical drift diffusion model to extract threshold ('*a*'- amount of evidence accumulated before making a decision) and drift rate ('*v*'- information processing speed) parameters.
Results: Using the conflict information alone, we show that HVs distinguish low and high conflict by accumulating more evidence (*a*) during high conflict, which was absent in both OCD and AD patients. We then included both uncertainty and conflict in the model and showed a critical interaction between them. HV accumulated more evidence when stimuli were high conflict-certain compared to low conflict-certain. But when the choices were high conflict with no certainty in reward, they unexpectedly did the opposite i.e., accumulated significantly less evidence. In contrast, OCD patients accumulated more evidence in the high conflict-uncertain condition yet performed sub-optimally. ADs showed deficits in processing conflict with similar threshold and drift rates for both high and low conflict conditions.
Discussion: We show that the interaction between conflict and uncertainty critically influences the choice selection mechanisms through evidence accumulation. We also show that OCD patients perform sub-optimally in the presence of high uncertainty especially during difficult decisions with increased thresholds reflecting their indecisiveness and 'checking' symptomology.



Disclosures: V. Voon: None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.22/III28

Topic: H.02. Human Cognition and Behavior

Title: A divisive model of evidence accumulation explains unequal weighting of evidence over time in an auditory perceptual decision making task

Authors: *W. KEUNG, T. A. HAGEN, R. C. WILSON
Univ. of Arizona, Tucson, AZ

Abstract: Effective decision making often requires us to integrate noisy evidence over time. For example, when listening to a talk, ideally we would integrate evidence equally from all parts of the presentation - the beginning, middle and end - to assess the quality of the science. However,

in practice we often weigh information differently over time leading us to make suboptimal decisions. Here we refer to this suboptimal weighting of information over time as the "kernel" of integration. For example, overweighing the beginning of the talk indicates a primacy kernel, while overweighting the end indicates a recency kernel. Several studies have shown that integration kernels on the order of 1 second vary considerably between species and task design with evidence for primacy, recency and flat integration kernels all existing in the literature. In addition we have recently found evidence in humans for a "bump" integration kernel in which in which evidence from the middle of the stimulus is weighed most strongly (Keung et al 2018 bioRxiv). In the present work we show how all four of these integration kernels can be accounted for by a single neural network with divisive normalization. In particular, we adapted the dynamic divisive normalization model of Louie et al (2014) that has previously been used to describe choices and neural firing in value-based decisions (that do not involve temporal integration of evidence over time). In this network, evidence for competing choices is accumulated in pools of neurons that self excite and compete via divisive inhibition. We show theoretically how this network acts as an integrator, and provide a formal expression for the integration kernel over time. This expression shows how the model can generate all all four types of integration kernel observed in the literature (primacy, recent, flat and bump) providing a qualitative account for previous results. In addition the model provides a close quantitative fit to human behavioral data. Overall our model provides a unifying account of evidence integration across species and makes testable predictions at the neural and behavioral levels.

Disclosures: W. Keung: None. **T.A. Hagen:** None. **R.C. Wilson:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.23/III29

Topic: H.02. Human Cognition and Behavior

Support: OMRON Corporation
Brain/MINDS from AMED (JP17dm0207001)

Title: A Bayesian model explains how individual and mutual properties of action and outcome affect sense of agency

Authors: *R. LEGASPI, T. TOYOIZUMI
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Abstract: *Sense of agency* is fundamental to the experience of volition, self-consciousness and responsibility for one's own actions, and the degradation of this experience characterizes certain psychiatric disorders. We have introduced a theoretical model of sense of agency (Legaspi &

Toyoizumi, SfN 2017), which adapted the Bayesian inference model of Sato, Toyoizumi & Aihara (Neural Comp 2007) originally used to explain the *ventriloquism effect* as an effort to estimate a common cause behind the audio-visual stimuli. However, we have yet to explain through our model how action and consequent outcome signals, when each happens in isolation or interact with each other, affect the experience of agency.
Our Bayesian model exhibits the following requirements to experience a high sense of agency: (A) the perceived action-outcome pairing must be *consistent* with the causal role of one's action in producing the immediate outcome, and (B) the perceived action or outcome signals must be *reliable* when they happen in isolation, i.e., the amplitudes of sensory jitters must be small enough not to increase sensory uncertainty. Both (A) and (B) increase the confidence of the Bayesian estimate modeled as sense of agency.
The above predictions of our Bayesian model accounted for the *intentional binding effect*, hailed as the implicit measure of agency, in two pertinent studies. The first is the seminal experiment reported by Haggard, Clark & Kalogeras (Nature 2002) that showed voluntary actions produced intentional binding but involuntary actions produced the prolonged opposite perception of the action-outcome interval, which was accounted for by (A). The second study is by Wolpe, Haggard, Siebner & Rowe (Exp Brain Res 2013) that showed the contribution of sensory uncertainty to intentional binding by manipulating the intensity of outcome tones, which was accounted for by (B).
Moreover, we now observe our Bayesian model also predicts that a prior belief of the action causing the outcome can modulate sense of agency, hence, also influences intentional binding. The strength of this prior moves the perception of the action and outcome towards each other, and weakening it consequently diminishes the action-outcome effect similar to when their signals are perceived as unrelated. This accounted for both the repulsion effect from involuntary actions reported by Haggard et al. and the diminished action binding reported by Wolpe et al.

Disclosures: R. Legaspi: A. Employment/Salary (full or part-time):; Full, RIKEN Center for Brain Science. **T. Toyoizumi:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.24/III30

Topic: H.02. Human Cognition and Behavior

Title: Decomposing Simon task BOLD activation using a drift-diffusion model framework

Authors: *J. R. MCINTOSH, P. SAJDA
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Abstract: The Simon effect is observed in spatial conflict tasks where the response time of subjects is increased if stimuli are presented in a lateralized manner so that they are incongruous with the response information that they represent symbolically. A limited number of studies have used fMRI to investigate this phenomenon, and while some have been driven by considerations of an underlying model, none have attempted to directly tie model and BOLD response together. It is likely that this is due to Simon models having been predominantly descriptive of the phenomenon rather than capturing the full spectrum of behavior at the level of individual subjects. Drift-diffusion models (DDM) which capture full response distributions for correct and incorrect responses have recently been extended to capture conflict tasks. In this study we fit a Simon-Effect DDM which includes specific estimates of automatic response bias and conflict monitoring based deployment of attention to individual subject behavioral data. Both of these parameters are needed because while a bias term captures the increased mean response time in incongruent trials, the attention term is needed to capture a compensatory decrease in the standard deviation.The expected decision-variable, across-trial model parameter modulations and overall parameter fits are used to interpret the BOLD response at multiple time scales. We find evidence of lateralized regions in visual cortex correlated with the decision-variable, with precuneus cortex being modulated by the expected decision-variable in conflict trials - a potential marker for conflict. We find neighboring regions of the precuneus are also correlated with across-trial fluctuations of drift or attention, and an across subject measure of bias. Taken together a potential interpretation is that precuneus is acting to locally monitor conflict which is then used by anterior cingulate cortex (ACC) in the deployment of attention to reduce the impact of lateralized stimuli on the representation of the decision-variable.
The model based analysis allows us to paint a rich picture of brain activity during spatial conflict tasks, with which we can in turn tease apart different patterns of activity which would be collapsed together with more standard analyses.

Disclosures: J.R. McIntosh: None. **P. Sajda:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.25/III31

Topic: H.02. Human Cognition and Behavior

Title: Model-based quantitative analysis of two ‘guilt aversion’s

Authors: *S. NUMANO[1], M. HARUNO[2]
[1]Grad. Sch. of Frontier Biosciences, Osaka Uni, Suita-Shi, Japan; [2]Natl. Inst. of Information and Communication Technol., Osaka, Japan

Abstract: It has long been proposed that ‘guilt’ has strong impacts on our behavior and mental states. However, there are at least two definitions of ‘guilt aversion’. One definition of ‘guilt aversion’ is the propensity to avoid imbalance between self and other’s outcomes (inequity guilt-aversion), and the other is the propensity to minimize the difference between other’s expectation and his actual outcome (intention guilt-aversion). A previous study tried to distinguish inequity and guilt aversions, and showed that these two aversions are computed in different cortical areas (Nihonsugi et al., 2015). However, no study have attempted to dissociate the two guilt aversions. In this study, we approached this issue based on the large amount of behavioral and personality traits’ questionnaire data collected online.More than 7000 volunteers participated in the online experiments. First, participants answered 24 psychological personality questionnaires, such as Big Five personality trait and Beck Depression Inventory II (BDI). Then, they performed a trust game (Nihonsugi et al., 2015) which can measure both inequity and intentional guilt aversions as regression coefficients. We analyzed the data, based on the logistic model which consisted of three separate components: reward, guilt, and inequity. We examined correlations between the regression coefficients and the personality traits scores. We found significant correlation between intentional guilt and BDI (r=0.225 and P=0.003, linear regression), as well as the sex differences in both intention and inequity guilt-aversions (P=0.0114 and P=0.0028, respectively, Welch’s t-test) .

Disclosures: S. Numano: None. **M. Haruno:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.26/III32

Topic: H.02. Human Cognition and Behavior

Support: John Templeton Foundation 42052

Title: Graph theory measures of functional connectivity in divergent and convergent thinking in "Big-C" creativity

Authors: *K. JAPARDI, A. ANDERSON, K. KNUDSEN, S. BOOKHEIMER, R. BILDER
Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA

Abstract: Objectives: Divergent thinking (DT) and convergent thinking (CT) are considered critical for creative thinking but the patterns of functional connectivity underlying these abilities remain unknown. The Big-C Study examined whether a “Big-C” (exceptionally creative) group and a smart comparison group: (1) display task-dependent group differences in functional connectivity across global and local graph theory metrics and (2) display significant group-by-network interactions across functional tasks. We hypothesized that Big-C individuals would

differ from the comparison group across graph theory metrics, showing greater network efficiency and highly clustered networks. Methods: We analyzed 66 participants including 21 Big-C visual artists (VIS), 21 Big-C scientists (SCI), and 24 smart comparison group individuals (SCG), matched on age, sex, and intelligence. Participants had fMRI scans during an Alternate Uses Task (AUT) and Remote Associates Task (RAT), to measure DT and CT respectively, and completed a six-minute resting state scan (REST). Analyses followed using a 333 ROI atlas using similar methods detailed in Power et al 2014 and Cole et al 2014. Graph theory metrics included modularity (Q), small worldness (SW), characteristic path length (CPL), local efficiency (EL), and clustering coefficient (CC). Local metrics were compared across six networks: default mode, dorsal attention, frontoparietal, salience, ventral attention, and visual. Results: Big-C visual artists and scientists, relative to SCG participants, displayed higher EL and CC in the visual network across multiple conditions, but Big-C visual artists showed lower EL and CC of the frontoparietal network at rest (See Table 1). Conclusions: Our findings are partially congruent with our initial hypothesis, suggesting that Big-C individuals differ from comparison individuals along network efficiency and clustering, but display similar global patterns of functional connectivity. These findings are also compatible with our hypothesis that Big-C creativity may rely on efficient visuospatial processing and disengagement of cognitive control.

Table 1: Group results for local efficiency and clustering coefficient. (df = 11,166; p < 0.001)

Metric	**Contrast**	**Task**	**Network**	***t-stat***
EL	VIS < SCG	REST	Frontoparietal	-3.77
EL	VIS > SCG	REST	Visual	4.5
EL	SCI > SCG	AUT Unusual Uses	Visual	4.26
EL	VIS > SCG	AUT Typical Qualities	Visual	3.65
EL	SCI > SCG	AUT Typical Qualities	Visual	3.76
CC	VIS < SCG	REST	Frontoparietal	-3.97
CC	SCI > SCG	AUT Unusual Uses	Visual	4.77
CC	VIS > SCG	AUT Typical Qualities	Visual	4.9
CC	SCI > SCG	AUT Typical Qualities	Visual	4.46

Disclosures: K. Japardi: None. **A. Anderson:** None. **K. Knudsen:** None. **S. Bookheimer:** None. **R. Bilder:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.27/III33

Topic: H.02. Human Cognition and Behavior

Title: Does seeing the world from the perspective of an autonomous vehicle alter the view of autonomous vehicles?

Authors: *J. PAK[1], C. WILLEY[2], N. AKRAM[2], U. MAOZ[3]
[1]Brain Inst., Irvine, CA; [2]UCLA, Los Angeles, CA; [3]Psychology & Brain Inst., UCLA, Orange, CA

Abstract: Numerous vehicles with some self-driving abilities now occupy the roads, and the number and level of autonomy of these vehicles are growing. Such autonomous vehicles (AV) are at the spotlight of both academia and industry. While many studies focus on algorithmic perfection and optimization of the operating artificial intelligence, less in known about how humans view such AVs. In the current study, we examined how participants viewed driving quality, safety, and other measures for a series of video clips depicting a car driving through city streets and interacting with other cars and pedestrians. Our video is a three-dimensional, internal reconstruction of actual footage of an AV driving in a city, occasionally with human intervention. The video clips were presented in random order, and participants answered questionnaires about the quality of driving in each video. Questionnaires were presented before, in-between, and after a series of video clips to detect any change in participants' opinion about AVs following the clips. Preliminary results suggest that subjects' opinion about quality of driving was lower when they believed an AV was driving than when they believed a human was driving.

Disclosures: J. Pak: None. **C. Willey:** None. **N. Akram:** None. **U. Maoz:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.28/III34

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant DGE-1644869

Title: Belief updating and demand for instrumental information

Authors: *N. M. SINGLETARY[1], G. HORGA[2], J. GOTTLIEB[1]
[1]Mortimer B. Zuckerman Mind Brain Behavior Inst., [2]Dept. of Psychiatry, Columbia Univ., New York, NY

Abstract: Real-world decisions typically start by determining which sources of information to sample before committing to a particular option. However, the vast majority of laboratory tasks

have eschewed this sampling process and provide DMs with preselected cues, leaving the mechanisms of information demand poorly understood. We developed a new task to test human information sampling behavior, its relation to belief updating, and its neural substrates. Bayesian theory predicts that the leverage an informative cue should have on a DM's current beliefs and the DM's willingness to pay for the cue is a function of the prior decision uncertainty and the anticipated information quality. Moreover, cue information gain should interact with the incentive structure, such that the willingness to pay (WTP) for a cue multiplicatively increases with the gain (loss) for a correct (incorrect) answer. To examine these predictions, we tested participants (n = 10, 3 female) on a 2-alternative forced choice (2-AFC) task where they declared their WTP for obtaining an additional cue (Exp. 1, WTP) or estimated the probability of one alternative being true with or without the benefit of an additional cue (Exp. 2, belief updating). In each trial block, participants saw a series of trials in which they were told the prior probability that they were in a portrait or a landscape gallery (i.e., a gallery where the majority of pictures are portraits or landscapes, respectively). In addition, participants were told the majority ratio of the pictures in the gallery, which established the likelihood that the cue came from its respective gallery (information quality). Finally, participants were told the penalty for making an error. At the end of each block, participants declared their decision on a randomly selected trial. Their payout for the block was the initial endowment minus the error penalty (if any) and minus the bid if it was high enough to purchase a cue on this trial. While the participants broadly conformed to Bayesian predictions, they also showed two noteworthy deviations. In the belief-updating task, beta coefficient for the log-odds of the likelihood (information quality) was greater than that of the prior. In the WTP task the participants showed sensitivity to error costs and information gain but not the predicted interaction between the two factors. These results are pilot results that will be expanded upon in a larger sample. The findings set the stage for understanding the neural substrates of specific cognitive processes underlying belief updating and information demand during decision making.

Disclosures: N.M. Singletary: None. **G. Horga:** None. **J. Gottlieb:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.29/III35

Topic: I.06. Computation, Modeling, and Simulation

Title: Application of entropy, information gain, and decision trees for intelligent decision making and data fusion

Authors: *H. C. YUAN[1], M. CHAO[2]
[1]Independent Lab., San Marino, CA; [2]Independent Lab., Rancho Palos Verdes, CA

Abstract: Intelligent decision makers need to be able to evaluate the consequences of their actions or the sequence of choices they have. In many problems involving intelligent decisions, the number of possible sequences can be quite large. This poster investigates how intelligent decisions can be made through construction of a decision tree and applying concepts from information theory such as information gain, entropy, and supervised datasets. A decision tree builds classification or regression models in the form of a tree structure. It breaks down a dataset into smaller and smaller subsets while at the same time an associated decision tree is incrementally developed. The final result is a tree with decision nodes and leaf nodes. A decision node has two or more branches. A leaf node represents a classification or decision. The root node is the topmost decision node in a tree. Decision trees can handle both categorical and numerical data. A decision tree is built top-down from a root node and partitions the data into subsets with similar or homogeneous values. Entropy is used to calculate the homogeneity of a dataset. If the dataset is completely homogeneous the entropy is zero, and if the dataset is uniformly divided, it has entropy of one. The information gain is based on the decrease in entropy after a dataset is split on an attribute. Constructing a decision tree is finding the attribute that returns the highest information gain or the most homogeneous branches. A decision tree is transformed to a set of rules by mapping from the root node to the leaf nodes. The rules can be applied to a new or unclassified dataset to predict which inputs will have a given outcome. This poster also examines the use of an algorithm for building decision trees called ID3 (Iterative Dichotomiser 3) by J. R. Quinlan employing a top-down, greedy search using entropy and information gain through the space of possible branches in the dataset with no backtracking. As an application, this poster examines how decision trees can be applied to fuse avionics data (aircraft range, velocity) in decision making for classification, surveillance, and early warning decisions. An application to airborne avionics for air vehicle classification for reconnaissance strategies is also given.

Disclosures: H.C. Yuan: None. **M. Chao:** None.

Poster

333. Decision Making I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 333.30/III36

Topic: H.02. Human Cognition and Behavior

Support: Templeton Foundation 60844
Columbia Aging Center - Internal Grant
NSF GRFP DGE-16-44869

Title: Increased curiosity enhances memory in older adults

Authors: *E. TEDESCHI, C. MARVIN, E. LANG, D. VARATHAN, D. SHOHAMY
Columbia Univ., New York, NY

Abstract: Curiosity is a fundamental aspect of intrinsically motivated learning, but there are many open questions regarding the cognitive and neural mechanisms by which curiosity drives learning. Previous research has suggested that curiosity may leverage basic reward mechanisms, where desired information is the reward, and curiosity can be viewed as the drive to obtain it. This framework makes predictions regarding how curiosity might change across the lifespan. Reward sensitivity is thought to decrease with healthy aging as a function of decreased dopaminergic activity. This suggests that, to the extent that curiosity is related to these same mechanisms, curiosity should also decrease with age. This prediction is consistent with the conventional wisdom that curiosity declines with age. However, few empirical studies have tested this prediction about aging, and those that do exist have provided inconsistent results. A better understanding of the relationship between curiosity and age could help test the reward hypothesis and potentially shed light on other potential mechanisms of curiosity.
We conducted two studies designed to examine age related changes in curiosity. In both studies, groups of older and younger adults were shown a series of trivia questions. For each question, participants chose whether to wait up to 30 seconds to see the answer, or to immediately skip to the next question. Choosing to wait was interpreted as a measure of curiosity. After the task, participants were given a surprise memory test for the answers to questions that they waited for. In Study 1, behavioral results showed that older adults were more likely to wait for answers than younger adults. Moreover, older adults were more likely to correctly recall the answers on the memory test. Study 2 sought to replicate and further investigate these findings, repeating the behavioral assessment while participants were scanned with fMRI with two new groups of older and younger adults. Behaviorally, the results of Study 2 replicated those of Study 1: older participants were more willing to wait for answers and also had better recall memory for the answers. fMRI results show that the decision to wait for information is related to increased BOLD activity in the striatum, DLPFC, and VMPFC in young participants, consistent with the "information as reward" hypothesis. Together, these results raise the possibility that while reward mechanisms may contribute to curiosity-driven learning in young adults, there may be other additional mechanisms contributing to curiosity in older adults, which may instead be related more to semantic knowledge.

Disclosures: E. Tedeschi: None. **C. Marvin:** None. **E. Lang:** None. **D. Varathan:** None. **D. Shohamy:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.01/III37

Topic: H.02. Human Cognition and Behavior

Title: Multimodal ERP analysis of mental arithmetic processing performance and its relationship to selective attention, and fatigue

Authors: M. N. BAKER, C. SHEN, S. J. PANZENHAGEN, B. CLARK, D. H. HUGHES, *A. W. CHIU
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Abstract: In this study, we investigated a person's evoked-response potentials (ERPs) to errors during mental arithmetic processing (MAP). The purpose of this project was to evaluate how ERPs were affected by the mode of stimulus delivery, the subject's language ability, self-identified learning style, selective attention, and fatigue. Gender non-specific, ethnicity non-specific human subjects between the ages of 18-55, capable of performing simple mental mathematical problems, were recruited. Each subject were given 360 simple math problems, along with the corresponding answers (80% correct; 20% incorrect). These questions were presented in batches of three alternating forms, visual only (shown on a computer screen), auditory only (presented via headphones), and mixed mode (a combination of visual and auditory). Subjects were instructed to solve the math problems mentally, and keep track of the correct solutions. When presented with errors in mathematical solutions, the averaged ERPs showed an increased latency. The longer latency suggested the possibility of a longer processing time when subjects realized that the answers were not what they had in mind. Not unexpectedly, there was also a significant increase in the averaged ERP peak amplitudes when presented with incorrect solutions, over four times as large as those derived from the correct solutions ($p<<0.01$). There was a weak correlation of theta rhythms ($R^2=0.68$) and alpha rhythms ($R^2=0.40$) at Fz with the visual ERP latency, and an even weaker correlation with auditory ERP latency ($R^2<0.30$). Consistent with recent publications in psychology and education journals, there was little or no evidence of any dependence between the ERP latency and amplitude to the reported visual/verbal dimensions in the Index of Learning Styles. On average, subjects missed an average of 34% of the problems when they are presented in the auditory mode, versus 24% in the visual mode. Follow-up research may involve tasks that are more conducive to other various mode of delivery, and may offer alternative ways to evaluate cognitive function and attention in a quantitative manner.

Disclosures: M.N. Baker: None. **C. Shen:** None. **S.J. Panzenhagen:** None. **B. Clark:** None. **D.H. Hughes:** None. **A.W. Chiu:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.02/III38

Topic: H.02. Human Cognition and Behavior

Title: The modified law of effect and the partial reinforcement extinction effect

Authors: *A. P. BLAISDELL, B. M. SEITZ, C. INDUDHARA
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Abstract: We present our recent modification to Thorndike's original Law of Effect (1911) that expands its explanatory power (Blaisdell, Stolyarova, & Stahlman, 2016). In addition to providing an account for the inverse relationship between reward probability and response variation, the Modified Law of Effect (MLOE) also provides an account for the partial reinforcement extinction effect (PREE). The PREE is the finding of more rapid extinction to an instrumental or Pavlovian response that had previously been reinforced continuously (CRF) compared to a response that had only been partially reinforced (PRF). According to the MLOE, a CRF cue acquires a strong excitatory S-R but very weak or no inhibitory S-R; while a PRF cue acquires strong excitatory and inhibitory S-R associations. During extinction, the inhibitory S-R association will increase rapidly for the CRF cue but much more slowly for the PRF cue (because learning is negatively accelerating). We tested the MLOE account of the PREE using a within-subject operant procedure in pigeons and humans in which we manipulate whether or not an inhibitory S-R association develops to the PRF cue. Results support predictions of the MLOE that inhibitory S-R associations play a role in the PREE.

Disclosures: A.P. Blaisdell: None. **B.M. Seitz:** None. **C. Indudhara:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.03/III39

Topic: H.02. Human Cognition and Behavior

Support: Russian Academic Excellence Project '5-100'

Title: Action in auctions: Neural and computational learning mechanisms of repeated bidding

Authors: *M. MARTINEZ-SAITO[1], R. KONOVALOV[3], M. PIRADOV[3], A. SHESTAKOVA[2], B. S. GUTKIN[4], V. KLUCHAREV[5]
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Abstract: Bidding is a pivotal socioeconomic process underlying consumer behavior dynamics. Yet how humans learn to bid efficiently in complex markets remains an open question. We used model-based neuroimaging to investigate the neural mechanisms of bidding behavior. Twenty-seven subjects (nine male) played a prototypical bidding game: a double action, with three market types, which differed in levels of supply and demand. We compared different computational learning models of bidding: directional learning models (DL), where the model bid is "nudged" depending on whether it was accepted or rejected, along with standard reinforcement learning models (RL). We found that DL fit the behavior best and resulted in higher payoffs. We found the binary learning signal associated with DL to be represented by neural activity in the striatum distinctly posterior to a weaker reward prediction error signal. We posited that DL is an efficient heuristic for valuation when the action (bid) space is continuous. Indeed, we found that the posterior parietal cortex represents the continuous action-space of the task, and the frontopolar prefrontal cortex distinguishes among conditions of social competition. These findings provide a conceptual model that accounts for a sequence of processes that are required to perform successful and flexible bidding: (a) market competition type recognition, (b) bid choice informed by the game structure, and (c) feedback-driven learning by means of a DL algorithm. Our results suggest that an efficient DL heuristic underlies price adjustments during repeated bidding.

Disclosures: R. Konovalov: None. **M. Piradov:** None. **A. Shestakova:** None. **B.S. Gutkin:** None. **V. Klucharev:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.04/III40

Topic: H.02. Human Cognition and Behavior

Title: Option transfer in humans enables faster exploration

Authors: *L. XIA[1], A. G. COLLINS[2]
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Abstract: Humans' ability to flexibly transfer previously learned skills to novel contexts is one of the fundamental gaps that sets humans apart from current state-of-the-art artificial intelligence (AI) algorithms. However, how humans transfer skills is not well understood. Studying how humans generalize learned skills will not only provide insights to how humans learn and adapt, but also help develop the next generation AI algorithms with more human-like learning efficiency and flexibility. Recent work showed that humans can transfer one-step policies to

novel contexts. However, flexible real world behavior often requires multiple steps. The options framework from hierarchical reinforcement learning (HRL) provides a potential solution to counter this complexity by introducing behavioral modules called “options”. Options are abstract multi-step policies, assembled from primitive actions or simpler options, that can represent meaningful reusable skills. Options induce hierarchical structure in the action space, coinciding with the hierarchical structure in natural human behavior. Therefore, the options framework is considered a promising upgrade from traditional flat reinforcement learning (RL) models. In this pilot study, we aim to test if humans can indeed learn and reuse options. We designed a novel sequential decision making protocol that provides behavioral markers of reusing learned options. Participants (N=29, age 18-24, 19 females) learned to choose the correct action at each step in order to receive reward. Results showed significant transfer effects that cannot be explained by traditional flat RL models. Furthermore, transfer was visible both in simple options including only primitive actions, and complex options that themselves recruited simpler options. This not only provides evidence for option learning and reuse, but also points to the possibility that option transfer happens at multiple levels of hierarchy. In conclusion, while previous theoretical work showed that reusing options promotes fast exploration of new environments, our results provide evidence that humans do transfer learned options and benefit from it by learning faster.

Disclosures: L. Xia: None. **A.G. Collins:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.05/III41

Topic: H.02. Human Cognition and Behavior

Support: KAKENHI17H06022
KAKENHI17H05933

Title: Credit assignment in reinforcement learning is impaired in individuals with obsessive-compulsive and schizotypal traits

Authors: *S. SUZUKI[1], K. KATAHIRA[2], Y. YAMASHITA[3]
[1]Frontier Res. Inst. for Interdisciplinary Sci., Tohoku Univ., Sendai, Japan; [2]Dept. of Psychology, Grad. Sch. of Informatics, Nagoya Univ., Nagoya, Japan; [3]Dept. of Functional Brain Research, Natl. Inst. of Neurosci., Natl. Ctr. of Neurol. and Psychiatry, Kodaira, Japan

Abstract: Learning from experience is indispensable for appropriate decision-making. The reinforcement learning framework posits that a trial-and-error learning enables the agent to make optimal decisions if the correct “credit assignment” is attained: that is, choices that lead to

reward delivery were reinforced. In other words, the optimal learning requires the agent to associate an outcome with the choice that leads to its delivery. Yet, little is known about how the credit assignment is modulated by psychiatric symptoms such as schizotypal personality, obsessive compulsivity, depression and anxiety. To address this issue, we conducted a large-scale online experiment (N = 876) consisting of a reinforcement-learning task and questionnaires about psychiatric symptoms. In the online experiment, participants were first engaged in a conventional three-armed bandit task (i.e., reinforcement-learning task), and then asked to complete questionnaires about schizotypal personality, obsessive compulsivity, depression, state anxiety, trait anxiety, impulsivity and socioeconomic status. Applying a factor analysis to the questionnaire data, we found evidence for two dissociable dimensions underlying the psychiatric symptoms: the first one was associated with anxious and depressive traits, while the second one was associated with obsessive-compulsive and schizotypal traits. Furthermore, a generalized linear mixed model analysis revealed that the correct credit assignment in reinforcement learning task was impaired selectively in participants with high obsessive-compulsive/schizotypal traits, but not with high anxious/depressive traits. These results obtained from the large-scale online experiment highlight a new link between credit assignment in reinforcement learning and self-reported psychiatric symptoms, and may potentially contribute to deeper understanding of obsessive-compulsive disorder and schizophrenia.

Disclosures: S. Suzuki: None. **K. Katahira:** None. **Y. Yamashita:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.06/III42

Topic: H.02. Human Cognition and Behavior

Support: Grant-in-Aid for Young Scientists (B) 15K16403 from the Japan Society for the Promotion of Science (JSPS)
Grant from Kitasato University School of Allied Health Sciences (Grant-in-Aid for Research Project, No. 2016)

Title: Transcranial direct current stimulation over the prefrontal cortex alters performance in trial-and-error behavioral learning

Authors: T. KAWAGUCHI[1], A. MATSUNAGA[2], M. SUZUKI[3], S. SHIMIZU[4], K. SHIBATA[2], A. WATANABE[2], M. WATANABE[4], H. AKITA[5], M. FUKUDA[2], *H. ISHIBASHI[6]
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Hlth. Sciences, Kitasato Univ., Sagamihara, Japan; [5]Dept Physiol Sch. Allied Helth Sci, Kitasato Univ., Sagamihara, Japan; [6]Kitasato Univ, Sch. Allied Hlth. Sci., Sagamihara-City, Japan

Abstract: Introduction: The left prefrontal cortex is known to play a key role in trial-and-error learning process that selects between competing rewards and costs. This study investigated a shift in the performance of trial-and-error behavioral tasks by transcranial direct current stimulation (tDCS) of the left prefrontal cortex.
Methods: Before the behavioral tasks, 13 healthy right-handed subjects (7 male, 6 female, aged 25.6±7.0 years) were stimulated with tDCS (2 mA) for 20 min. The tDCS was conducted with anode or cathode electrode placed over F3 (International 10-20 system) and the other electrode placed over the right supraorbital area. In sham experiments, tDCS was turned off after 60 s.
In each of 30 behavioral trials, one of three colored circles showing 10%, 50% or 90% reward probability was randomly presented for 2 s as a cue, and the subject was required to decide as quickly as possible whether to perform first finger abduction in response to the circle's color. If the picture of a coin (100 Japanese yen) appeared as a reward stimulus after finger abduction, the subject received the actual coin after the experiment. However, if a mauve circle appeared as a cost stimulus after finger abduction, the coin was deducted from the total reward per occurrence. The total reward amount and number of correct behaviors and commission errors as the behavioral data were counted. The differences in behavioral data and the total reward after each tDCS were statistically analyzed by repeated measures ANOVA. This study was approved by our institution's ethical committee.
Results: The number of correct behaviors was significantly greatest in cathode tDCS, and that of commission errors was significantly lowest in cathode versus anode tDCS. The total reward of the subjects was also significantly highest in cathode tDCS.
Discussion: Cathode tDCS of the left prefrontal cortex induced an increase in sensitivity for reward/cost selection and a shift in the performance of correct behavior. These results imply that trial-and-error behavioral learning including the reward-related circuit might be altered by tDCS.

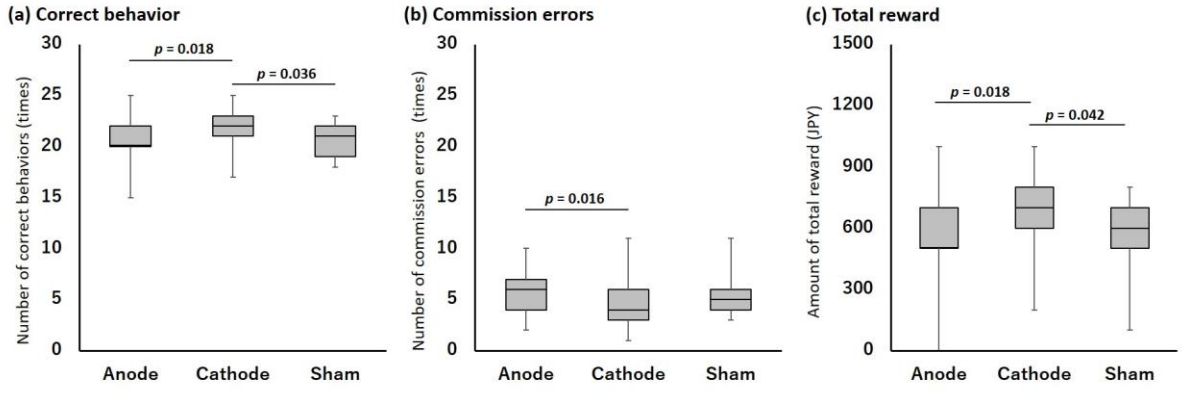

Figure. Behavioral data and amount of total reward
JPY: Japanese yen [100 JPY = 0.91 United States dollar (May 2, 2018)]

Disclosures: T. Kawaguchi: None. **A. Matsunaga:** None. **M. Suzuki:** None. **S. Shimizu:** None. **K. Shibata:** None. **A. Watanabe:** None. **M. Watanabe:** None. **H. Akita:** None. **M. Fukuda:** None. **H. Ishibashi:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.07/III43

Topic: H.02. Human Cognition and Behavior

Support: R01MH105535
The National Center for PTSD

Title: Cortical thickness and volume of the right posterior parietal cortex predict individual learning rate in healthy adults

Authors: *M. CHAWLA[1,2], P. HOMAN[5], C. GORDON[3], E. FELTHAM[2], I. HARPAZ-ROTEM[3], D. SCHILLER[6], I. LEVY[4]
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Abstract: Introduction: Gray-matter volume (GMV) of a region in the right posterior parietal cortex (rPPC) has been shown to predict individual risk attitudes over and above the effects of age, such that individuals with higher GMV in this region have higher risk tolerance in financial decision-making (Gilaie-Dotan *et al.*, 2014; Grubb *et al.*, 2016). We hypothesized that decreased GMV and cortical thickness in this region is associated with reduced computational capacity, which in turn gives rise to reduced risk tolerance. Here we tested whether structure of the same region also accounts for individual differences in another type of computational capacity - the ability to learn flexible associations between cues and outcomes.
Methods: A reversal-learning task (Schiller *et al.*, 2008) was administered to 61 healthy adults (mean age = 28.10 [18 - 46], 14 Females, 47 Males) while in the scanner. In this task, participants were presented with two stimuli. In the first part of the task, one stimulus (CS+) was sometimes co-terminated with a mild electric shock, while the other stimulus was never co-terminated with a shock. An unsignaled switch between the CS+ and the CS- occurred halfway through the task, without the participants' foreknowledge, and outcome contingencies were reversed. Skin conductance responses (SCR) were used to indicate learning of conditioned associations. Hierarchical Bayesian analysis was used to fit the SCR with a Rescorla Wagner model, and calculate the learning rate for each participant. The Freesurfer pipeline was used to extract neural structural measures of GMV and cortical thickness using a mask for the rPPC region-of-interest.

Results: Multiple regression models were calculated to predict learning rate based on either the rPPC cortical thickness or its GMV. Mean thickness/volume, movement parameters, age and gender were also included in the models. Cortical thickness of the rPPC significantly predicted the learning rate (B= -.025, p = .017). In a separate regression, GMV of the rPPC showed a trend towards significance (B = -.012, p = .077). Age was a significant predictor in both regressions (p < .001).
Conclusion: Our results suggest a general role for the structure of rPPC in shaping individual differences in learning and decision making under uncertainty, with both appetitive and aversive outcomes.

Disclosures: M. Chawla: None. **P. Homan:** None. **C. Gordon:** None. **E. Feltham:** None. **I. Harpaz-Rotem:** None. **D. Schiller:** None. **I. Levy:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.08/III44

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 AT007922-01

Title: A randomized controlled trial of neurofeedback-augmented meditation training

Authors: *R. VAN LUTTERVELD, A. ROY, P. PAL, J. BREWER
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Abstract: Introduction: Meditation has shown a number of beneficial effects, including lowering stress and improving attention. However, learning to meditate is not straightforward as there are no easily discernible outward signs of performance and thus direct feedback is currently not possible. Real-time neurofeedback based on brain activity patterns that are associated with effective meditation practice may provide a solution to this issue. Previous neuroimaging studies showed that brain activity in the posterior cingulate cortex (PCC) is related to the subjective experience of effortless awareness (which is a major component of meditation). In the present study, we tested the efficacy of EEG neurofeedback from the PCC during meditation practice as an add-on treatment to a Mindfulness-Based Stress Reduction (MBSR) course. We hypothesized that 1) The neurofeedback group would show a larger change in PCC activity during meditation vs a resting-state baseline from pre- to post-MBSR compared to an active control group as assessed using fMRI and 2) These changes in PCC activity from pre to post were associated with changes in selective attention and perceived stress.
Methods: Sixty-three novice meditators participated in this randomized controlled trial. All

participants participated in an MBSR course and in addition performed 5 EEG sessions during which participants meditated (breath awareness meditation). Participants were randomized to receive neurofeedback or no neurofeedback during the EEG sessions. At pre- and at post-intervention, participants performed 3 meditation runs that included a resting-state baseline in an fMRI scanner. Perceived stress was measured using the Perceived Stress Scale and sustained attention was measured using a Rapid Visual Information Processing task at the same time-points. fMRI data were analyzed using SnPM and MarsBar in a region-of-interest approach. Correlations between changes in PCC activity and changes in behavioral outcomes were assessed using Spearman's rank-order correlation.
Results: No significant interaction effect between groups and time was observed for PCC activity. Also, no main effect of time was observed. No significant associations were observed between changes in PCC activity from pre to post and changes in behavioral outcomes.
Discussion: These negative findings highlight a number of issues that arose during the study that apply to neurofeedback protocols in general, including type of feedback and dosage of neurofeedback.

Disclosures: R. Van Lutterveld: None. **A. Roy:** None. **P. Pal:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yale University has filed for patent protection of the application of providing neurofeedback from the PCC. Dr. Brewer owns stock in a company that has rights to license this patent. **J. Brewer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Yale University has filed for patent protection of the application of providing neurofeedback from the PCC. Dr. Brewer owns stock in a company that has rights to license this patent..

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.09/III45

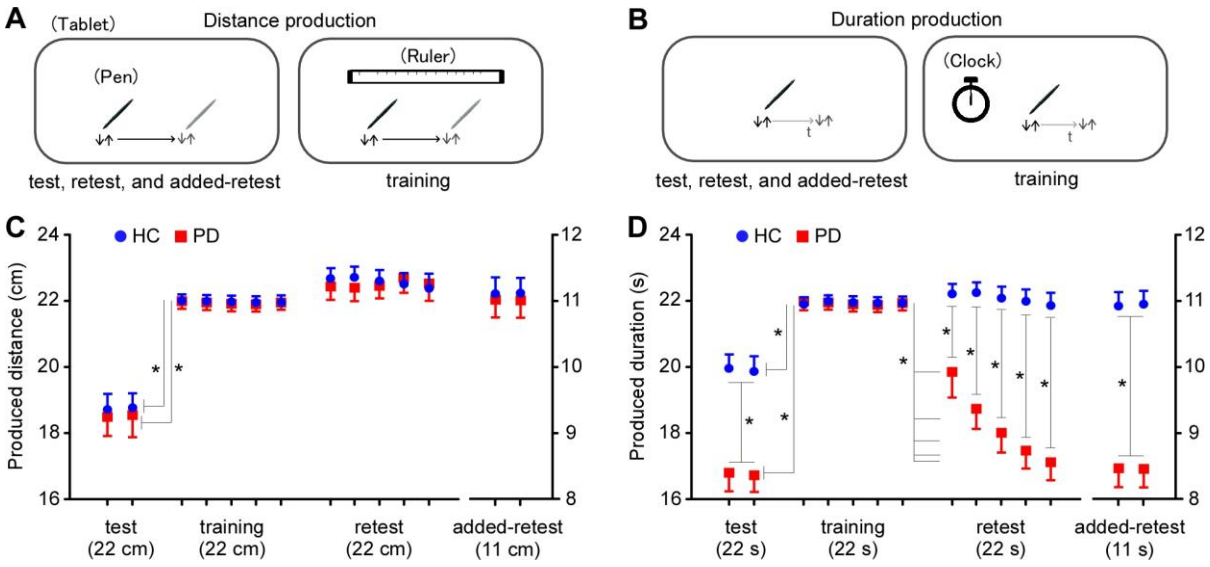
Topic: H.02. Human Cognition and Behavior

Support: KAKENHI 18K03185

Title: Impairment of cognitive alteration for duration production in Parkinson's disease

Authors: *M. HONMA[1], Y. MASAOKA[3], S. KOYAMA[5], T. KURODA[4], A. FUTAMURA[4], A. SHIROMARU[4], Y. TERAO[2], K. ONO[4], M. KAWAMURA[4]
[1]Kyorin Univ. Sch. of Med., Mitaka-Shi, Japan; [2]Kyorin Univ. Sch. of Med., Tokyo, Japan; [3]Dept. of Physiol., [4]Showa Univ. Sch. of Med., Tokyo, Japan; [5]Fac. of Art and Design, Univ. of Tsukuba, Tsukuba, Japan

Abstract: The ability to accurately recognize and produce mental durations is fundamentally important in everyday life, and a self-setting of durations without cue is affected by various factors. Parkinson's disease (PD) is associated with various cognitive impairments, however, a cognitive modification for production remains to be elucidated in patients with PD. Here, we examined whether patients with PD can correct and maintain a subjective duration/distance production. After training sessions in which participants repeatedly memorized a duration or distance, we compared a learning performance of duration with distance productions in 20 PD patients and 20 healthy controls. Results were further analyzed in relation to deficiency of presynaptic dopamine transporter (DaT) in the striatum. We observed that learned durations immediately returned to baseline values in pre-training within a few minutes, but that the patients were able to continue the learned distance production. In contrast, healthy controls were able to maintain the learned duration and distance productions. Time compression in PD's internal clock may become entrained to their altered duration production even after learning of accurate duration. We also observed that striatal DaT deficits positively correlated with duration underproduction in patients with PD. These deficits may be associated with severe time compression and entrainment, thus disturbing cognitive modification for duration production.



Disclosures: M. Honma: None. **Y. Masaoka:** None. **S. Koyama:** None. **T. Kuroda:** None. **A. Futamura:** None. **A. Shiromaru:** None. **Y. Terao:** None. **K. Ono:** None. **M. Kawamura:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.10/III46

Topic: H.02. Human Cognition and Behavior

Support: N.M.C. da Costa is supported by FCT grant number, PD/BD/114033/2015, in the scope of the MIT Portugal Program in Bioengineering Systems

Title: Development of a framework to improve neurofeedback self-regulation performance and provide new insights to the inefficacy problem

Authors: *N. M. C. DA COSTA[1,2,3,4], E. BICHO[1], N. S. DIAS[2,3,5]
[1]ALGORITMI Ctr., Sch. of Engineering, Univ. of Minho, Guimaraes, Portugal; [2]Life and Hlth. Sci. Res. Inst. (ICVS), Sch. of Medicine, Univ. of Minho, Braga, Portugal; [3]ICVS/3B's - PT Government Associate Lab., Braga/Guimarães, Portugal; [4]MIT Portugal Program in Bioengineering Systems, Lisboa, Portugal; [5]2Ai – Polytechnic Inst. of Cávado and Ave, Barcelos, Portugal

Abstract: Neurofeedback training (NFT) is a non-invasive technique for real-time self-regulation of brain activity, with benefits on human cognition, health, and task performance optimization. However, in current protocols, the benefits differ between subjects, leading to frustration of potential users, economic costs, and discredit in NFT and its professionals. Self-regulation is an important adaptation process to environmental and social challenges. In fact, self-regulation deficits are associated with diverse behavioral problems and mental disorders such as depression, rumination, distraction, anxiety, stress, and attention control. Therefore, understanding how to influence individual self-regulation learning ability through training methods could be the key to unlock predictors and optimize the success of NFT, and vice-versa.
In literature, it has been hypothesized that the "optimal" state of NFT learning is reached when irrelevant associations between internal states and external reward are avoided, and when the learner stays engaged, focused and undistracted. If these conditions hold, the learner should be skillful in gating incoming information provided by the NFT system and avoiding task-irrelevant thoughts. Also, current literature speculates that these states relate with up-regulation of sensory motor rhythm (SMR) and/or upper alpha rhythm (UA), and can be potentially provoked by relaxation/attentional stimulus tasks, like mindfulness meditation techniques.
In this way, during our intervention, healthy adult participants (18-65 years old) receive sequentially implicit (pre-)training of self-regulation (PRET) then NFT. PRET consists of one run per randomized stimulus task, to potential induce the "optimal" state (audio and/or visual relaxation/attentional stimulus tasks), in a within-subject ABA design (A condition: target condition - stimulus tasks; B condition: reverse target condition - active baseline), to facilitate the analysis of stimulus dependent oscillations. NFT of SMR or UA, follows a pre-post training design to investigate changes in the learning outcome (self-regulation performance) and behavioral outcome (mindfulness trait changes) possibly induced by PRET.
In conclusion, our framework is trying to uncover some of the aspects of the "optimal" mental state to self-regulate brain activity with neurofeedback. Namely, how can we stimulate subjects to get in this personalized "optimal" state? Also, if the stimulated "optimal" state affects Neurofeedback self-regulation performance?

Disclosures: N.M.C. Da Costa: None. **E. Bicho:** None. **N.S. Dias:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.11/III47

Topic: H.02. Human Cognition and Behavior

Support: SFB TRR 169 "Crossmodal Learning: Adaptivity, Prediction and Interaction"

Title: Elucidating cross-modal integration in the superior temporal sulcus via representational similarity analysis

Authors: *C. W. KORN[1], J. P. GLAESCHER[2]
[1]Inst. for Systems Neurosci., [2]Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: The superior temporal sulcus (STS) has been shown to integrate information across stimuli from different sensory modalities such as vision and audition. However, it is unclear to which extent neural representations in the STS relate to representations in unisensory brain areas such as visual and auditory cortices. Here, we harnessed representational similarity analysis (RSA) to address this question. Our study also addressed how reward learning may influence crossmodal representations in the STS. Our fMRI task employed a block design in which human participants (n=43) were repeatedly presented with semantically congruent pictures and sounds (e.g., a picture of a guitar and a 400 ms sound of guitar strings). Visual and auditory stimuli were presented simultaneously or in isolation. In the middle of the experiment, participants learned in a separate fMRI session that for some stimulus combinations either the visual or the auditory stimulus were rewarded. Reward learning behavior was analyzed using hierarchical Bayesian modelling. To define functional regions of interest, we administered a localizer task with an independent set of stimuli. Crossmodal integration in the STS was evident in the pattern of representational similarities between the unimodal and crossmodal stimuli. Crucially, multivariate analyses showed that activations in unisensory brain areas predicted activations in the STS. Reward learning behavior could be well described by a simple variant of reinforcement learning and reward information altered the representation of auditory stimuli in the STS. Taken together, our results provide a refined framework for interpreting the role of the STS in crossmodal integration.

Disclosures: C.W. Korn: None. **J.P. Glaescher:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.12/III48

Topic: H.02. Human Cognition and Behavior

Support: Queen Elizabeth II Graduate Scholarship - Full

Title: The signal for good news and value of information in human choice behavior

Authors: *J. SAWALHA[1], M. L. SPETCH[2], C. S. CHAPMAN[3]
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Abstract: Surprisingly, pigeons have been shown to sacrifice food rewards to get information about the upcoming outcome when making choices in a delay decision task. For instance, when choosing between an option which offers a reward 100% of the time after a delay (e.g. 10 s), versus an option that gives rewards only 50% of the time after the same delay but gives information about the reward (pecking it leads to a color that signals reward / no reward), pigeons sometimes prefer the 50% option. However, when the information is not immediate (e.g. it takes a few seconds after the peck for the color change to occur) pigeons almost exclusively choose the 100% option. Here, we tested if this same preference for immediate information would be evident in human choice behavior. In four experiments we adapted the pigeon task to a human reaching choice task to test two questions: 1) Do humans prefer information over no information, especially when it is received immediately? 2) Do humans show an asymmetry for information biased by valence, preferring good news and avoiding bad news? In Experiments 1 (n = 30) and 2 (n = 30) participants reached to choose between shapes on a touchscreen that either revealed the outcome (turned green for good or red for bad) or not (stayed the same color) and did so either immediately or after a delay (2s). Unlike pigeons, the results show that humans do not have a preference for information (immediate or delayed), instead choosing almost exclusively based on the probability of payoff. In Experiments 3 (n =20) and 4 (n=25), participants again reached to choose between shapes, a “good news” shape that sometimes changed color when the outcome was good, a “bad news” shape that sometimes changed color when the outcome was bad, and a neutral shape which never changed color. Here we see a significant preference to choose “good news” shapes and avoid “bad news” shapes. These results support the Signal for Good News (SiGN) hypothesis which argues that receiving a signal of good news in a 50/50 gamble task is more rewarding because it causes a large positive reward prediction error. However, our results also show that, unlike pigeons, humans avoid bad news, suggesting loss aversion may spill into the information domain.

Disclosures: M.L. Spetch: None. **C.S. Chapman:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.13/III49

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant MH63901

Title: Learning to learn: Lateral frontal and cingulo-opercular cortex support the learning and transfer of hierarchical task structure

Authors: *A. EICHENBAUM, J. SCIMECA, M. D'ESPOSITO
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Abstract: Lateral frontal cortex supports the learning and execution of hierarchical rules, and increasingly abstract hierarchical rules recruit increasingly rostral areas of frontal cortex. Rule learning can be bolstered by applying knowledge of previously learned rules to novel environments that share a common hierarchical structure. Here we used fMRI to characterize the contributions of frontal cortex to the transfer of abstract hierarchical rule structure. Human subjects (N = 19, 13 females, mean age = 19.3 years) performed 5 blocks of a reinforcement-learning task in which a hierarchical rule structure could be learned from deterministic binary feedback. The first block contained no hierarchical structure ("Flat") and required learning to occur independently for each stimulus. All subsequent blocks ("Hier") contained structure that allowed more efficient learning to occur. Stimuli were composed of features from several dimensions (shapes, colors, and textures). Each block used novel features for each dimension, however the Hier blocks all shared a 2^{nd}-order hierarchical rule structure: shapes cued 1^{st}-order rules based on either color or texture.
Subjects learned stimulus-response pairings more efficiently and to a greater extent in the Hier blocks compared to the Flat block, an index of hierarchical learning. Moreover, we observed markedly greater learning efficiency in the final two Hier blocks compared to the first two, providing evidence that subjects discovered and generalized the global hierarchical rule structure. In the brain, we observed elevated activity in lateral frontal cortex (left dorsal premotor cortex (PMd), left anterior dorsal premotor cortex (prePMd), left mid inferior frontal sulcus (Mid-IFS)) across all blocks. Activity in these regions peaked in the 2^{nd} Hier block, when participants could first search for and discover the global hierarchical structure. Of these lateral frontal regions, only PMd activity in the final two Hier blocks predicted behavioral transfer (behavioral improvement from the 1^{st} to 4^{th} Hier block). To identify other regions that correlated with behavioral transfer, we performed a whole-brain analysis, revealing regions in bilateral anterior insula (AI) and anterior cingulate cortex (ACC). These regions constitute the core nodes

of a “cingulo-opercular network” (CON), and activity across the CON (bilateral AI, anterior prefrontal cortex, thalamus, and ACC) strongly correlated with behavioral transfer. These results extend existing models of hierarchical gradients in the frontal cortex and provide novel evidence that regions in the CON support generalization of structured knowledge.

Disclosures: A. Eichenbaum: None. **J. Scimeca:** None. **M. D'Esposito:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.14/III50

Topic: H.02. Human Cognition and Behavior

Title: Hippocampal GABA differences based on video game genre preferences

Authors: *K. PRENA, H. CHENG, S. D. NEWMAN
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Abstract: We have previously demonstrated that time spent gaming weekly is positively related to declarative memory performance. One possible explanation for this is that video games trigger the reward cascade, which increases dopamine and decreases gamma aminobutyric acid (GABA) in the hippocampus (both of which improve declarative memory formation). Recent video game research has demonstrated that changes to game structure can cause differences in cognitive performance. Our previous work showed that differences in game reward conditions caused variations in declarative memory performance. In this preliminary study differences in game genre preferences was related to hippocampal GABA. GABA was measured from 19 males between the ages of 18 and 25 (20.58, *SD* = 1.92) using magnetic resonance spectroscopy. Participants were asked to list their favorite games, how frequently they have played that game in the recent month, and the categories that best describe each game (education, sports, fighting, action, puzzle, skill, racing, exergame). Each genre was dummy coded to identify two groups of participants for each category: those who recently played those categories and those who did not. Participants started playing video games at the age of 8.95 (*SD* = 2.99). There was a significant difference in GABA between those who play fantasy games (*n* = 6, *M*=111.33, *SD*=37.82) and those who do not (*n* = 13, *M* = 162.54, *SD*=38.69); *t*(17) = 1.90, *p* = .015. There was a no significant difference in GABA between those who play action games (*n* = 6, *M*=119.67, *SD*=37.31) and those who do not (*n* = 13, *M* = 158.69, *SD* = 43.46); *t*(17) = 1.90, *p* = .075, between those who play skill games (*n* = 7, *M*=159.67, *SD*=48.54) and those who do not (*n* = 12, *M* = 123.57, *SD* = 26.46); *t*(17) = 1.80, *p* = .089, and between those who play fighting games (*n* = 7, *M* = 123.43, *SD* = 36.94) and those who do not (*n* = 12, *M* = 159.75, *SD* = 44.57); *t*(17) = 1.82, *p* = .087. These results indicate the importance of understanding video game reward

structure to explain differences in hippocampal behavior, and suggest that fantasy games may lead to differences in GABA.

Disclosures: K. Prena: None. **H. Cheng:** None. **S.D. Newman:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.15/III51

Topic: H.02. Human Cognition and Behavior

Title: Computations of volatility in complex, uncertain environments

Authors: *M. RAKHSHAN[1], B. Y. HAYDEN[2], A. IZQUIERDO[3], A. SOLTANI[1]
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Abstract: The world is both uncertain and variable. When an unpredicted outcome occurs, a decision-maker must be able to distinguish randomness that reflects the stochastic nature of events from randomness that reflects changes in the underlying outcome probabilities. For learning to be successful, the decision-maker must distinguish variability (or *expected uncertainty*), which should not lead to behavioral adjustments, from *volatility* (or unexpected uncertainty). Although expected uncertainty can be specific to a stimulus or an action, it is unclear how expected uncertainty of an individual option interacts with environmental volatility, or how rapidly reward contingencies change. Here, we developed a novel concurrent probabilistic reversal learning task to study how volatility and its influence on learning may depend on the relationship between actions in more complex environments. Human subjects learned about the associations between three stimuli (two main stimuli, S_1 or S_2, and one modulating stimulus, S_m, each with different levels of volatility) and two sets of actions. Stimuli S_1 and S_2 were associated with two different sets of actions (left /right and up/down) that were rewarded with complementary probabilities and these probabilities reversed every L_1 and L_2 trials ($L_1 << L_2$), respectively. Reward probabilities for actions associated with stimulus S_m reversed every L_m trials. Using this task, we examined how the influence of S_m volatility depends on whether its actions match those of either S_1 or S_2, or by similarity of L_m to L_1 or L_2. First, we found that for the volatile stimulus (S_1), learning was slower when its actions matched those of the stable S_m ($L_m \sim L_2$). In contrast, learning of the stable stimulus (S_2) was enhanced when its actions matched those of the stable S_m. Overall performance was attenuated for stimuli with actions matching those of S_m, perhaps due to interference. Second, subjects showed a stronger difference between WinStay and LoseSwitch strategies, as a measure of differential response to reward vs. nonreward, for the volatile compared to stable stimulus. At the same time, matching

S_m enhanced this differential response for the volatile stimulus but decreased it for the stable stimulus. Third, the difference between WinStay and LoseStay strategies, as a measure of overall response to reward, was weaker for the volatile relative to stable stimulus. This measure was reduced most by the stable than volatile matching S_m. Overall, these results reveal multiple forms of interactions between volatility associated with individual stimuli/actions and how these interactions influence learning in complex environments.

Disclosures: M. Rakhshan: None. **B.Y. Hayden:** None. **A. Izquierdo:** None. **A. Soltani:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.16/III52

Topic: H.02. Human Cognition and Behavior

Support: Army Research Office W911NF-14- 1-0101

Title: Separable attention processes constrain multidimensional reinforcement learning

Authors: *A. RADULESCU[1], Y. NIV[2]
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Abstract: Two prominent theories suggest different targets for selective attention in reward learning: Mackintosh (1975) suggests that attention should be directed towards stimulus features that are most predictive of reward; Pearce and Hall (1980) suggest instead that attention should be directed to features that we are most uncertain about. Both theories have received empirical support, leading Dayan et al. (2000) to suggest that both should exist concurrently - when making choices, one should attend to the most predictive features, whereas when learning from prediction errors one should attend to (and learn about) the most uncertain features.
Here we combine eye tracking with a multidimensional reinforcement learning task in order to simultaneously measure the dynamics of attention for valuation and attention for learning and test for this dual-attention theory. In each trial of the 'Dimensions Task' (Leong et al. 2017), human participants chose between 3 multidimensional stimuli that differed along 3 spatially distinct dimensions: faces, houses and tools. In each block of trials there was one relevant dimension. Within that dimension, the stimulus containing a "target" feature yielded 1 point 75% of the time. The two other stimuli yielded 1 point only 25% of the time. To maximize reward, participants had to learn which dimension determines reward and, within this dimension, what is the target feature. To measure participants' focus of attention, we continuously monitored eye movements during the choice and learning phases of each trial.

We found that while attention for valuation and attention for learning became similar over the course of a block, they reflected separate computations. Trial-by-trial computational modeling in combination with an empirically derived index of attention, showed that this dissociation is behaviorally relevant: the best predictor of choices was a reinforcement learning model that used attention measured during the choice and learning phases of the task to separately bias valuation and learning. Our results establish that attention for choice and attention for learning are separable cognitive processes, and provide a framework for building computational models that predict how their dynamics shift as a function of learning.

Disclosures: A. Radulescu: None. **Y. Niv:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.02. Human Cognition and Behavior

Support: NIH/NICHD Grant P2CHD0886844
Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation Medical Research Grant

Title: Establishing targets for fMRI neurofeedback in sensorimotor cortex

Authors: *E. OBLAK[1], J. S. SULZER[1], J. A. LEWIS-PEACOCK[2]
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Abstract: Neural activity patterns associated with individual finger movements can be decoded from fMRI data. Here we demonstrate the feasibility of using real-time fMRI neurofeedback to modify patterns of activity related to finger individuation, with implications for sensorimotor rehabilitation. First we investigate whether we can reliably decode patterns associated with individual finger movements, in real-time, from short (6 sec) time windows. We designed an fMRI experiment to localize the brain activity patterns elicited by pressing each of the four fingers of the right hand. This experiment had the same timings and stimuli as a subsequent neurofeedback experiment in which an initial baseline period was followed by blocks of finger pressing with intermittent feedback provided every 16 sec. Subjects participated in two finger localizer sessions, identical except for the order of finger presses. Decodability of finger presses within each session was excellent within primary somatosensory (S1, 90%) and motor (M1, 75%) cortices compared to chance (25%). When real-time processing limitations were imposed on within-session decoding, the decodability suffered (S1: 80%; M1: 65%), and further worsened between sessions (S1: 75%; M1: 60%), yet was still reliably above chance. Next, we investigated whether these brain patterns could be identified in real-time and recognized by human

participants using explicit search strategies (in this case, finger presses). We designed a neurofeedback experiment where participants had to determine which of the four fingers was being presented by the visual feedback of the real-time decoder output. After each trial of finger presses, if the decoder output for a target finger exceeded a threshold (50% probability), the target was considered found, and a new random finger target was selected. If the decoder output was perfectly accurate, it should take on average 2.5 trials for participants to discover the target. In a simulated experiment (10,000 targets), we found it took a simulated participant 3.5 trials to discover targets from S1, and 4.3 trials to discover targets from M1. Because success was based on decoder output and not the pressed finger, we also checked how often success corresponded to pressing the correct finger (S1: 82%; M1: 55%). Overall, our results show that decodability of individual finger presses is impaired by ~15% due to real-time limitations. While neurofeedback targets can be found using activity spread across sensorimotor cortex, targets are found quicker and more accurately within S1 than M1. This work provides a framework to investigate the limitations associated with ROI selection and real-time neurofeedback.

Disclosures: E. Oblak: None. **J.S. Sulzer:** None. **J.A. Lewis-Peacock:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.02. Human Cognition and Behavior

Support: ESRC Grant ES/J500112/1

Title: Confidence modulates feedback processing during human probabilistic learning

Authors: *M. BEN YEHUDA, R. A. MURPHY, N. YEUNG
Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Background & Aims: Learning stimulus-response contingencies with noisy feedback comes with an inherent degree of uncertainty. The aim of this project was to investigate how people's subjective sense of confidence about their knowledge affects how they learn and process incoming feedback, as
well as how confidence guides decisions about further information seeking.
Method: Three experiments (n = 25 in each) used a combination of behavioral and scalp electrophysiological (EEG) measures. Participants were required to learn associations between two stimuli and two responses.
Following probabilistic feedback (75% reliable), participants rated their confidence in having responded correctly. This allowed us to track changes in confidence during learning, and to relate

these to changes in feedback processing as indexed by EEG event-related potentials (ERP) in Experiment 2 and by participants' choices to pay for vs. decline feedback in Experiment 3.
Results: Participants' response accuracy followed a traditional learning curve that reached asymptote relatively quickly, but their explicitly reported confidence lagged accuracy and continued increasing, reaching asymptote significantly later than accuracy did ($p < .001$ for all experiments). Analysis of the period following accuracy asymptote indicated that, while their behavioural policy remained stable, the extent to which surprising negative feedback impacted confidence decreased as subjects progressed through a learning block, despite the increasing reward prediction errors (RPE) as learning continued ($p < .05$ in Experiment 1 and $p < .01$ in Experiment 2).
This behavioural effect was mirrored in ERPs time-locked to feedback delivery on trials following the accuracy asymptote. Specifically, confidence at trial t-1 negatively predicted the size of the P3 at trial t ($\beta = -0.09$; $p < .001$), indicating decreased processing of feedback as confidence increased. Consistent with this account, confidence also significantly predicted the trial in which people stopped paying for feedback in Experiment 3 ($\beta = 0.52$; $p = .01$), whereas accuracy did not ($\beta = 0.02$; $p = .93$).
Conclusions: The results suggest that subjective confidence adjusts how feedback is processed and incorporated in one's model of stimulus-response contingencies, regulating the weighting of the impact of RPE: higher confidence leads to a higher RPE upon receiving negative feedback, but decreased feedback processing. Consistent with this confidence-modulated change in feedback processing, participants' confidence ratings also predicted when they would stop paying for further feedback.

Disclosures: M. Ben Yehuda: None. **R.A. Murphy:** None. **N. Yeung:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.19/III55

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH9743
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Title: Mesolimbic connectivity during neurofeedback training predicts learning to volitionally activate the ventral tegmental area

Authors: J. N. THORP[1], *S. HAKIMI[1], K. C. DICKERSON[1], J. J. MACINNES[2], R. A. ADCOCK[1]

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Abstract: Activation of the ventral tegmental area (VTA) and mesolimbic networks is essential to motivation and learning, however current interventions to target these regions can come with unmanageable financial and physical costs. Neurofeedback has been shown to be an effective, non-invasive therapy in a variety of contexts, however the ability to learn from and properly use neurofeedback is highly variable across subjects. In a recent study, MacInnes & Dickerson et al. (2016) showed that participants could learn to volitionally sustain their VTA activation through fMRI neurofeedback training, and that this feedback was accompanied by increased functional connectivity between the VTA and other mesolimbic areas, namely the hippocampus (HPC). However, the mechanism through which this training impacts learning is not yet known. Here, we test a mechanistic model of how mesolimbic functional connectivity drives learning from neurofeedback to self-activate the VTA. The activation task itself was divided into 5 runs: a pre-test without neurofeedback, three training runs with neurofeedback, and a post-test without neurofeedback. Connectivity was calculated for each run from the VTA to the HPC, due to the HPC's overall role in learning as well as mental imagery - a common strategy for VTA activation. A repeated measures ANOVA was then run with connectivity during each of the three runs as within-subject measures, sex as a between-subjects factor, and overall change in VTA activation from pre-test to post-test as well as age as covariates. Results show a trend-level relationship between connectivity and VTA change ($F = 3.272$, $p = 0.052$), in which higher VTA-HPC functional connectivity over the course of the training period predicts greater VTA activation change from pre-test to post-test, an initial demonstration that prompts further interrogation; there was no effect of age or sex. This approach provides new insight into the mechanisms of learning from neurofeedback, and therefore can inform the propagation of volitional brain activation for basic science and development of new interventions.

Disclosures: J.N. Thorp: None. **S. Hakimi:** None. **K.C. Dickerson:** None. **J.J. MacInnes:** None. **R.A. Adcock:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.20/III56

Topic: H.02. Human Cognition and Behavior

Support: National Institutes of Health P20 GM113109-01A1

Title: Reinforcer inflation in humans using inter-trial interval alterations as reinforcers

Authors: *C. LONG, C. L. PICKENS
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Abstract: Reinforcer revaluation experiments are multi-stage experiments in which a subject learns that a cue predicts, or a response earns some outcome in the first phase. In a subsequent phase, the value of the outcome is altered and the subject needs to spontaneously adjust their behavior. These experiments are common in non-human animals, but less common in humans. One possible reason why revaluation experiments are rare in humans is that these experiments tend to use consumable items (ex: foods) or physically aversive stimuli (ex: shocks) as the outcomes, and it is more difficult to use these outcomes with human participants. The purpose of this study was to examine whether reinforcer inflation, in which the value of an outcome is increased, can be performed in humans using a more innocuous outcome. For this, we used changes in the inter-trial interval (ITI) in a discrimination task as our outcome, as humans are often very eager to complete an experiment as quickly as possible. Undergraduate students were given cue exposure phases alternating with response phases. In the cue exposure phases, the participants were exposed to colored squares (red, green, yellow, blue) associated with delays that were longer (13-second) or shorter (0.5-second) than the standard delay of 4 seconds (associated with a black square stimulus). In the response phases, the participants were presented with different shapes (clubs, hearts, spades, diamonds). Responses during the shape presentations would earn a colored square (ex: responses during the club earned the red square and a 0.5-second ITI, responses during the heart earned the green square and a 13-second ITI). Withholding responses during the shapes always earned the black square and a 4-second ITI. In the final cue exposure phase, the value of one of the colored squares that previously predicted a long delay was increased/inflated by now having it predict a shorter delay (ex: the green square went from predicting a 13-second delay to predicting a 0.5-second delay). In the subsequent response phase (which functioned as an extinction test, as responses always led to the black square and 4-second delay), responses to the shape that predicted the inflated colored square stimulus increased compared to responses to another shape that continued to predict a colored square associated with a 13-second delay. This suggests that ITI changes can act as reinforcers to support responding, and that these reinforcers are sensitive to inflation.

Disclosures: C. Long: None. **C.L. Pickens:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.21/III57

Topic: H.02. Human Cognition and Behavior

Title: The effects of tyrosine supplementation on classical conditioning

Authors: T. N. OCHOA[1], A. BICCUM[1], *E. BARKLEY-LEVENSON[2]
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Abstract: The role of dopamine in classical conditioning has not been extensively studied. Prior studies demonstrate the amino acid tyrosine to be an effective method of increasing cerebral dopamine levels. This study studied the effects of dopamine, through the supplementation of tyrosine, on associative learning task performance in 37 (females = 22) healthy, human participants. Participants were randomly assigned to either the tyrosine supplemented group (n=19) or to a placebo group (n=18) who received a microcrystalline cellulose powder. A complex, real world scene containing four embedded items was presented to participants both prior to and after supplementation to measure its effects on learning. One item embedded in the scene served as the conditioned stimulus (CS). One version of that item (e.g. a black spoon) was paired with a loud, aversive tone (CS+) while a second version of the item (e.g. a brown spoon) was not paired the aversive stimulus (CS-). The remaining items were never paired with the stimulus and served as distractor variables. Participants rated their expectation of hearing the loud tone during each trial; these expectancy ratings were used to determine when each participant became aware of the contingency. A pre-test was conducted to determine baseline learning scores while the post-test was conducted to determine if tyrosine supplementation enhanced learning as demonstrated through: (1) fewer trials to learn the contingency, (2) decreased reaction time, (3) increased total number of correct predictions. The experimental group displayed a significant increase in total number of correct responses, relative to the control group ($F(35)=8.43$, $p=0.006$). The experimental group also displayed a significant decrease in average reaction time, relative to the control group in the post-test ($F(35)=5.17$, $p=0.029$). No sex differences were found ($F(35)=3.294$, $p=0.078$). These results demonstrate a significant main effect of tyrosine supplementation on associative learning task performance. Furthermore, the results help establish dopamine as a neurochemical component involved in associative learning.

Disclosures: T.N. Ochoa: None. **A. Biccum:** None. **E. Barkley-Levenson:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.22/III58

Topic: H.02. Human Cognition and Behavior

Title: Working memory contributions to probabilistic reinforcement learning

Authors: *W. RYAN[1], A. G. E. COLLINS[2]
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Abstract: Two major brain networks contribute to learning: a cortico-striatal network thought to implement instrumental, value-based reinforcement learning (RL), and a prefrontal cortex centered executive function network thought to be crucial for flexible, goal-directed learning, an important part of which is working memory (WM). WM is commonly believed to be critical for learning in deterministic settings, where feedback is always accurate and fast learning is key, such that holding a past trial's information in WM for future decision is useful. By contrast, RL is crucial in stochastic settings, where feedback is noisy and learning requires new and conflicting information to be integrated over time.
However, WM could also be used in stochastic environments; either holding in memory past trials, thus implementing win-stay lose-shift strategies, or maintaining internally generated hypotheses about the best choices for each stimuli. In this work we aim to show evidence that WM also contributes to learning in stochastic environments. Furthermore, we investigate the nature of the information held in WM in such cases. We hypothesize that participants may maintain both types of information, and that the balance may change as learning progresses.
We used a probabilistic reinforcement learning task. In multiple independent learning blocks, participants used binary probabilistic feedback to learn which of three actions was most likely to lead to reward for each stimulus. There were two key manipulations. First, the number of stimuli being learned during each block (set size) was either low (3) or high (6), changing the cognitive load on WM (Collins & Frank 2012). Second, the feedback reliability also independently varied across blocks from low (65%) to high (92%). We predicted that participants would learn slower in high than low set sizes, reflecting WM limitations. Furthermore, we expected that WM would be used less when feedback was less reliable and RL more useful.
Results with 40 laboratory participants confirmed our predictions, and were replicated with 55 Amazon Mechanical Turk participants. Logistic regression analyses showed that participants learned more slowly in high vs. low set size blocks, and that this effect of set size on learning was weaker in low vs. high reliability blocks, indicating a trade-off between WM and RL contributions. We will use computational modeling to identify the nature of the information held in WM in stochastic environments. Our results highlight the fact that human learning is always a mixture of multiple processes, and further our understanding of working memory contributions to reinforcement learning.

Disclosures: W. Ryan: None. **A.G.E. Collins:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.23/III59

Topic: H.02. Human Cognition and Behavior

Support: DFG, EXC 1086

Title: Out-of-the-box decoding of error-related brain signals with deep learning

Authors: *J. BEHNCKE[1], R. SCHIRRMEISTER[1], W. BURGARD[2], T. BALL[1]
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Abstract: Assistive devices controlled by human brain signals exhibit a high potential to enhance processes in everyday life or even to endow severely impaired persons with more autonomy. Though, cooperative brain-controlled systems require a proper error management, depending on a highly accurate decoding framework. Deep learning (LeCun et al. 2015) has not only boosted performances in classical fields like computer vision, but recently has also been applied to problems in neurological contexts. Thus, deep learning methods could perfectly serve to decode error-related brain signals. Still, performances have substantial space for improvement and techniques have to be adjusted to specific needs.Here, we present findings from error-related analyses of invasive and non-invasive recordings obtained by several experimental paradigms. For discrimination of erroneous and correct realization of a task, conventional methods like regularized Linear Discriminant Analysis (rLDA) or Filter Bank Common Spatial Patterns (FB-CSP) combined with rLDA were compared to a deep learning implementation (Schirrmeister et al. 2017) based on Deep Convolutional Neural Networks (deep ConvNets), both, when observing or performing the task. Beyond, transfer learning techniques were utilized to generalize across paradigms and to overcome typical problems when only few data are available.We can show a significant improvement of decoding when the classifier relied on deep ConvNets instead of using rLDA or FB-CSP+rLDA. Utilizing data of the same participant but gained in different paradigms, a transferability of learned patterns in error-related brain signals could be proved, emphasizing the beneficing of transfer learning techniques in this context. Especially when only little data is available, the pretraining on a different data set significantly improves the decoding performance, according to examples in conventional computer science classification problems. Astonishingly, the deep ConvNet implementation was always used “out of the box”. That suggests a simple utilization in numerous contexts but also indicates space for improvement by fine-tuning the network.
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Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.24/III60

Topic: H.02. Human Cognition and Behavior

Title: Improving face recognition in older adults with real-time magnetoencephalography (MEG) neurofeedback

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Abstract: Introduction
The causes for the age-related decline in visual recognition have not been fully explored. Although vision impairments associated with aging are an important factor, age-related alteration in cognitive processing also appears to be a factor. Prior studies have shown that cognitive processing improves with age, peaking during early adulthood and declining thereafter as a result of age-related cognitive slowing. As cognitive processing declines, so too does visual object category response selectivity. The fusiform face area (FFA) is selective for faces and is involved in higher-order visual processing, but it is not clear whether FFA activation improves face recognition. We hypothesized that alteration of FFA activity through neurofeedback training may improve face recognition.
Method
We developed a neurofeedback training system using real-time magnetoencephalography (MEG). FFA cortical activity was estimated online from MEG signals, based on which a decoder was trained to classify images of faces and houses. The performance of 15 healthy older adults (aged 56–76) in recognizing these images was measured by a part-to-whole matching test before and after a 10-minute training to control decoder output.
Results
Accuracy in the part-to-whole matching test significantly improved after neurofeedback training ($p = 0.0000356$, Student's t-test, uncorrected), and FFA activity also increased. We found that increased FFA activation correlated with greater test accuracy.

Conclusion
Neurofeedback training successfully improved face recognition ability based on FFA activation. We suggest that degeneration of FFA activity results in elderly subjects' decreased ability to recognize faces.

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Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

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Program #/Poster #: 334.25/III61

Topic: H.02. Human Cognition and Behavior

Support: NSF Faculty Early Career Development Award 1654393
NSF GRFP

Title: Adolescent-specific attenuation of Pavlovian biases on motivated behaviors

Authors: *H. A. RAAB, S. HIRALALL, C. A. HARTLEY
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Abstract: Over the course of development, a repertoire of behaviors is critical to support adaptive function in diverse environments. This behavioral repertoire can be acquired through distinct learning systems. Pavlovian learning yields reflexive approach behaviors to cues predicting reward and behavioral inhibition in the face of anticipated punishment, whereas instrumental learning fosters goal-directed actions that bring about beneficial outcomes. In the present study, we investigated the extent to which these learning systems cooperate or compete in children, adolescents, and adults aged 8-25 (n = 61). To examine the degree to which reflexive Pavlovian responses bias instrumental learning, we used a Go/No Go task that orthogonalizes valence and action. There are four resulting trial types: Go to Win, No Go to Win, Go to Avoid Losing, and No Go to Avoid Losing. Critically, for Go to Win and No Go to Avoid Losing the

Pavlovian expectancies are aligned with the instrumental contingencies, whereas for No Go to Win and Go to Avoid Losing Pavlovian and instrumental responses are in conflict. Children and adults performed more accurately on the trials for which Pavlovian expectancies and instrumental contingencies are aligned as compared to in conflict, indicating a robust Pavlovian bias on instrumental learning. However, this valence-by-action interaction was not evident in adolescents, whose performance was comparable across trial types. Computational models of participants' behavior further corroborated the attenuation of Pavlovian biases on instrumental learning, specifically during adolescence. This developmental shift in Pavlovian and instrumental contributions to motivated behaviors may foster a more flexible behavioral repertoire during the transition from adolescence into adulthood. Across development the neural circuitry implicated in motivated behavior undergoes significant structural and functional changes. In future studies, we aim to examine how these age-related changes in the brain may underlie this nonlinear behavioral trajectory.

Disclosures: H.A. Raab: None. **S. Hiralall:** None. **C.A. Hartley:** None.

Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.26/III62

Topic: H.02. Human Cognition and Behavior

Support: BLG was supported by UK's Biotechnology and Biological Sciences Research Council (grant BB/M009742/1)

Title: Brain network dynamics of arbitrary visuomotor learning

Authors: *A. BROVELLI[1], R. BASANISI[1], B. L. GIORDANO[1], S. PANZERI[2]
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Abstract: Acquisition and consolidation of instrumental behaviors are known to engage two distinct decision-making processes. Acquisition relies on flexible goal-directed actions selected according to expected outcomes as well as current goals and motivational state. Consolidation is characterised by the gradual formation of stimulus-driven habitual responses. At the neural level, goal-directed actions are thought to be primarily controlled by the associative fronto-striatal circuit, whereas selection of action during gradual automaticity and consolidation recruits the sensorimotor fronto-striatal territories. Although the functional specificity of different fronto-striatal areas is relatively well understood, little is known about the dynamics of interaction between brain regions, or functional connectivity dynamics, during learning.To address this

issue, we measured brain activity using magnetoencephalography (MEG) while participants learned deterministic relations between stimuli, actions and outcomes by trial-and-error (arbitrary visuomotor learning). Single-trial high-gamma activity (HGA) from 60-120Hz aligned on motor response was estimated at the single-trial level within 96 anatomically-identified brain regions of the MarsAtlas parcellation scheme. To characterise the dynamics of learning-related modulations at the area-level, we computed the mutual information between HGA and learning phases. To quantify whether directional influences between areas encoded learning phases, we used a novel information theoretical metric that is able to track, in a time-resolved manner, the amount and content of information flow between neural signals. Statistical significance was assessed by means of cluster-based permutations tests. Regions in the ventromedial prefrontal and orbitofrontal cortex were found to encode learning phases prior to action selection. Anatomically, these regions are part of the limbic and associative fronto-striatal circuits, and may thus reflect goal-directed processes. In addition, the dorsolateral premotor and motor regions in sensorimotor territories were found to encode learning after action execution. Preliminary results on directional influences between these brain areas will be presented.

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Poster

334. Human Cognition and Behavior: Human Learning: Feedback, Reinforcement, and Reward

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 334.27/III63

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01DC015426

Title: Targeted non-invasive stimulation of human orbitofrontal networks disrupts outcome-guided behavior

Authors: *J. D. HOWARD[1,2], R. REYNOLDS[2], D. SMITH[2], J. L. VOSS[2,3,4], G. SCHOENBAUM[6], T. KAHNT[2,3,5]
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Abstract: In order to make adaptive decisions, humans and other animals must flexibly represent the current value of expected outcomes. The ability to infer values “on-the-fly” has been classically examined using the reinforcer devaluation paradigm, in which responses to a conditioned stimulus (CS) are probed before and after selective devaluation of the unconditioned stimulus (US) predicted by the CS. Intact animals respond less to the CS predicting the devalued

US. Rodent and non-human primate studies demonstrate that lesions of the orbitofrontal cortex (OFC) result in continued responding to the CS predicting the devalued US, suggesting that this region is necessary for inferring the current value of the predicted US. Human neuroimaging studies have established a correlational link between OFC activity and updated reward expectations in devaluation tasks, but whether this region plays a causal role in human outcome-guided behavior has not been determined. Here we used a between-subjects design in which we temporarily disrupted OFC activity by applying continuous theta burst stimulation (cTBS) to a dorsolateral prefrontal cortex target that was determined to be maximally functionally connected to the OFC in resting-state fMRI scans. Subjects first underwent conditioning to learn associations between two sets of visual CS's and individually selected, value-matched appetitive sweet and savory food odors (US's). On a subsequent day, hungry subjects made free choices between pairs of CS's to receive the sweet or savory food odor associated with the selected CS. Next, cTBS was applied at either 80% (STIM: N=28) or 5% (SHAM: N=28) of resting motor threshold. After stimulation, subjects were provided with an *ad libitum* meal corresponding to one of the two food odors, after which they performed the free choice task in extinction. Odor pleasantness ratings acquired before and after the meal showed robust and selective devaluation of the odor related to the eaten meal in both STIM and SHAM subjects, demonstrating that cTBS did not disrupt devaluation of the US. However, whereas SHAM subjects significantly reduced choices of CS's predicting the devalued US in the early trials of the choice task, STIM subjects failed to exhibit a significant devaluation effect, and selected the CS associated with the devalued US significantly more often compared to the SHAM group. These results demonstrate that indirect stimulation of the human OFC using connectivity-based cTBS disrupts outcome-guided behavior in humans. They further support mounting evidence across species that the OFC represents the identity of expected outcomes, and uses this information to infer their current value.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.01/III64

Topic: H.02. Human Cognition and Behavior

Title: Pupil size predicts memory performance and is correlated with high gamma activity in humans

Authors: *M. T. KUCEWICZ[1], J. DOLEZAL[2], V. KREMEN[1], B. M. BERRY[1], L. R. MILLER[1], A. L. MAGEE[1], V. FABIAN[2], G. A. WORRELL[1]
[1]Neurol., Mayo Clin., Rochester, MN; [2]Czech Tech. Univ. in Prague, Prague, Czech Republic

Abstract: Pupil responses are known to indicate brain processes involved in perception, attention and decision-making. They can provide an accessible biomarker of human memory performance and cognitive states in general. Here we investigated changes in the pupil size during encoding and recall of word lists, and compared them to electrophysiological changes recorded in epilepsy patients implanted with intracranial electrodes. Consistent patterns in the pupil response were found across and within distinct phases of the free recall task. The pupil was most constricted in the initial fixation phase and was gradually more dilated through the subsequent encoding, distractor and recall phases of the task, as the word items were maintained in memory. Within the final recall phase, retrieving memory for individual words was associated with pupil dilation in absence of visual stimulation. Words that were successfully recalled showed significant differences in pupil response during their encoding compared to those that were forgotten - the pupil was more constricted before and more dilated after the onset of word presentation. This pattern of changes was also observed for intracranially recorded high gamma activity, revealing consistent sequence of latencies during word encoding. A model is proposed for the role of pupil dilation and the correlated high gamma activity in the brain. Our results suggest pupil size as a non-invasive biomarker of brain activities associated with memory processing in the brain, which can be used for modulation and treatment of deficits in memory and cognition.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.02/III65

Topic: H.02. Human Cognition and Behavior

Support: NIMH - R01 MH100121
NSF CAREER - BCS1056019

Title: Hippocampal representations of temporal statistics predict subsequent reasoning

Authors: *A. PUDHIYIDATH[1], A. C. SCHAPIRO[2], R. J. MOLITOR[1], A. R. PRESTON[1]
[1]The Univ. of Texas at Austin, Austin, TX; [2]Psychiatry, Beth Israel Deaconess Med. Ctr. / Harvard Med., Boston, MA

Abstract: Events unfold in a continuous fashion, and yet we segment experience into discrete memories with both a beginning and an end. Recent data indicate that hippocampus and prefrontal cortex play critical roles in representing the temporal structure of experience. Here, our goal is to test how hippocampal and prefrontal representations that code temporal statistics of the environment bias reasoning decisions about relationships among memory elements that occur within the same or different temporal contexts. We used a modified version of the temporal community structure paradigm developed by Schapiro et al. (2013) to generate an iterative sequence of novel, 3D objects that participants viewed while undergoing fMRI scanning. Unbeknownst to the participants, the sequence was structured in such a way that each object belonged to one of three highly structured temporal communities. The presentation order of the objects followed a mutually predictive temporal order, shifting into another temporal community via 'boundary objects' that demarcated the entry and exit points of a temporal cluster. After viewing the temporally mediated sequence, participants completed a series of reasoning tasks outside of the scanner, including inductive generalization. We hypothesized that participants' knowledge of the temporal community structure would bias their choices during inductive reasoning. Behaviorally, we found that participants were more likely to induce that members of the same temporal community shared non-temporal properties (e.g., preferred habitat) than members of different communities. At the neural level, we found that bilateral anterior hippocampus representations were more similar for objects in the same temporal community relative to those in different communities, with the degree of similarity predicting participants' decisions about the objects. Moreover, we found that medial prefrontal cortex representations differentiated boundary items from one another, suggesting that this region may be integral to event segmentation processes that guide temporal knowledge acquisition. Collectively, these findings add to a growing body of literature demonstrating how spatial and temporal codes within the hippocampus influence decision-making beyond the domain of memory.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.03/III66

Topic: H.02. Human Cognition and Behavior

Support: Canadian Institutes of Health Research

Title: Subsequent memory and hippocampal activation in borderline personality disorder

Authors: *D. CARCONE, A. C. LEE, A. C. RUOCCO
Univ. of Toronto, Toronto, ON, Canada

Abstract: Background: Individuals with borderline personality disorder (BPD) report everyday problems with forgetfulness and display deficits on standardized measures of memory functioning. The medial temporal lobe, involved in memory encoding and consolidation, is smaller in individuals with BPD and shows an altered pattern of resting metabolism. The neural correlates of memory encoding in BPD have not been studied outside of the context of emotionally-valenced material. The goal of this study was to examine the neural underpinnings of memory encoding in BPD using fMRI and compare how patterns of brain activation associated with subsequent successful memory performance may be different than healthy controls.
Method: The present study assessed 20 individuals with BPD and 21 healthy controls. Participants viewed emotionally-neutral scenes during fMRI scanning and subsequently completed a recognition memory test. The difference in brain activation during presentation of later-remembered versus forgotten scenes was examined using non-parametric statistics. Analyses considered the bilateral hippocampus as an *a priori* region of interest.
Results: Left hippocampal activation was observed when contrasting activation during subsequently remembered versus forgotten trials for healthy controls, while no significant hippocampal activation was observed for the BPD group. Comparing BPD and healthy control groups on these contrasts revealed no significant differences in hippocampal activation. However, the magnitude of left hippocampal response for healthy controls was moderately correlated with memory performance ($r = .45$, $p<.04$), while no correlation was observed for participants with BPD ($r = -.33$, $p=.18$). The strength of this correlation was significantly different between groups ($z=2.3$, $p<.02$).
Conclusions: These results demonstrate that the memory disruptions associated with BPD may not be wholly driven by emotional interference. The results also suggest that hippocampal dysfunction at the time of memory formation may be meaningfully associated with the deficits in memory retrieval exhibited by individuals with BPD. Follow-up analyses will use multi-voxel pattern classification to determine whether a multivariate statistical approach is more sensitive to differences in hippocampal activity between BPD and healthy control groups.

Disclosures: D. Carcone: None. **A.C. Lee:** None. **A.C. Ruocco:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.04/III67

Topic: H.02. Human Cognition and Behavior

Support: JSPS Grant-in-Aid for Young Scientists (B) (26870934)

Title: Selectivity in knowledge acquisition effectively confers productivity: Behavioral experiments and neural network simulation

Authors: *H. KURASHIGE[1,2], Y. YAMASHITA[2], T. HANAKAWA[2], M. HONDA[2]
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Abstract: Knowledge acquisition is not a passive process. Many studies in cognitive neuroscience psychology have shown that we actively select information from the environment and have identified several factors governing the selectivity, such as congruency with prior knowledge, familiarity, curiosity, anticipation to use, and actual use. In addition, the results of functional imaging and neurophysiological measurements have shown several brain regions are involved with these factors and resultant selective knowledge acquisition. On the other hand, functional consequence of the selectivity in knowledge acquisition is unclear even though it is vital determinant for our cognitive development. In this study, we hypothesized that selectivity in knowledge acquisition results in effective augmentation of productivity, especially in creativity-demanding task. To test this, we conducted two human experiments using novel compositional Japanese words. Both experiments consisted of knowledge acquisition through a flash presentation of these compositional words, memory recognition test for these words, and essay composition task based on these words. In experiment 1, we showed that the acquisition strength of these compositional words was positively related to the productivity for the essay composition based on the words. While this result seemed to support our hypothesis, it might also reflect better memory independent of spontaneous selection. Therefore, in experiment 2, we confirmed that spontaneous selectivity in knowledge acquisition, rather than memory strength per se, conferred greater productivity. The results of these experiments suggested that the selective acquisition of knowledge effectively augmented productivity. In addition, we conducted neural network simulation in which Hebbian and homeostatic plasticity rules were incorporated. In this simulation, we found that novel information that was assigned to locations more easily accessible to the entire network was better assimilated and therefore selectively acquired. Because information encoded in such location is probably able to activate vast network regions, this mechanism of selective acquisition may explain the link between selectivity in knowledge acquisition and productivity observed in our experimental observations. Together, the present study showed a rational aspect in knowledge acquisition.

Disclosures: H. Kurashige: None. **Y. Yamashita:** None. **T. Hanakawa:** None. **M. Honda:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.05/III68

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant F32 AG054204

Title: Tracking the development of specific and generalized representations during concept learning

Authors: *C. R. BOWMAN, D. ZEITHAMOVA
Univ. of Oregon, Eugene, OR

Abstract: Healthy memory function allows us to both remember specific past experiences as well as link across experiences to form new knowledge. Recent work has shown that the ventromedial prefrontal cortex (VMPFC) and hippocampus support integration across events in both episodic memory and in concept learning. The detection of generalized representations within a single session contrasts with memory consolidation studies that often show generalized memories in the VMPFC only after a delay, thought to reflect consolidation of representations from the hippocampus to cortex. Using a category-learning task, we sought to better understand how concept representations emerge across learning in a single session, and how they relate to the development of specific representations of individual category exemplars. While undergoing fMRI, subjects completed an observational category-learning task where they learned to classify cartoon animals into two species. Subjects completed runs of study interspersed with generalization tests. In study runs, subjects saw multiple repetitions of 8 training items presented individually along with their species labels. In test runs, subjects saw the training items as well as new items that had never been given a species label. Subjects were asked to classify items into the two species. Behavioral results showed that subjects classified new items at above-chance levels from the first test, suggesting they may be able generalize based on limited experience. Across generalization tests, classification accuracy for the old items steadily improved, whereas accuracy for new items remained relatively constant, leading to a classification advantage for old relative to new items late in learning. Pattern similarity analysis was used to track the development of specific and generalized representations in the VMPFC. Across pairs of study runs, we compared patterns of activation for repeated presentations of the same item to items in the same category (item representations), as well as the similarity of items within the same category to items in different categories (category representations). Mirroring behavioral increases in accuracy for classifying old items, we found that VMPFC representations of individual items grew stronger from the first half of training to the second half. We did not, however, find evidence of category representations in the VMPFC during training, suggesting

that generalized representations in the VMPFC may instead arise during test in response to generalization demands. These results may reconcile the conflicting findings regarding early VMPFC contributions to memory generalization.

Disclosures: C.R. Bowman: None. **D. Zeithamova:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.06/JJJ1

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01

Title: Exploring event structure in music perception

Authors: *J. A. WILLIAMS[1], C. BALDASSANO[1], J. CHEN[2], U. HASSON[1], K. NORMAN[1]
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Abstract: While perceiving continuous natural stimuli, humans automatically segment experiences into discrete events (Baldassano et al., 2017). To better understand how these experiences are discretized, recent fMRI studies of event segmentation have employed the use of stimuli like movies and audio narratives. These studies have identified brain regions that transition between long-lasting (on the order of minutes) stable patterns of activity. There is reason to believe that music contains a similar hierarchical structure to movies and audio narratives (Farbood et al., 2015). We hypothesize that brain activity patterns reflect the event structure of songs, and that event boundaries from higher-order cortical regions are inherited (in a hierarchical fashion) by lower-order regions. To test this we used fMRI to record participants' brain activity as they listened to 16 familiar songs (8 jazz and 8 classical). The song durations ranged from 90 seconds to 225 seconds. Next, we collected annotations for these songs by asking a separate group of subjects to mark when "meaningful" changes occurred in a song. Then, for each song, we identified temporal boundaries between stable patterns of brain activity using a Hidden Markov Model, and compared these model boundaries to the human annotations. Compared to a null model with random boundaries, we identified multiple brain regions with significant matches to the observer-identified boundaries, including A1, mPFC, superior parietal cortex, and angular gyrus ($p<0.05$, FDR-corrected). The higher-order regions found in this analysis resemble the network of regions found in previous event segmentation studies, with some differences that may reflect the difference between event segmentation in narratives and music. Furthermore, the overlap between regions in this study and previous studies suggests that a shared network of regions is involved in representing hierarchical structure in complex time-varying stimuli and detecting meaningful changes in these types of stimuli.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.07/JJJ2

Topic: H.02. Human Cognition and Behavior

Support: Russian Academic Excellence Project '5-100'

Title: Effects of transcranial direct current stimulation (tDCS) on episodic memory: A systematic review and meta-analysis

Authors: *G. GALLI[1], M. VADILLO[2], M. SIROTA[3], M. FEURRA[4], A. MEDVEDEVA[1]
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Abstract: In the past decade, several studies have examined the effects of transcranial direct current stimulation (tDCS) on long-term episodic memory formation and retrieval. These studies yielded conflicting results, likely due to differences in stimulation parameters, experimental design and outcome measures. Here, we conducted four meta-analyses to assess the robustness of tDCS effects on episodic memory. We analysed the effects of anodal and cathodal tDCS on episodic memory accuracy and response times. Although all selected studies reported a significant effect of tDCS in at least one condition in the published paper, we found only statistically non-significant close-to-zero effects of anodal and cathodal stimulation on accuracy and reaction times. A moderator analysis suggested that the location, duration, and time of administration of the stimulation moderated the effectiveness of tDCS. To warrant theoretical advancement and practical implications, more rigorous research is needed to fully understand whether tDCS reliably modulates episodic memory, and the specific circumstances under which this modulation does, and does not, occur.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

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Program #/Poster #: 335.08/JJJ3

Topic: H.02. Human Cognition and Behavior

Support: NIA Grant AG039103
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Aging Mind Foundation

Title: Neural pattern similarity during encoding tracks subsequent memory in young, but not older, adults

Authors: *J. D. KOEN[1], N. HAUCK[2], M. D. RUGG[3]
[1]Univ. of Texas at Dallas, Dallas, TX; [2]Ctr. for Vital Longevity, Univ. of Texas At Dallas, Dallas, TX; [3]Ctr. for Vital Longevity, Univ. of Texas at Dallas Ctr. for Vital Longevity, Dallas, TX

Abstract: We conducted a study to examine the hypothesis that age-related neural dedifferentiation -reduction in the regional specificity and precision of neural representations in older relative to younger adults - during memory encoding results in degraded memory representations that contribute to age differences in episodic memory. This hypothesis was tested using trial-level neural (BOLD) responses elicited in the parahippocampal place area (PPA) and lateral occipital cortex (LOC) while young and older adults studied pictures of objects and scenes for a subsequent memory task. Pattern similarity was computed as the difference in the across-voxel correlation within (e.g., scenes and scenes) versus between (e.g., scenes and objects) categories. In young adults, trials that were subsequently recollected were associated with higher values of within-category pattern similarity compared to trials for which subsequent recollection failed. This effect was limited to the PPA, and was graded such that trials that were subsequently recognized in the absence of recollection also had higher measures of pattern similarity when compared to trials that were subsequently forgotten. These subsequent memory effects were not present in older adults. In addition, although older adults demonstrated higher levels of within- versus between-category pattern similarity in the PPA for scenes than for objects, the difference was smaller than that evident in young participants (there was no analogous age difference in the LOC). The above pattern of results are consistent with our prior findings using a differentiation index - a measure of neural selectivity for a regions preferred stimulus category (e.g., scenes in the PPA) - which showed age differences in differentiation limited to the PPA. This finding might indicate that age is associated with differences in the stability with which individual events are represented in category-selective cortical regions or, at least, in the PPA. Together, the results

are consistent with the hypothesis that neural dedifferentiation is associated with less effective memory encoding.

Disclosures: J.D. Koen: None. **N. Hauck:** None. **M.D. Rugg:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.09/JJJ4

Topic: H.02. Human Cognition and Behavior

Support: NMRC Grant STaR/0015/2013

Title: Split sleep is superior to consolidated nocturnal sleep for the retention of factual knowledge

Authors: *J. N. COUSINS, E. VAN RIJN, K. WONG, T. TEO, M. W. L. CHEE
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Abstract: Chronic sleep restriction is widespread, yet we know little about how to apportion the limited amount of sleep people obtain in order to minimize cognitive impairment. Should sleep in humans be obtained in a single bout of nocturnal sleep or split between nocturnal and daytime sleep periods? Daytime naps provide benefits for consolidation of material learned before sleep, and encoding of new information after sleep. However, it remains unclear how pre and post-nap learning are affected under a habitual split sleep schedule. We compared long-term memory in 58 participants who learned across 3 consecutive days with consolidated (6.5-hour nocturnal sleep opportunity) or split sleep (5h nocturnal sleep +1.5h daytime nap opportunities). On each day, participants spent one-hour learning detailed facts about six species of amphibian in the morning (11:00), and one-hour learning six different species of amphibian after the nap period in the afternoon (17:00). Participants were tested the following evening after a nocturnal recovery sleep opportunity (9-hours), via 360 two-alternative forced choice questions. A mixed ANOVA with group (5h+Nap/6.5h) and learning-time (morning/afternoon) showed a significant main effect of group ($p=0.046$) and a group*learning-time interaction ($p=0.021$). The 5h+Nap group remembered significantly more about species learned in the afternoon ($p=0.01$), while groups did not differ for species learned prior to the nap in the morning ($p=0.23$). This suggests that when available nocturnal sleep is curtailed to suboptimal levels, a split sleep schedule enhances learning after a nap opportunity, but critically this schedule does not impair morning learning, where less preceding nocturnal sleep was obtained. A split sleep schedule may therefore optimize the cognitive functions that underpin learning.

Disclosures: J.N. Cousins: None. **E. van Rijn:** None. **K. Wong:** None. **T. Teo:** None. **M.W.L. Chee:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.10/JJJ5

Topic: H.02. Human Cognition and Behavior

Title: Prefrontal - temporal interactions underlie successful long-term memory encoding: A meta-analytic functional co-activation mapping study

Authors: *R. S. BLUMENFELD, S. E. DUARTE, K. K. CHENG
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Abstract: The ability to successfully encode information into long-term memory (LTM) is fundamentally important for our daily functioning. Results from neuroimaging studies of successful LTM encoding consistently implicate a network of brain regions including areas within the lateral prefrontal cortex, inferotemporal cortex, and within medial temporal lobe. We were interested in investigating the interactions amongst these regions during successful LTM encoding. We hypothesized that during successful encoding, left mid-ventrolateral prefrontal cortex (VLPFC) would act as a global hub playing an essential role in mediating communication between other prefrontal regions and temporal regions. To test this hypothesis, we used meta-analytic functional co-activation mapping to construct a network model (graph) representing patterns of co-activation amongst brain regions associated with LTM encoding success across 80 studies in the LTM encoding neuroimaging literature. In this graph, nodes represent brain regions and edges represent the normalized number of times two regions are co-activated across studies in the successful encoding (subsequent memory effect) literature. Interrogating this network using graph-theoretical metrics, we find, consistent with our hypothesis, that a region of left VLPFC (pars triangularis) has the highest degree centrality in the network. Further results from community detection analyses demonstrate that the encoding network is decomposable into separate prefrontal and temporal sub-networks with left VLPFC, left fusiform gyrus and left inferior temporal cortex forming the network core. Although medial temporal regions are important central nodes in this network, our data indicates that the strongest paths do not flow through them, but rather through inferior temporal regions. Overall in this graph, we find the pattern and the extent of prefrontal-temporal interactions are different than those within a larger-scale control graph constructed from the BrainMap database. Next, we constructed separate graphs associated with successful “item” and “associative” encoding co-activation. We find that these graphs have similar properties but differ in their prefrontal contributions, with “item” having stronger co-activation within VLPFC subregions and “associative” encoding having

stronger connectivity between dorsolateral prefrontal cortex (DLPFC) and VLPFC. In conclusion, our pattern of results is consistent with the idea a unique pattern of prefrontal-temporal interactions underlies successful LTM encoding.

Disclosures: R.S. Blumenfeld: None. **S.E. Duarte:** None. **K.K. Cheng:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.11/JJJ6

Topic: H.02. Human Cognition and Behavior

Support: DGAPA-UNAM Grant IN217918
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Title: Theta oscillaton is associated with the amount of successful context encoded

Authors: *U. CABALLERO SANCHEZ, T. ROMAN-LOPEZ, C. SANCHEZ-GACUZ, M. MENDEZ-DIAZ, O. PROSPERO-GARCIA, A. RUIZ-CONTRERAS
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Abstract: Episodic memory is the ability to remember events in a temporal and spatial context. Subsequent memory effect is defined as the brain responses during encoding when the retrieval of information was successful. Subsequent memory effect has been related with theta oscillation which is higher, particularly at occipital and frontal regions, depending on the context awareness during retrieval, evaluated by a self-reported manner by means of the “remember/know” paradigm; however, it is required a more direct measure for a specific context encoding. Noteworthy, it is not clear if theta activity during encoding is related to the type of context retrieved, i.e., spatial, temporal or both. The aim of this study was to evaluate theta oscillation associated to subsequent memory effect depending on the context recollected during retrieval, at occipital and frontal regions. Participants solved a source memory task, which consisted in six blocks where natural and artificial images were shown. Each block was composed by an encoding, followed by a retrieval phase. During encoding, to manipulate the spatial context, each image was displayed over or under the fixation point for 1000 ms; to manipulate the temporal context, two independent lists of images were presented. Thus, spatial and temporal context were imbedded in each block. Participants had to classify, by a button press, images as natural or artificial. During the retrieval phase, participants had to indicate, by button press, where and when the image was showed up during the encoding phase. A subsequent memory effect was evidenced by higher theta amplitude (detected by the Hilbert transform) at O2 when participants recollected both spatial and temporal contexts than when they failed to remember one of the

contexts, both of them or when they classified incorrectly an old image as a new one. There were no differences at frontal regions. Our results showed that theta in occipital region, specifically at O2, was associated only with the whole acquisition of the context, suggesting theta activity might be associated with the amount of information, and not with the type of context, encoded.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.12/JJJ7

Topic: H.02. Human Cognition and Behavior

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Wellcome Trust Senior Investigator Award WT106931MA

Title: Memory integration and separation during learning are mediated by distinct hippocampal and cortical networks

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Abstract: Successful learning depends on encoding new information relative to existing knowledge. Neurobiological memory theories attribute such encoding to complementary functions of the hippocampus (HPC) and its interactions with neocortex. Specifically, HPC comparator processes that evaluate the overlap between new experiences and current knowledge trigger either pattern separation, wherein new memories are made representationally distinct from existing knowledge, or pattern integration, wherein new information is incorporated into existing memories. Recent behavioural and electrophysiological data suggest that the tendency of the HPC to trigger separation or integration may fluctuate on a moment-by-moment basis; yet, characterizing such moments of learning have proved challenging in humans given the lack of empirical methods to identify precisely when knowledge is created versus updated. Here, we overcome this challenge with SUSTAIN, a computational learning model that makes explicit predictions about when newly-encountered information is encoded through pattern separation or integration. During fMRI scanning, participants learned to categorize complex objects composed

of multiple features across four category learning tasks, with each task defined by different associations between category labels and combinations of object features. The learning model was fit to participants' behavior during the learning tasks to derive trial-by-trial predictions of when a new separated memory was formed versus when existing memory representations were updated. These model predictions were then leveraged in a fMRI regression analysis to characterize the neural circuits underlying moments of knowledge creation and integration. This approach led to two central findings: First, the creation of new memories was preceded by elevated activation in anterior HPC, consistent with HPC's role in detecting mismatch and triggering new encoding. A similar striatal signal also preceded new encoding. Second, distinct cortical networks were functionally coupled with HPC during the different encoding operations. We found a knowledge creation network involving higher-level visual representation areas including lateral occipital and ventral temporal regions, and a knowledge updating network comprised of the angular gyrus and regions of lateral prefrontal and frontopolar cortices. By leveraging a neurocomputational framework grounded in cognitive theory, our findings reveal the neural mechanisms of critical learning moments and characterize how new information is successfully reconciled with prior knowledge.

Disclosures: M.L. Mack: None. **B.C. Love:** None. **A.R. Preston:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.13/JJJ8

Topic: H.02. Human Cognition and Behavior

Title: Differential modulation of reward on memory encoding for objects and scenes is reflected in functional connectivity patterns

Authors: *J. YOO[1,2], H. SCHULTZ[2,3], D. MESHI[2,4], S. HAN[1], H. HEEKEREN[2]
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Abstract: This study builds on two lines of research investigating long-term memory processing in the brain: (1) anterior and posterior medial temporal lobe (MTL) pathways process different stimuli categories—object-based and spatial-based (scene) memory, respectively, and (2) reward-induced stimuli value enhances long-term declarative memory for these stimuli, which is mediated by the MTL and the dopaminergic midbrain. Taken together, these two findings lead to the question: is reward-induced memory enhancement for stimuli mediated differentially, by these different pathways in the brain? We hypothesized differences in value-related encoding

between objects and scenes due to different functional connectivity patterns of the anterior and posterior MTL.
To address this, we recruited 25 participants (5 males, mean age=25) for a two-day fMRI experiment (Siemens 3T, 1.5x1.5x2 mm EPI sequence, TR=1.8s, multiband factor=2). On Day 1, they performed a memory encoding task in the scanner in which they were differentially rewarded (high/low) for correctly classifying stimuli with regard to color (blue/yellow) and category (object/scene). On Day 2, participants returned to perform a surprise retrieval, recognition-memory task. Behaviorally, we found an asymmetric memory enhancement due to reward, in which high-reward objects were remembered significantly better than any other condition. With regard to the analysis of neuroimaging data, we employed functional connectivity multivariate pattern analysis (fcMVPA) to test our hypothesis: a linear support vector machine was trained to classify pairwise cross-correlation coefficients (edges) of the weighted time-series of predefined regions of interest. fcMVPA iteratively classified edges weighted with object & high-value vs. scene & high-value as a function of the number of edges included, with a peak accuracy of 82.5% when the 104^{th} edge was included. To characterize the patterns for two conditions, we divided the 104 edges into two groups which showed stronger correlation when weighted with object & high-value and vice versa, and performed centrality analysis for each network. As a result, right lateral occipital cortex showed the greatest eigenvector centrality for 63 edges which showed stronger correlation in regard to object & high-value. For 41 edges showing stronger connectivity for high-value scenes, left parahippocampal gyrus acted as the central hub.
Our results demonstrate reward-enhancement of object and scene memory due to differential functional connectivity patterns, suggesting that when value and stimulus category interact, the information follows distinct neural pathways.

Disclosures: J. Yoo: None. **H. Schultz:** None. **D. Meshi:** None. **S. Han:** None. **H. Heekeren:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.14/JJJ9

Topic: H.02. Human Cognition and Behavior

Title: The hippocampus and early visual regions are functionally connected during spatial memory encoding

Authors: *B. M. JEYE, S. D. SLOTNICK
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Abstract: The hippocampus and contralateral early visual regions are known to be activated during spatial memory; however, there is no evidence in humans, to our knowledge, that these regions are functionally connecting during this cognitive process. In the current functional magnetic resonance imaging (fMRI) study, we assessed whether the hippocampus and early visual regions were functionally connected during spatial memory encoding. During the study phase, participants maintained fixation and viewed abstract shapes presented in the upper-right quadrant, the lower-right quadrant, the upper-left quadrant, or the lower-left quadrant. During the test phase, old shapes were presented at fixation and participants classified each shape as previously in the "upper-right", "lower-right", "upper-left", or "lower-left". Encoding of shapes in the left visual field (collapsed over visual field location to increase power) produced activity in a left posterior hippocampal region, while encoding of shapes in the right visual field produced activity in another left posterior hippocampal region. To identify the early visual regions that might be connected to each of these hippocampal activations, we conducted a functional connectivity analysis between each hippocampal region and the rest of the brain. A preliminary analysis revealed the hippocampal activation associated with the encoding of shapes in the right visual field had greater functionally connectivity to contralateral (left hemisphere) early visual regions, including V1, than ipsilateral early visual regions. The hippocampal activation associated with the encoding of shapes in the left visual field did not show this contralateral pattern of early visual area connectivity. These findings suggest that the hippocampus and early visual regions interact to support the encoding of spatial memories.

Disclosures: B.M. Jeye: None. **S.D. Slotnick:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

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Program #/Poster #: 335.15/JJJ10

Topic: H.02. Human Cognition and Behavior

Support: 5R01MH074692-12

Title: Event segmentation of repeated information

Authors: *O. BEIN, L. DAVACHI
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Abstract: Most of our everyday life events contain repetition. For example, we typically take the same route to the same building and office. Event segmentation theories posit that continuous experience is segmented into discrete episodes, or events, at event boundaries. Specifically, it has been hypothesized that an "event model" is maintained to guide behavior within each event or context and that 'event-boundaries' are encountered as a result of prediction-errors that signal the

need for a new event model (Zacks et al., 2007). But how is event segmentation influenced by repeated events as they become more predictable, as in our everyday life? Are events nevertheless segmented, in the potential absence of prediction error, or does repetition reduce segmentation processes and lead to more integration across event boundaries? While previous studies in the field have typically used once-presented lists, here we repeated the lists, and examined behavioral and neural effects of event segmentation using high-resolution functional magnetic resonance imaging (hr-fMRI). Participants viewed black-and-white objects superimposed on a color background. The background color changed every 4 objects, thus an event boundary was defined as a change in background color. Participants made pleasantness judgement on the object-color combination. Each list repeated 5 times, and was followed by an order memory test. Upon completion of all lists, participants were tested on their memory for object-color associations. Participants highly accurate in the order memory test, indicating that the indeed the lists were well-learned. Behaviorally, markers of event-segmentation previously found in once-presented lists (Heusser et al. 2018) persisted over repetition: reaction times (RTs) during the list-learning phase were greater for items presented at the boundary compared to non-boundary items. Interestingly, we observed this effect, and in similar magnitude, even when the lists repeated. Additionally, memory for the object-color association was greater for boundary items compared to non-boundary items. In our analyses of the hr-fMRI data, we examined the contributions of hippocampal subfields and medial temporal lobe regions to event-segmentation across multiple repetitions, as well as to potential integration mechanisms. These results are suggestive of the neural and cognitive processes underlying event segmentation over multiple repetitions. They suggest that even in repeated and well-learned experiences, events are still segmented in memory.

Disclosures: O. Bein: None. **L. Davachi:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.16/JJJ11

Topic: H.02. Human Cognition and Behavior

Title: Novelty processing associated with neural beta oscillations improves recognition memory across the lifespan

Authors: *T. K. STEIGER, A. SOBCZAK, R. REINEKE, N. BUNZECK
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Abstract: Background: Previous imaging studies in healthy young subjects could show that the anticipation of novelty recruits the mesolimbic system and drives subsequent recollection. Since the mesolimbic system undergoes age related changes, we expected that the effect of novelty

anticipation is diminished during healthy aging. **Method:** To test this hypothesis and the underlying neural oscillatory mechanisms, we used EEG in combination with a previously established paradigm in a group of healthy younger (18-31) and elderly (55+) subjects. Here, coloured cues predicted the subsequent presentation of either a novel or previously familiarized image (75% validity), and subjects indicated at outcome whether the cue-image combination was correct or incorrect. On the subsequent day, recognition memory for the novel images was tested using a modified remember/know procedure. **Results:** Overall recognition memory was significantly lower in the elderly subjects; however, novelty prediction improved recognition performance independent of age and memory quality (i.e. recollection and familiarity). At the neural level, expected vs unexpected novel images were accompanied by an increase in beta power (i.e. 13-25 Hz) peaking at around 1-1.5 s after stimulus onset. Importantly, this effect was observed in both age groups but significantly enhanced in the elderly. **Conclusion:** Our data provide further evidence that novelty anticipation improves recognition memory performance, and they suggest that this is not impaired during healthy aging. While beta oscillations appear to provide the underlying mechanism, the increased responses in the elderly suggest compensatory effects.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

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Program #/Poster #: 335.17/JJJ12

Topic: H.02. Human Cognition and Behavior

Support: Spanish Government (PSI2013-46057-P)

Title: Across-episode memory formation is facilitated by their conceptually-related overlapping content

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Abstract: Individual experiences often overlap in their content, offering the possibility to build links across separate events. However, in daily-life different episodes rarely occur within the same scenario (i.e., entrance of the Parc Güell) and links among them need to be created on the bases of more abstract overlapping features (e.g., parks in Barcelona). Here, participants engaged in a two-phase learning and generalization task, wherein they learned an intermixed set of associations (i.e., face-scene) that overlapped by same scene or by conceptually-related scene information and subsequently generalized to novel stimulus combinations. Participants successfully learned the associations and were capable to generate inferences in both conditions,

indicating that the emergence of across-episode memory representations can rely on overlapping content of conceptual nature.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

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Program #/Poster #: 335.18/JJJ13

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery Grant
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Title: Selective attention to perceptual versus semantic features at encoding impacts neural engagement and memory behaviour

Authors: *S. VIJAYARAJAH, M. L. SCHLICHTING
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Abstract: We know that attention impacts what we remember, yet the specific mechanism by which attention to different kinds of features influences memory for our experiences remains unclear. Prominent theories disagree as to whether attention to semantic or perceptual features at encoding should yield better memory, with empirical work supporting both claims. We propose that these mixed findings may be due to differences in the nature of the encoded representation—specifically, whether memories are maintained as separate or integrated into existing knowledge—across these states. Previous work has shown that the human brain can store both separated and integrated memory representations (Schlichting et al., 2015). Moreover, selectively attending to different features at encoding (room layout vs. paintings in an art gallery) both influences neural patterns and promotes memory for the attended information (Aly & Turk-Browne, 2016). Here, we build on this prior work with complementary behavioural and fMRI studies asking whether attending to semantic vs. perceptual features at encoding impacts representation of the event as a whole. In a 1-back task, participants viewed fairy tale illustrations that varied in semantic (story) and perceptual (artist) features while searching for either story or artist repeats across blocks. Behavioural results showed that participants were able to detect repeats along both semantic and perceptual dimensions. Moreover, fMRI revealed that semantic attention engaged parietal cortex (including angular gyrus) as well as lateral and anterior temporal regions. In contrast, perceptual attention activated visual regions (occipital pole, lateral occipital cortex) and lateral prefrontal cortex. Following the 1-back, participants completed a surprise memory test that included all illustrations seen in the 1-back (old), illustrations similar to those seen in the 1-back (lures), and new illustrations. Participants had

better memory for non-repeat illustrations encoded during semantic vs. perceptual attention. However, memory for repeats showed the opposite pattern: memory was better (more hits) for repeats encoded during perceptual attentional states and worse (more false alarms to lures) for repeats from semantic attentional states. These behaviours are consistent with perceptual attention promoting mnemonic separation and semantic attention facilitating integration of new experiences into existing semantic networks. Our findings suggest that attention to perceptual vs. semantic features shifts the neural networks engaged during encoding, providing a mechanism by which attention mediates memory representation.

Disclosures: S. Vijayarajah: None. **M.L. Schlichting:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

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Program #/Poster #: 335.19/JJJ14

Topic: H.02. Human Cognition and Behavior

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NSF EPSCoR Award Number 1632738

Title: Disruption of verbal episodic memory encoding by epileptiform discharges is greatest in the left perirhinal and entorhinal cortex

Authors: *L. CAMARILLO-RODRIGUEZ[1], Z. J. WALDMAN[2], D. RUBINSTEIN[2], A. SHARAN[1], R. GORNIAK[1], J. TRACEY[1], G. A. WORRELL[3], B. C. LEGA[4], R. E. GROSS[5], K. DAVIS[6], B. C. JOBST[8], S. A. SHETH[9], K. A. ZAGHLOUL[10], J. M. STEIN[7], S. DAS[11], P. A. WANDA[12], M. SPERLING[13], S. A. WEISS[1]
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Abstract: A comorbidity of epilepsy is memory impairment. It is thought that inter-ictal epileptiform activity in certain brain regions may interfere with memory formation. In this study, we asked if spikes and high-frequency oscillations (HFO) that spontaneously occur during word presentation in a free recall list learning task decrease the probability of recalling that word correctly. The patient cohort included 181 subjects who consented to undergo intracranial monitoring and participate in the task. Intracranial EEG was recorded at 500-1600 Hz and

analyzed using a spike and HFO detector utilizing a topographical analysis of the depth iEEG wavelet convolution. We quantified spike and HFO events during 118,892 word encoding trials, and confirmed spike and HFO detections using visual validation and annotation editing. The electrode sites were classified using co-registered pre-implant MRI and post-implantation CT images that were segmented on the basis of several published brain atlases. A naive Bayesian machine learning model was used to calculate the posterior probabilities of word recall given a spike or HFO, and the significance of this prediction was determined using bootstrapping. In the left hemisphere, but not the right, ripples ($p< 0.01$), fast ripples ($p<0.01$), and spikes ($p<0.01$) disrupted word encoding. In the left temporal neocortex, spikes in the middle temporal gyrus decreased the probability of correct word recall by 11.9% ($p<0.001$, n=1,379). In the left mesial temporal lobe, spikes did not disrupt verbal memory encoding in area CA1 ($p>0.05$, n=364) nor in the dentate gyrus ($p>0.05$, n=417). However, spikes in the left entorhinal cortex (prob= -54.2%, $p<0.001$, n=81) and perirhinal cortex (prob=-15.6%, $p<0.01$, n=167) did strongly disrupt memory encoding. Encoding was not disrupted by spikes in right mesial temporal lobe structures. These results suggest that normal physiological function in the left entorhinal and perirhinal cortices are required for verbal memory encoding. Also, verbal memory impairment in patients with mesial temporal lobe epilepsy may be attributed, in part, to inter-ictal epileptiform activity in the left entorhinal and perirhinal cortices.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.20/JJJ15

Topic: H.02. Human Cognition and Behavior

Title: Functional-anatomical alignment between brains using a naturalistic stimulus in healthy individuals and a hippocampal amnesic

Authors: *X. ZUO[1], M. D. BARENSE[4], C. J. HONEY[2], J. CHEN[3]
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Abstract: MOTIVATION. A fundamental and persistent challenge in fMRI research is aligning brain areas and functional responses across individuals. This is particularly difficult when anatomical or functional reorganization may have occurred, as in many clinical populations. How can we compare the neural responses of healthy individuals to patients, when the anatomical relationship between their brains is uncertain? One solution is functional co-registration: define a correspondence between voxels in different subjects, based on each voxel's response profile to a wide range of stimuli (e.g., Haxby et al. 2011; Chen et al., 2015). However, functional alignment sometimes leads a single voxel in one brain to be associated with a weighted combination of widespread voxels in another brain; these alignments may be *a priori*implausible and difficult to interpret. Therefore, we set out to develop a more interpretable functional alignment method that (i) combines anatomical and functional constraints and (ii) establishes a one-to-one match for regions-of-interest across brains. **METHODS.** We establish baselines using healthy controls, then characterize anatomical/functional restructuring in a hippocampal amnesic patient's brain. 36 participants listened to a 7-minute audio story during fMRI. We also collected fMRI data using the same stimulus from an amnesic patient with bilateral medial-temporal lobe damage (Rosenbaum et al., 2008). We calculated inter-subject correlation between a) control subjects, and b) controls and patient, using Shen et al. (2013)'s resting-state parcellation. In a classification analysis, we split the control data in half and compared group average parcel timecourses parcel by parcel. **RESULTS.**Using 56 parcels, classification performance was 84.0% (chance = 1.8%), indicating high between-group correspondence of functional responses, i.e. anatomically corresponding parcels almost always exhibit the strongest correlation between groups.When classification was performed using each subject in one group compared to the other group mean, accuracy was also well above chance (22.9%). Our amnesic-to-control classification accuracywas still above chance (9.3%), but the parcel matching was substantially lower than between controls. **CONCLUSIONS and NEXT STEPS.** Visual inspection suggested that low patient-control correspondence of response was due, at least in part, to poor anatomical correspondence between their brains: portions of the patient brain might have shifted to accommodate damaged or missing tissue. Next, we will use control parcels to generate optimized parcel layouts of functional reorganization in the patient's brain.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

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Program #/Poster #: 335.21/JJJ16

Topic: H.02. Human Cognition and Behavior

Support: School of Psychology, Cardiff University, Cardiff, United Kingdom

Title: Curious connections: White matter microstructure correlates of types of curiosity

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Abstract: Curiosity - the desire to acquire new information - influences learning and memory. While fledgling neuroscience research has shed light on how state curiosity affects hippocampus-dependent learning, the effect of curiosity on learning is highly variable between individuals. The neuroanatomical substrates underpinning these individual differences in trait levels of curiosity are unknown. Furthermore, curiosity itself is a multifaceted construct, and thus may be supported by multiple neural systems. Here, we used diffusion-weighted imaging to investigate how specific white matter pathways (i.e., the fornix and the inferior longitudinal fasciculus [ILF]) relate to individual differences in distinct types of curiosity: epistemic curiosity (i.e., the desire to acquire new knowledge), social curiosity (i.e., curiosity in obtaining information about others), and perceptual curiosity (i.e., curiosity in an environment rich with novel stimuli). Given that the fornix supports exploratory behaviour and information seeking via hippocampal-striatal connections, we asked the question whether there would be a correlation between fornix microstructure and all three different types of curiosity. In contrast, given that the ILF is involved in networks supporting semantic processing, we predicted a correlation between ILF microstructure and specifically epistemic curiosity. Fifty-one female participants underwent a two-shell diffusion magnetic resonance imaging sequence and completed a set of well-validated questionnaires measuring different types of curiosity. Using deterministic constrained spherical deconvolution tractography, mean fractional anisotropy (FA) and mean diffusivity (MD) values for the fornix and ILF were extracted for each participant and correlated with the self-report measures of curiosity. In line with our predictions, we found a significant negative correlation between epistemic curiosity and MD of the ILF. In addition, fornix microstructure was found to significantly correlate with multiple aspects of curiosity, namely interest-based epistemic curiosity, general-based social curiosity and specific-based perceptual curiosity. The present findings suggest that curiosity is a multifaceted concept that relies on distributed but interacting structural brain networks where fornix microstructure is potentially associated with a variety of curiosity traits whilst the ILF is associated with epistemic curiosity.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.22/JJJ17

Topic: H.02. Human Cognition and Behavior

Title: Theta coherent ensembles in the human anterior temporal lobe mediate episodic memory encoding

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Abstract: The electrophysiological underpinnings of human episodic memory have been well characterized by measuring broadband high frequency activity in neocortical areas from macroscopic intracranial electrodes used to detect epileptic seizures. However, the role of narrowband oscillations in human memory formation, particularly in local neocortical circuits, is largely unknown. Here we measure spike-field coherence from micro-electrode arrays implanted in the human anterior temporal lobe in order to assess how local circuits contribute to memory processes. We find that anterior temporal lobe neurons are coherent with narrowband theta oscillations locally and across the cortical surface, and that spikes preferentially occur at a specific phase within the theta cycle. The extent of coherence and phase locking to narrowband theta during memory encoding was significantly greater when those memories were subsequently remembered versus those that were forgotten. These results suggest that theta-coherent networks in the anterior temporal lobe and across the cortical surface promote memory encoding.

Disclosures: R. Haque: None. **S. Inati:** None. **K.A. Zaghloul:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

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Program #/Poster #: 335.23/JJJ18

Topic: H.02. Human Cognition and Behavior

Support: H2020-MCSA-IF-2015 - 705641
UK Medical Research Council Programme (SUAI/010/ RG91365 and SUAI/013/RG91365)

Title: Imaging the consolidation of distressing memories: Dissociating voluntary versus involuntary recall

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Abstract: A key question in emotional memory research is how a traumatic event may result in intrusive, involuntary memories of that event - the core clinical feature of psychological disorders such as post-traumatic stress. Previous behavioural work shows that the strength of voluntary recall of traumatic events is not necessarily related to the frequency or vividness of the involuntary recall of those events, a dissociation that is not readily explained by mainstream episodic memory theories. Here, we investigated whether the two types of recall may be associated with distinct neural profiles at the time of encoding and shortly after. For this, 32 healthy participants underwent functional Magnetic Resonance Imaging while viewing clips of distressing events (the so-called 'trauma film paradigm'), with periods of resting state in between consecutive clips. Next, we applied 'multi-voxel correlation structure' to assess the degree to which voxel-by-voxel connectivity profiles related to the encoding of a specific clip persisted during the immediately-following post-encoding rest period. In the hippocampus, higher similarity between post-encoding rest and encoding profiles, compared to immediately-preceding pre-encoding rest periods, predicted the voluntary recall (both verbal and visual recognition) of the distressing events, a week later. This neural profile was not however related to the frequency or variety of intrusive memories that participants recorded in a daily diary, which they kept for a week following film viewing. These findings corroborate behavioural observations and tentatively suggest that voluntary and involuntary memories of the same event may to some extent rely on separate neural systems.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.24/JJJ19

Topic: H.02. Human Cognition and Behavior

Title: Medial prefrontal cortex has a causal role in selectively enhanced consolidation of emotional memories: A TMS-EEG study

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Abstract: Abstract Emotional aspects of episodic memory are preferentially benefited at the expense of co-occurring neutral aspects. This is known as the emotional memory trade-off effect, which is enhanced over consolidation delays that include a period of sleep. Previous fMRI research has shown a correlation between retrieval-related activation of medial prefrontal cortex

(mPFC) and memory for emotional (versus neutral) information after a night of sleep compared to after a day spent awake. Moreover, sleep has been proposed to exert its strongest effects on gist-based familiarity, rather than specific recollection of memory details. However, little is known about how mPFC activity during encoding interacts with consolidation processes to enhance emotional aspects of memories after a night of sleep. This study goes beyond correlational findings to casually investigate the role of mPFC activity during encoding in the enhancement of emotionally salient aspects of episodic memory. At encoding, healthy young adult participants (N = 22) viewed negative (e.g. snake) or neutral (e.g. chipmunk) objects placed on plausible neutral backgrounds (e.g. forest scene), while undergoing simultaneous EEG recording with 2s trains of intermittent theta burst stimulation (iTBS) to either the mPFC (i.e., experimental condition) or motor cortex (i.e., active control/sham condition) at 80% of active motor threshold. Memory was assessed with two delayed (i.e., 30 minutes, 24 hours) incidental recognition tests by decomposing the scenes into individually presented objects and backgrounds. The results replicated the emotional memory trade-off with negative objects better remembered than their neutral backgrounds after 30 minutes, with a more pronounced trade-off following a delay (24hr) that included sleep. Consistent with our hypothesis, iTBS to the mPFC led to enhanced gist memory for negative objects following a 24 hour delay that included sleep compared to control stimulation, despite equivalent false alarms rates. Thus, these findings suggest that iTBS to the mPFC during encoding may interact with consolidation processes to selectively preserve the gist of negatively salient information.

Disclosures: N. Yeh: None. **S.Y. Kim:** None. **J. Payne:** None. **N.S. Rose:** None.

Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.25/JJJ20

Topic: H.02. Human Cognition and Behavior

Title: Neural correlates underlying the effect of value on recognition memory encoding

Authors: *B. ELLIOTT, C. BLAIS, S. M. MCCLURE, G. A. BREWER
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Abstract: The ability to prioritize and encode important or valuable information is an essential aspect of human memory. However, the processes underlying how value can affect memory are not yet well understood. One hypothesis is that value affects memory via top down executive control processes, where after recognizing that a stimulus is valuable, a participant would selectively engage an elaborative or effective rehearsal strategy. A second hypothesis is that value affects memory involuntarily through the dopamine system that determines reward valuation. Here we examined the behavioral and neurophysiological correlates of value-directed

recognition memory. Participants encoded words that were assigned varying point values (1,3,7, or 9) and were instructed that their goal was to maximize their score on a subsequent word recognition test in multiple study-test phases. Subjective states of recollection (i.e., "Remember") and familiarity (i.e., "Know") were assessed at retrieval. Words assigned higher values at study were discriminated more effectively than lower valued words. This difference was primarily driven by increases in Remember responses with no difference in Know responses. During encoding, we examined the extent to which an early parietal P3 component (450-650 ms post-stimulus) thought to index dopamine driven attention allocation and a late sustained frontal positivity (1000-2000 ms post stimulus) that has been related to elaborative rehearsal strategies and executive resources predicted the subjective state of recollection. Our data indicate that that the effect of value on recognition memory is primarily driven by the dopamine-driven reward valuation system as compared to more strategic selective rehearsal processes. Specifically, we found a positive relationship between the amplitude for the P3 component that scaled linearly with the value assigned to each word. Furthermore, this effect was also positively related to behavioral measures of each participants' sensitivity to value. No such relation was observed on the late sustained frontal positivity, and the amplitude of this component was not related to related to each participants' sensitivity to value. Together, these data suggest (1) a need for two distinct processes to support recognition memory decisions, and (2) that value-directed encoding results in a greater effect on subjective states of recollection.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.26/JJJ21

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
WFBMC Dept. of Neurosurgery
NIBIB

Title: Facilitating memory: Individualized prosthetic stimulation for memory categories

Authors: *R. E. HAMPSON[1], B. M. ROEDER[1], C. A. JOHNSON[1], A. S. DAKOS[1], X. SHE[2], D. SONG[2], T. W. BERGER[2], S. A. DEADWYLER[1]
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Abstract: Development of a neural prosthetic for human memory requires an understanding of how mnemonic information is categorized and encoded for storage. Our recent report (Hampson et al. J. Neural Eng, 2018, 15:036014) showed that human memory could be successfully

facilitated by delivery of patterned electrical stimulation to CA1 electrode sites in human hippocampus. In prior studies, the patterns were derived by nonlinear multi-input, multi-output (MIMO) modeling of hippocampal CA3 and CA1 ensemble activity during the encoding phase of a visual delayed-match-to-sample (DMS) task. We now extend this study to derive and deliver patterned stimulation in a DMS+Delayed Recognition (DMS+DR) task, to facilitate memory of category content for DMS+DR visual stimuli.

In human patients undergoing Phase II invasive monitoring for intractable epilepsy, recordings from an initial DMS (training) session were employed to determine neuron firing patterns for five categories of images; animal, building, plant, tool, and vehicle. Previous use of a MIMO model only allowed stimulation of CA1 neurons based on CA3 activity. Calculation of category specific stimulation patterns prior to the stimulation session now allows for selection of both CA1 and CA3 neurons as stimulation targets. During a second (stim test) session, subjects received microelectrical stimulation on approximately 60% of trials during the sample phase of the DMS portion of the DMS+DR task. Stimulation trials were a combination of positive stim (stim category matches sample image category), negative stimulation (stim category does not match sample image category) and ambiguous stimulation (image during stimulation was a blank grey square) trials.

Positive stimulation trials for all patients resulted in a reduction of errors in three of the five categories, with the remaining stimulation category performance level near unstimulated performance. Negative stimulation resulted in reduction in errors for at least three of the twenty possible cross category combinations. Ambiguous trial stimulation also resulted in increased performance over chance. Analysis of the survey used to categorize images combined with stimulation results suggest that category stimulation works, but effectiveness is dependent on selection of images used during the recording session to derive category patterns. These results thus provide an important foundation for further design considerations for the current neural prosthetic to restore human memory damaged by injury or disease.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.27/JJJ22

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
WFBMC Dept. of Neurosurgery
NIBIB

Title: Facilitating memory: Shared codes for prosthetic stimulation of memory categories

Authors: *B. M. ROEDER[1], C. JOHNSON[2], A. S. DAKOS[3], X. SHE[4], D. SONG[4], T. W. BERGER[4], S. A. DEADWYLER[3], R. E. HAMPSON[3]
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Abstract: In prior demonstrations of category stimulation by a neural prosthetic for human memory (Hampson et al. J. Neural Eng, 2018, 15:036014) we utilized models that were developed from a patient's own hippocampal CA3 and CA1 neural ensemble firing. With this technique, as long as there was a mixture of correct and error trials when the ensembles were recorded, it was possible to detect patterns of neural firing associated with correct memory performance, and utilize those patterns to facilitate performance within a delayed-match-to-sample + delayed recognition (DMS+DR) task. In the adjacent poster (Hampson et al. this meeting) we extended this technique to facilitate specific content categories within visual stimuli. Here we explore whether similar encoding for such categories exists across human subjects. Category patterns from other subjects performing the same DMS+DR task were tested to determine if stimulation patterns would have a shared effect between subjects. Stimulation patterns were matched between subjects through use of common channels on electrodes targeted for implantation in the same location of the hippocampus. This resulted in stimulation of analogous areas between subjects donating and receiving the stimulation pattern. Stimulation testing was performed the same as in the adjacent poster, with a combination of positive, negative, and ambiguous trials. Positive stimulation trials for all patients resulted in a reduction of errors in two of the four categories tested, with the remaining categories performance level near that of unstimulated performance. Categories that showed enhancement were the same as those that showed enhancement with individualized codes (Hampson et al. this meeting). Negative stimulation has resulted in no significant change in performance, while ambiguous trial stimulation has resulted in increased performance over chance in the one subject tested so far. Stimulation effects are similar to, but less effective than, when a subject's own codes are used, and indicate that there may be shared aspects of the neural codes for category representations between subjects. These results indicate that implementation of a neural prosthetic to restore human memory may also facilitate learning and/or rehabilitation via shared representations of memory encoding.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.28/JJJ23

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
NIH U01 GM104604

Title: Facilitating memory: An ensemble sparse classification model for decoding memory categories and features from hippocampal spike patterns recorded in epilepsy patients

Authors: *X. SHE[1], D. SONG[1], R. E. HAMPSON[3], G. NUNE[2], B. LEE[2], C. N. HECK[2], C. Y. LIU[2], V. Z. MARMARELIS[1], S. A. DEADWYLER[3], T. W. BERGER[1]
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Abstract: To build hippocampal prostheses for enhancing memory functions, it is essential to understand how memories are encoded in the hippocampus. For this purpose, we have developed a multi-resolution, multi-trial (MRMT) sparse classification model to decode hippocampal spiking activities into memory labels. Mode inputs are spatio-temporal patterns of hippocampal CA3 and CA1 spikes collected from epilepsy patients performing a delayed match-to-sample (DMS) task. Model outputs are non-mutually exclusive memory labels describing categories and feature of sample images presented in the sample phases of the DMS task. The classification model consists of a B-spline filter bank with a large range of temporal resolutions and a sparse logistic regression classifier. Sparse model coefficients are calculated with multiple trials of 10-fold estimation and cross-validation, with different random partitioning of data into training and testing sets. Model performances are evaluated with a Matthews correlation coefficient (MCC). To ascertain the significance of decoding performance of the classification model, two additional classification models are estimated using the same procedure as negative controls. In the first control model, values of memory labels (model output) are randomly shuffled to remove the correlation between spike patterns and memory labels; in the second control model, the time window of spike patterns (model input) is shifted to be before the sample presentation event so the spike patterns contain no information about their corresponding sample images. Results show that the classification model yields significantly non-zero MCCs in predicting multiple memory labels in all patients (n = 8), while the two control models obtain zero-valued MCCs in all memory labels and a large majority of memory labels, respectively. These results indicate that (1) the ensemble MRMT sparse classification model effectively avoids overfitting even when the number of features is large (i.e., over a thousand) and the data length is short (i.e., 100 - 200),

and (2) spike patterns during sample response events of the DMS task encodes categories and features of sample images.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 335.29/JJJ24

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
NIH U01 GM104604

Title: Facilitating memory: Enhancing human memory function with endogenous hippocampal neural code predicted by a closed-loop nonlinear dynamical model

Authors: *D. SONG[1], X. SHE[1], R. E. HAMPSON[3], G. NUNE[2], B. LEE[2], C. N. HECK[2], C. Y. LIU[2], V. Z. MARMARELIS[1], S. A. DEADWYLER[3], T. W. BERGER[1]
[1]Biomed. Engin., [2]Keck Sch. of Med., USC, Los Angeles, CA; [3]Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Hippocampal prostheses are biomimetic devices designed to restore and enhance memory functions. They bypass damaged hippocampal circuits by stimulating a downstream (output) hippocampal region using output signals predicted from upstream (input) hippocampal signals with a multi-input, multi-output (MIMO) nonlinear dynamical model. To build a MIMO model that restores normal input-output functions of the hippocampal circuit, intact input-output signals, which are impaired or even absent in the damaged hippocampus, are required. Similarly, to build a MIMO model that enhances memory functions, input-output signals underlying above-normal hippocampal functions are needed. One approach for solving this "missing data" problem is to obtain input-output data and MIMO model from different subjects, who have normal or above-normal memory functions. This memory transfer approach relies on the existence of similarities in neural recordings and encodings between subjects and thus can be challenging. In this abstract, we describe an alternative self-learning approach that allows building normal or above-normal MIMO models by exploiting the input-output data recorded from the same subjects. In this approach, memory states are assessed with a classifier that takes neural signals as inputs and memory strength as output. MIMO models are adaptively estimated from the input-output data controlled by the memory strength. When the memory strength is high, which reflects a strong memory state, MIMO models are updated using the strong-state input-output

data; when the memory strength is low, which indicates a weak memory state, MIMO model are used to stimulate the downstream regions to restore the strong memory codes learned during strong memory states. This closed-loop strategy essentially elevates weak memory states into strong memory states and thus enhances the overall memory functions of subjects. Our experimental-modeling studies in human subjects have shown that the outcomes (i.e., correct or error responses) of delayed match-to-sample (DMS) task, which result from the strength of memory states, can be predicted from the hippocampal CA3 and CA1 spike trains. Using MIMO models estimated from CA3-CA1 spiking data recorded during correct DMS trials (i.e., strong memory states) to drive stimulations to CA1 can improve memory performance of the DMS task. These results provide strong supports for the feasibility of building such a self-learning memory prosthesis for enhancing memory functions.

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Poster

335. Human Cognition and Behavior: Human Long-Term Memory: Encoding

Location: SDCC Halls B-H

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Program #/Poster #: 335.30/JJJ25

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016
WFBMC Dept. of Neurosurgery
WFBMC Dept. of Radiology

Title: Facilitating memory: Localization of ensembles and neural correlates of encoding contributing to a neural prosthetic for human memory

Authors: *S. A. DEADWYLER[1], B. M. ROEDER[2], C. JOHNSON[3], A. S. DAKOS[1], R. T. WICKS[1], D. E. COUTURE[1], A. W. LAXTON[1], G. POPLI[1], C. T. WHITLOW[1], R. E. HAMPSON[1]
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Abstract: Further development of the neural prosthetic for human hippocampal-dependent memory (Hampson et al. J. Neural Eng, 2018, 15:036014) requires refinement of electrode placement within the hippocampus which can be guided by anatomical localization and confirmed via neurophysiological recording characteristics. In this study we expanded hippocampal morphometric measurements to include normal subjects, subjects with a known history of epilepsy, as well as subjects tested with the neural prosthetic for hippocampal memory

(Hampson et al. & Roeder et al., this meeting). In addition we have analyzed neurons recorded from the human hippocampus to determine functional relationships of those neurons to memory function.
A morphometric survey was conducted using 3-T MRI scans of 100 hippocampi from normal subjects, 50 hippocampi from subjects with a known history of epilepsy, as well as more than 50 hippocampi from epilepsy patients who were eventually implanted with electrodes for Phase II diagnostic mapping of seizures (Wicks et al., 2018). Average dimensions of the hippocampus along typical implantation tracks within these populations were then utilized for localization of over 400 neurons recorded from anterior and posterior hippocampal CA3 and CA1 electrode sites in 16 subjects undergoing diagnostic mapping of seizures. Pairs of neurons from putative CA3 and CA1 sites were analyzed for correlation indicative of localization within the respective hippocampal cell fields, while single neurons and ensembles were analyzed for neural correlates of the memory tasks.
Hippocampal neural firing conformed to expected cross-correlation and task correlates predicted by preclinical studies in rodents and nonhuman primates. On average, neurons exhibited transient increased firing rate (i.e. firing peaks) immediately prior to the Sample (encoding) and Match (recall) responses within a delayed-match-to-sample (DMS) memory task. Further, ensembles showed distinct firing patterns on correct trials that were distinct from error trials. Notably, neurons exhibited peak and latency differences in both the encoding phase (i.e. predicting the error) as well as the recall phase of error trials, confirming that mnemonic errors resulted from failure to appropriately encode task-relevant information. These results provide an important foundation for understanding the neural principles underlying memory and contribute to advancement of the design of our neural prosthetic for human memory.

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Poster

336. Schizophrenia: Behavior and Symptoms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 336.01/JJJ26

Topic: H.03. Schizophrenia

Support: NIH MH101506

Title: Multivariate pattern analysis in psychotic-like experiences

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Abstract: There is a growing interest in using neuroimaging measures in conjunction with machine learning to classify individuals with schizophrenia (SCZ) from healthy controls (HC). Little research has investigated classifying individuals with high levels of psychotic-like experiences (H-PLE) symptoms from low (L-PLE). Here, a linear class-weighted support vector machine (LC-SVM) trained on structural magnetic resonance imaging (sMRI) measures, i.e. volume and thickness, achieved an accuracy of 71%, a sensitivity of 65%, and a specificity of 75% discerning between SCZ (n = 85) and HC (n = 101) groups split into a training and testing datasets. The five most important areas in the brain for classification were left pericalcarine, right pericalcarine, right middle temporal, left parahippocampal, and right fusiform. Next, we employed the same method to label H-PLE (n = 67) and L-PLE (n = 145) individuals from the Human Connectome Project (HCP), identified based on item scores in the Achenbach Self Report. Using a LC-SVM to H-PLE and L-PLE had an accuracy of 51%, a sensitivity of 55%, and a specificity of 46% using sMRI data. Using a stacked classifier achieved an accuracy of 58%, a sensitivity of 53%, and a specificity of 65% in the same group. The five most important areas in the brain for classification were the right middle temporal, right inferior temporal, left inferior parietal, right lateral orbital frontal, and right caudal anterior cingulate. This proof of concept shows it is possible to use neuroimaging measures to predict levels of PLE in a healthy population, although there may be differences in which regions are most predictive. Future analyses will include training a classifier to differentiate between SCZ and HC and then use it to classify H-PLE and L-PLE. In addition, the inclusion of other neural data such as resting-state MRI and/or diffusion tensor imaging (DTI) will improve the predictive power of the classifier and indicate if the same or different brain areas are important in other neural biomarkers.

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Poster

336. Schizophrenia: Behavior and Symptoms

Location: SDCC Halls B-H

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Program #/Poster #: 336.02/JJJ27

Topic: H.03. Schizophrenia

Support: NIMH Grant R01MH112189

Title: Neuro-behavioral relationshipns in dimensional geometric embedding

Authors: *J. JI[1], B. ADKINSON[1], A. KOLOBARIC[1], M. FLYNN[1], R. A. ADAMS[2], J. B. BURT[1], A. SAVIC[1,3], J. D. MURRAY[1], A. ANTICEVIC[1]
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Abstract: A key challenge in the field of neuropsychiatry lies in matching patients with effective treatments. Most studies operate under the canonical assumption that categorical diagnostic groupings and/or pre-existing clinical assessments are the 'gold standard' for describing behavioral and therefore neural variation in patients. Attempts to robustly characterize the neural substrates of these variables have yielded limited success, suggesting an inadequate mapping to neurobiologically meaningful variation. Notably, a great deal of heterogeneity exists even within groups of patients with the same diagnosis. Thus, understanding the mapping between specific behaviors and clinically meaningful variation in neural properties is critical to developing and ultimately administering effective individualized treatment.

Here, we describe a multivariate neuro-behavioral framework under which behavioral variation can be mapped to features of specific neural systems in a data-driven way. We leverage neural (fMRI-derived) and behavioral data from 436 psychosis-spectrum patients that are publicly available via the NIMH Data Archive as part of the Bipolar & Schizophrenia Consortium for Parsing Intermediate Phenotypes study. We first identify dimensions of behavioral variation in patients by performing a PCA across all behavioral measures. Importantly, these dimensions are not parallel to traditional symptom scales from pre-existing clinical instruments, and do not reflect conventional diagnostic boundaries. We then demonstrate that variation along these behavioral dimensions relates to variation in the global brain connectivity of specific neural systems. Critically, these robust neuro-behavioral relationships were not observed using either traditional diagnostic groups or *a priori* clinical scales. We also demonstrate the flexibility to embed both categorical and continuous features within the same generalized geometry. We further show that this framework can inform the identification of pharmacological targets for specific symptom profiles and may assist in selecting behavioral measures that precisely pinpoint neural variation at the individual level.

Characterizing how and which specific sets of symptoms map to neural circuitry is a key step towards developing targeted and effective treatments for psychiatric disorders. We propose the Neuro-Behavioral Relationships In Dimensional Geometric Embedding (N-BRIDGE) framework as a key step towards unified mapping between the geometry of behavioral variation and the geometry of neural variation, thus integrating both categories and continuous features in psychiatry.

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Poster

336. Schizophrenia: Behavior and Symptoms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 336.03/JJJ28

Topic: H.03. Schizophrenia

Support: AMED Brain/MINDS Grant 17dm0207004h0004

Title: Reduced mismatch negativity reflects impaired deviance detection in schizophrenia

Authors: *D. KOSHIYAMA, K. KIRIHARA, M. TADA, T. NAGAI, M. FUJIOKA, K. USUI, T. ARAKI, K. KASAI
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Abstract: Background: Mismatch negativity (MMN) is a promising candidate of translatable biomarker for schizophrenia that can link preclinical animal studies to clinical studies. Previous studies have proposed stimulus specific adaptation and deviance detection as the mechanism underlying MMN. Recent animal studies are now revealing neural mechanisms underlying stimulus specific adaptation and deviance detection. Although many previous studies reported reduced MMN in patients with schizophrenia, there is no study to examine whether reduced MMN in patients with schizophrenia is due to impairments of stimulus specific adaptation or deviance detection. In this study, we measured MMN, evaluated effects of adaptation and deviance detection, and examined whether reduced MMN in patients with schizophrenia is due to impairments of adaptation or deviance detection. Methods: Patients with schizophrenia (N=25) and healthy comparison subjects (N=27) participated in this study. We recorded electroencephalography during an oddball paradigm and a many standards paradigm. We measured MMN and evaluated effects of adaptation and deviance detection on MMN amplitude. Results: MMN amplitude was reduced in patients with schizophrenia compared to healthy comparison subjects. Patients with schizophrenia showed no impairments in the effects of adaptation on MMN compared to healthy comparison subjects. On the other hand, patients with schizophrenia showed impairments in the effects of deviance detection on MMN compared to healthy comparison subjects. Impaired deviance detection was correlated with severe positive symptoms in patients with schizophrenia. Conclusion: We found that impaired deviance detection, but not adaptation, affected reduced MMN amplitude in patients with schizophrenia. In addition, the impaired deviance detection was significantly correlated with severe positive symptoms. These findings show that reduced MMN in patients with schizophrenia is due to impairments of not adaptation but deviance detection, and that impaired deviance detection is associated with positive symptoms in schizophrenia. Therefore, investigating neural mechanisms underlying deviance detection may be useful for revealing the pathophysiology of schizophrenia and developing new treatments for schizophrenia.

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Poster

336. Schizophrenia: Behavior and Symptoms

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Brain & Behavior Research Foundation NARSAD Young Investigator Award to AM
VA Research Enhancement Award Program (REAP) on Enhancing Community Integration for Homeless Veterans to MG

Title: Evaluating a potential marker of plasticity in schizophrenia: Perceptual learning in visual search

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Abstract: Numerous forms of learning and memory are impaired in schizophrenia, and these impairments are strong predictors of functional disability in the disorder. Similarly, various abnormalities in visual perception exist in schizophrenia and predict individuals' level of functioning. However, little is known about potential impairments in perceptual learning, at the intersection of these two cognitive domains. In the present study, we adapted an established paradigm to rapidly induce and measure perceptual learning using a visual search task in both outpatients with chronic schizophrenia (N=31; mean age=49; 20 male/11 female) and matched healthy controls (N=17; mean age=47; 11 male/6 female). Across five 20-minute testing sessions completed over two days, participants viewed arrays of visual stimuli in which a target stimulus could be present (50% of trials) or absent (50%), among a variable number of similar distractor stimuli. All search stimuli were bisected disks with red and green halves; targets could be distinguished from distractors by the configuration of the two elements (e.g., red-left/green-right vs. green-left/red-right). Such searches are ordinarily slow and inefficient but tend to become more efficient with training in healthy undergraduates. Participants responded 'target' or 'no target' to each array, and reaction times were recorded. Search efficiency was quantified by assessing the relationship between the number of search stimuli and reaction time, from which the search time per item was inferred. Decreases in the search time per item were considered evidence of perceptual learning. Steady-state visually evoked potentials associated with search targets and distractors were also assessed using electroencephalography before and after training. Behavioral data from both groups showed an expected linear relationship between the number of search stimuli and reaction time, indicating that participants performed the task correctly and the data were valid. However, the two groups combined showed only marginally significant

perceptual learning (p=0.09), and there was no significant difference in the amount of learning between the two groups. This could suggest that this type of perceptual learning might be relatively impaired by mid to late adulthood in general, but not substantially different between people with chronic schizophrenia and matched community controls.

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Poster

336. Schizophrenia: Behavior and Symptoms

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Program #/Poster #: 336.05/JJJ30

Topic: H.03. Schizophrenia

Support: JP16H05380
JP25861040
JP25253074

Title: Pyridoxamine, a novel treatment for negative symptoms of schizophrenia

Authors: *M. ARAI[1], M. MIYASHITA[2], K. TORIUMI[3], Y. HORIUCHI[4], A. KOBORI[4], M. ITOKAWA[4]
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Abstract: The aim of this clinical trial was to obtain proof of concept for high-dose pyridoxamine as a novel treatment for schizophrenia with enhanced carbonyl stress. Ten Japanese schizophrenia patients with high plasma pentosidine, which is a representative biomarker of enhanced carbonyl stress, were recruited in a 24-week, open trial in which high-dose pyridoxamine (ranging from 1200 to 2400 mg/day) was administered using a conventional antipsychotic regimen. Main outcomes were the total change in Positive and Negative Syndrome Scale score and the Brief Psychiatric Rating Scale score from baseline to end of treatment at week 24 (or at withdrawal). Decreased plasma pentosidine levels were observed in eight patients. Two patients showed marked improvement in their psychological symptoms. A patient who harbors a frameshift mutation in the Glyoxalase 1 gene also showed considerable reduction in psychosis accompanied with a moderate decrease in plasma pentosidine levels. A reduction of greater than 20% in the assessment scale of drug-induced Parkinsonism occurred in four patients. Although there was no severe suicide-related ideation or behavior, Wernicke's encephalopathy-like adverse drug reactions occurred in two patients and were completely suppressed by thiamine supplementation. High-dose pyridoxamine add-on treatment was, in part, effective for a subpopulation of schizophrenia patients with enhanced carbonyl stress. Further randomized,

placebo-controlled trials with careful monitoring will be required to validate the efficacy of high-dose pyridoxamine for these patients.

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Poster

336. Schizophrenia: Behavior and Symptoms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 336.06/JJJ31

Topic: H.03. Schizophrenia

Support: NIH grants R01 MH37705 and P50 MH066286
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Title: White matter integrity correlates with measures of insight in first-episode schizophrenia: A diffusion tensor imaging study

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Abstract: Poor awareness that one has a psychotic disorder is common in schizophrenia, and negatively impacts clinical treatment and symptom management. Following our previous magnetic resonance imaging (MRI) study of schizophrenia patients, which was suggestive of poor connectivity being associated with unawareness, we hypothesized that the disruption of white matter integrity underlies poor insight. This study utilized diffusion tensor imaging (DTI) data from 1.5T MRI scans and data quantifying insight using the Scale for Unawareness of Mental Disorder-Revised (SUMD-R). Tract-Based Spatial Statistics (TBSS, part of FSL) were used to quantify regional differences in average fractional anisotropy (FA), which provides information about white matter microstructural integrity. A preliminary cross-sectional analysis of 35 subjects with first-episode schizophrenia showed that lower average FA values of the following white matter regions of interest were associated with unawareness of the patient's own reduced information processing speed: portions of the corona radiata, the corpus callosum (genu, body, and splenium), the tapetum, the uncinate fasciculus, the medial lemniscus, portions of the cingulum and fornix, portions of the internal capsule, and portions of the external capsule. These preliminary findings suggest that reduced white matter integrity may be associated with poor insight in individuals with first-episode schizophrenia. The significance of these findings lies in the value of creating a more complete neuroanatomical profile for insight in schizophrenia, both

for developing a better understanding of insight and to improve opportunities for successful clinical interventions and treatment.

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Poster

336. Schizophrenia: Behavior and Symptoms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: H.03. Schizophrenia

Support: Swiss National Science Foundation (320030_122419 to P.C. and KQ.D., 310030_156874 to PH)
National Center of Competence in Research (NCCR) "SYNAPSY - The Synaptic Bases of Mental Diseases" financed by the Swiss National Science Foundation (n° 51AU40_125759)

Title: Redox dysregulation: A link between childhood trauma and poorer clinical outcome in early psychosis patients

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Abstract: Exposure to childhood trauma (CT) increases the risk for psychosis and affects the development of brain structures, possibly through oxidative stress (OS). Since OS is also linked to psychosis, it may interact with CT, leading to a more severe clinical phenotype. In a cohort of 133 early psychosis patients (EPP), we explored the relationships between CT and hippocampal volume, blood antioxidant defense systems (glutathione peroxidases (GPx) and thioredoxin/peroxiredoxin (Trx/Prx), and psychopathological and neuropsychological outcomes. We found that in CT patients, the hippocampal volume correlated negatively with GPx activity, which was not the case for patients without CT. In CT patients with high GPx activity (High-GPx+CT patients), hippocampal volume was decreased compared with that in Low-GPx+CT patients and patients without CT who had similar hippocampal volumes. High-GPx+CT patients had more severe positive, negative and disorganized symptoms than the other patients. Interestingly, Trx levels and oxidized Prx levels correlated negatively with GPx only in Low-GPx+CT patients. Moreover, Low-GPx+CT patients perform better than other patients on cognitive tasks. Discriminant analysis combining redox markers, hippocampal volume, and clinical and cognitive scores allowed for the stratification of the patients into subgroups. In conclusion, traumatized EPP with high peripheral oxidation status (high GPx activity) had smaller hippocampal volumes and more severe symptoms, while those with a lower oxidation status (low GPx activity) showed better cognition and regulation of GPx and Trx/Prx systems. These results suggest that maintained regulation of various antioxidant systems allowed for compensatory mechanisms preventing long-term neuroanatomical and clinical impacts. The redox marker profile may thus represent important biomarkers for defining treatment strategies at early stages of psychosis.

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Poster

336. Schizophrenia: Behavior and Symptoms

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Topic: H.03. Schizophrenia

Support: NIMH Grant R21 MH096177
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Title: Dysrupted modulation of thalamus activation and thalamocortical connectivity during task performance in schizophrenia

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Abstract: Introduction: Modulation of thalamic connectivity with the prefrontal cortex (PFC), a region believed to be core to the pathogenesis of schizophrenia, is required for higher-order cognitive abilities, including attentional control, which are often impaired in schizophrenia. Despite considerable evidence finding that thalamus anatomy and connectivity are abnormal in schizophrenia, how these abnormalities are reflected in thalamus function during cognition is relatively understudied. To address this gap, we investigated how thalamic function and thalamus-PFC connectivity under different levels of cognitive demand may be dysrupted in schizophrenia.
Method: Thirty-nine participants (19 healthy individuals and 20 individuals with schizophrenia) underwent fMRI scanning while performing an event-related two-alternative forced choice task under Single and Dual Task conditions. In the Single Task condition, participants responded either to a visual cue with a well-learned motor response, or an audio cue with a well-learned vocal response. In the Dual Task condition, participants performed both tasks. Thalamic connectivity with task relevant regions of the PFC for each condition was measured using beta-series correlation.
Results: Individuals with schizophrenia demonstrated an ability to modulate PFC, but not thalamic activation by task demand, while healthy subjects showed modulation in both regions. They also failed to demonstrate the expected modulation of thalamus-PFC connectivity by task demand observed in healthy subjects.
Discussion: Individuals with schizophrenia showed a reduced ability to modulate both thalamic responses and thalamus-PFC connectivity with increased cognitive demand, while, in the current task, their ability to modulate PFC function appears to be maintained. It is possible that in schizophrenia, the thalamus may be dysrupted at lower levels of task demand than the PFC.

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Poster

336. Schizophrenia: Behavior and Symptoms

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 336.09/JJJ34

Topic: H.03. Schizophrenia

Title: Schizophrenia and semantic processing: Cognitive state and brain electrical activity

Authors: *F. A. ROBLES[1,2], L. R. ROMERO[1], V. VALDEZ VELASCO[1], D. L. CANELA[1], A. LARA ZARAGOZA[3]
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Abstract: Schizophrenia affects more than 21 million people worldwide (WHO, 2016). In Mexico, 11,553 are treated (WHO, 2016-2012). Studies have shown a progressive grey-matter loss from parietal and temporal to frontal lobes with overactivation of cortico-limbic circuits, correlated with early deficits in neuropsychological function (Pantelis *et al*., 2003). A core feature of Schizophrenia is the disorganized speech that aims to particularities in semantic processing. For example, N400 has shown an enhancement in amplitude for sentence priming tasks (Nestor *et al.* 1997) or a reduction of the N400-effect in the evaluation of congruity in sentence endings or priming words (Ohta, 1999; Kiang *et al.,* 2012), suggesting Schizophrenia patients exhibit distinct functional connections among concepts within semantic memory depending on the differences in controlled (decreased amplitudes at longer SOA) or automatic semantic processing (increased activation at short SOA) (Minzenber *et al.*, 2002; Ditman and Kuperberg, 2007). Cohn and Kutas (2015) proposed N400 frontal negativity probably indexes working memory instead of semantic processing. The present study evaluates Schizophrenia patients (n=10, 5 patients, 6 women, ages *M*=31.4*; t=1.67, p=0.13;* 8.6, Spanish speakers) that responded to three tasks: 1) semantic congruity (100 trials, 4-word phrase, “A cat can bark”); 2) visual sequences (80 trials with 4 images, 40 exchanged endings); 3) semantic matching (100 trials with 4 images, 50 with unrelated final stimuli). Trials began with a plus sign in a dark screen center for 400 ms, followed by 4 stimuli (1350 ms each), separated by a 200 ms dark screen. Last stimulus was preceded by an interrogation sign. ITI was variable (216.67-1366.67 ms). Patients presented normal-to-mild cognitive impairment (MMSE: *M*=27.40 *SD*=2.19; CI: *M*= 68.80, *SD*=14.44) and a prolonged time without treatment (*M*=9.76, *SD*=9.72 years). Patients were significantly slower (t=2.387; p=.04) and made more errors (t=3.819; p=.005) in semantic congruity. They also differ from controls in the number of errors in visual sequences (t=0.301; p=.01) but not in semantic matching (t=1.87; p=.09). This shows deficits in the semantic congruity seem related to sequential more than semantic processing in Schizophrenia patients. During tasks electrical activity was registered (19 electrodes, 10-20 system). N400 amplitudes and latencies will be shown. As typical antipsychotic medication provides modest-to-moderate gains in multiple cognitive domains (Mishara and Golberg, 2004), the delay in receive treatment in these patients adds to the cognitive deterioration.

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Poster

336. Schizophrenia: Behavior and Symptoms

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Topic: H.03. Schizophrenia

Support: NIH MH112793
CTRI 02789

Title: Update on a longitudinal pilot study to assess the effects of gamma neurofeedback on cognitive function in schizophrenia patients

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Abstract: Cognitive deficits are a common and recalcitrant symptom of schizophrenia (SCZ) spectrum disorders and have been associated with reduced gamma band (35-50Hz) responses (GBR) in frontoparietal regions of the brain. Neurofeedback (NFB) is an operant conditioning methodology used to train individuals to volitionally control brain oscillatory activity, and has been shown to influence frontoparietal neural circuitry in healthy populations. Therefore, we tested the feasibility of administering NFB to enhance GBR in patients with SCZ. The primary aim of the study is to assess target engagement, and determine whether GBR can be trained reliably in a SCZ population. A secondary aim is to determine whether changes in GBR influence downstream targets, including behavioral variables. We are conducting an open label study in adults between the ages of 18-65, who met DSM-V criteria for SCZ or schizoaffective disorder. All subjects will undergo 12 weeks of NFB, for 2 sessions a week. Brain function (EEG), neuropsychological variables and community functioning assessments are conducted at baseline and post-treatment. To date, 6 subjects have completed 4 weeks of NFB training. Preliminary data analysis indicates 1) target engagement as evidenced by changes in NFB training threshold, 2) changes in brain function as assessed by EEG, including increased gamma power in the resting state over frontal brain regions (F3, F4) and 3) and increases in Processing speed, attention/vigilance and visual learning. Additional analyses are underway to determine NFB's effects on event-locked brain activity, specifically in response to cognitive tasks.These early results indicate that patients with SCZ can implement operant conditioning approaches such as NFB, and that EEG can be used to detect brain changes as early as 4 weeks. Therefore, NFB has the potential to serve as a useful adjunctive treatment in clinical settings to help treat cognitive deficits associated with schizophrenia spectrum disorders.

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Poster

337. Schizophrenia: Circuits and Systems

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Program #/Poster #: 337.01/JJJ36

Topic: H.03. Schizophrenia

Title: Bayesian inference explains frequency perception in humans: Neural correlates and relationship to psychosis

Authors: *E. LAGACHE[1], G. HORGA[2]
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Abstract: Bayesian models of perception posit that percepts result from an optimal integration of new sensory information and prior knowledge or beliefs. In turn, prominent models of altered perception in psychosis suggest that pathological illusions and hallucinations may represent percepts that are excessively biased towards prior beliefs. The current study represents an ongoing effort to determine the neural mechanisms underlying the integration of new sensory information and prior knowledge in healthy and pathological conditions.
To this end, we have designed a new magnitude-estimation task in which subjects reproduce the frequency (pitch) of tones drawn from uniform distributions with varying widths. In parallel, we are leveraging recent advances in population receptive field (pRF) models of functional magnetic resonance imaging (fMRI) to optimize tonotopic mapping of the primary auditory cortex (PAC). Finally, we are testing the ability of Bayesian models of perception to explain the behavioral data and changes in the individual tonotopic maps that may underlie interindividual differences in frequency-reproduction behavior.
In a pilot study in healthy individuals (n=10), frequency-reproduction behavior exhibits a significant characteristic signature of Bayesian perception. These individuals tend to overestimate frequencies lower than the mean of the sampled distribution and underestimate frequencies higher than the mean. This “central tendency” suggests integration of prior knowledge and can be well explained by a Bayesian model that seeks to minimize reproduction error by incorporating a central-tendency prior. Data collection for psychosis-prone individuals is in progress. We expect that psychosis-prone individuals will exhibit higher central tendency than socio-demographically matched healthy controls, indicating a greater bias toward prior beliefs. Interindividual differences in tonotopic maps in PAC derived from fMRI data in patients and controls are expected to match the interindividual differences in frequency-reproduction behavior.

In conclusion, our pilot results provide a first demonstration that models of Bayesian inference can be applied to frequency perception in humans. Leveraging this novel approach and pRF methods for tonotopic mapping may provide a fruitful avenue to understand the neural mechanisms of perceptual inference in the human brain. In turn, an improved understanding of these neural mechanisms may advance our understanding of pathological conditions characterized by perceptual abnormalities, including hallucinations in schizophrenia and those in other neuropsychiatric illnesses.

Disclosures: E. Lagache: None. **G. Horga:** None.

Poster

337. Schizophrenia: Circuits and Systems

Location: SDCC Halls B-H

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Program #/Poster #: 337.02/JJJ37

Topic: H.03. Schizophrenia

Title: Thalamo-cortical structural connectivity in schizophrenia and bipolar disorder

Authors: *J. CHO[1], J. C. THOMPSON[2]
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Abstract: Schizophrenia (SZ) and bipolar disorder (BD) are debilitating mental illnesses with overlap in genetic, cognitive, clinical and functional brain connectivity characteristics. Recent resting-state (rsfMRI) connectivity studies have found a pattern of over-connectivity between the thalamus and sensory-motor regions but under-connectivity between the thalamus and prefrontal cortex in SZ as well as BD, but with attenuated effects. Structurally, abnormalities between the thalamus and cortex have been observed in SZ and BD but studies examining the structural relationship between the thalamus to frontal and motor cortices are sparse. The aim of this study was to investigate structural connectivity from specific thalamic nuclei to the cortex and its relationship to clinical symptoms.
All subjects were part of the UCLA Consortium for Neuropsychiatric Phenomics dataset freely shared online through the OpenfMRI project. First, masks of the prefrontal (PT) and motor (MT) regions of the thalamus were created using the Johansen-Berg et al, thalamic atlas in FSL to perform tractography between the thalamic regions and the fronal and motor cortices. Diffusion weighted images were preprocessed using FSL's FDT toolbox and underwent DTIFIT, BEDPOSTX and PROBTRACKX. Tracts were thresholded using the waypoint method and binarized to create a mask for extraction of fractional anisotropy (FA).
There was a significant difference between groups on tract FA as determined by a one-way MANCOVA after controlling for age, $F(4,428) = 2.701$, $p < 0.05$, *Pillai's* Trace = 0.049, partial $\eta 2 = 0.025$. Follow-up univariate tests revealed a significant difference between groups on PT to frontal tract FA, $F(2,214) = 3.340$, $p < 0.05$, partial $\eta 2 = 0.030$, but no difference between

groups on MT to motor cortex tract FA. A Tukey-kramer post hoc test showed significantly greater tract FA in HC (.144±0.90) compared to SZ (-.284±.142), $p < 0.05$). BD showed intermediate values between HC and SZ but no significant differences in pairwise tests. Correlation analyses revealed a significant positive correlation between PT to frontal FA and MT to motor cortex FA, ($r = .536$, $p < 0.05$) and a significant negative correlation between PT to frontal FA and negative symptoms ($r = .225$, $p < 0.05$) - patients with greater thalamo-frontal tract FA have less severe negative symptoms. We replicated findings that SZ is associated with abnormal structural connectivity between the thalamus and frontal cortex but not in BD. However, our cohort showed a relationship between the two thalamo-cortical tract FAs in addition to clinical symptoms. This might indicate that BD shares similar but reduced structural abnormalities with SZ.

Disclosures: J. Cho: None. **J.C. Thompson:** None.

Poster

337. Schizophrenia: Circuits and Systems

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 337.03/JJJ38

Topic: H.03. Schizophrenia

Support: NIH Grant R01MH101102

Title: KCNH2-3.1 impairs neural connections between hippocampus and mPFC

Authors: *F. YANG, Z. HU, M. REN, D. R. WEINBERGER
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Abstract: The KCNH2-1A potassium channel conducts delayed-rectifier potassium currents that have a rapid activation and relatively slow inactivation in deactivation kinetics. Our previous work has identified a novel primate isoform of KCNH2-1A channel, the KCNH2-3.1 potassium channel, in human brain that is upregulated in schizophrenia. Our previous studies also showed that KCNH2-3.1 transgenic mice exhibit alterations in neuronal structure and microcircuit function in the hippocampus and prefrontal cortex, areas affected in schizophrenia. It has been proposed that failure of functional integration and flow of information between hippocampus and mPFC results in cognitive deficits in schizophrenia patients. The possibility of synaptic impairments between hippocampus and mPFC as key pathophysiological mechanisms associated with schizophrenic phenotypes in KCNH2-3.1 mice has not been explored before. In this study, to investigate structural connectivity in these mice, we measured synaptic density on mPFC layer V pyramidal neurons innervated from hippocampal CA1 axonal terminals. To examine this, we injected AAV DJ-CaMKIIa-hChR2(H134R)-eYFP into the ventral hippocampus of KCNH2-3.1

and control litter mates, and used Imaris software to perform 3D reconstruction of confocal images to quantify the number of hippocampal CA1 axonal boutons in mPFC. Confocal imaging showed a substantial reduction of synaptophysin+ puncta density in the mPFC innervated from ventral hippocampal CA1 pyramidal neurons of KCNH2-3.1 mice. We further injected AAV DJ-syn-VAMP2-Flag into the ventral hippocampus of Thy1-eYFP-H/NSE/KCNH2-3.1 transgenic mouse, and used the Imaris software to quantify hippocampal CA1 VAMP2-Flag-expressing boutons over the YFP-expressed dendritic spine formation of layer V pyramidal neurons of mPFC in KCNH2-3.1 transgenic mice. Compared to control mice, pyramidal neurons in KCNH2-3.1 mice showed significantly decreased synaptic innervation, further confirming that overexpression of KCNH2-3.1 isoform impairs synapse formation of hippocampal CA1 axonal boutons onto mPFC layer V pyramidal neurons. These findings provide further insights into the precise alterations in hippocampal-mPFC connectivity observed in this schizophrenia-associated animal model, and could ultimately help elucidate the molecular and cellular basis underlying schizophrenia pathogenesis.

Disclosures: F. Yang: None. **Z. Hu:** None. **M. Ren:** None. **D.R. Weinberger:** None.

Poster

337. Schizophrenia: Circuits and Systems

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Program #/Poster #: 337.04/JJJ39

Topic: H.03. Schizophrenia

Title: Schizophrenia is characterized by reduced functional connectivity between memory and reward circuits during learning

Authors: *S. HASAN[1], M. HUQ[1], A. Z. CHOWDURY[1], J. A. STANLEY[1], A. ROBISON[2], K. N. THAKKAR[3], V. A. DIWADKAR[1]
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Abstract: Background
Schizophrenia (SCZ) is characterized by altered dopamine sensitivity, which may in turn affect reward related processes that are omnipresent during task acquisition and processing (Gray et al.,1991). From this general framework, compared functional connectivity (FC) between three regions of the brain, the Nucleus Accumbens (NAcc), Ventral Tegmental Area (VTA), and the Hippocampus (Hipp) in a task-active state in SCZ and healthy controls (HC). Experimentally driven associative memory was induced using an established paradigm (Stanley et al., 2017). The three regions are noted for their roles in reward processing (NAcc & VTA) and memory (Hipp). Our interest was whether FC was significantly lower in SCZ. Alterations in FC between either of the NAcc and/or VTA and Hipp would suggest abnormal functional interactions between

memory and reward related circuits in SCZ.

Methods

fMRI data were acquired from forty one participants (22 SCZ, 19 HC; 3T Siemens Verio) while they performed an associative memory task. During the task they learned associations between nine object-location pairs (~13 minutes). fMRI data were processed using typical methods (SPM12) with epochs representing distinct task phases (Encoding, Rest and Retrieval). The sub-network of regions (NAcc, VTA, Hipp) were motivated using previously defined nodes (Kahn et al, 2013). Montreal Neurological Institute (MNI) coordinates used were: NAcc [-11 4 0]; VTA [-4 -15 -9]; Hipp [-26 -22 14]. Time series from these coordinates were forwarded for FC analyses. Correlation coefficient were computed and normalized to bivariate distribution curve (Fisher's Z) and were submitted for statistical inference. Independent sample t-tests were employed to assess differences between each of the sub-network pairs.

Results

SCZ participants were characterized by reduced FC between the Hipp and VTA ($p<0.02$), with marginally significant reductions between the NAcc and VTA ($p=0.05$, one-tailed).

Discussion

Because reward related processing is expected to underlie successful acquisition of complex tasks, it is expected that brain regions associated with reward and task processing will show functional integration. We proposed that impaired reward sensitivity in SCZ may mediate a loss of functional integration between task relevant regions (Hipp) and reward related regions (VTA and/or Nacc). Our results provide preliminary evidence for this effect, as well as a loss of integration within the reward circuit (VTA and Nacc). Impaired cognitive processing in SCZ may be integrally linked to impaired reward processing, and the disconnection between these underlying systems should be further investigated.

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Poster

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Program #/Poster #: 337.05/JJJ40

Topic: H.03. Schizophrenia

Support: NIMH Grant P50 MH084053
NIMH Grant K08 MH080329

Title: Recovery of theta-gamma phase-amplitude coupling following single dose administration of amphetamine in patients with schizophrenia

Authors: *N. MURPHY[1], N. R. POLIZZOTTO[2], C. P. WALKER[1], N. RAMAKRISHNAN[1], R. Y. CHO[1]
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Abstract: Background
Dopaminergic modulation of sensory cortical gamma oscillations in schizophrenia patients, through single dose amphetamine administration remediates impaired entrainment to levels closer to that of control subjects after placebo administration (Komek et al., 2012). However, it remains unclear whether this is linked also to any improvements of amplitude modulation by the phase of low frequency oscillations. Our aim was to investigate the link between dopaminergic drive and the modulation of gamma oscillations via cross-frequency coupling (CFC) in patients with schizophrenia.
Methods
N = 12 patients with schizophrenia and N = 12 healthy controls were presented with 40 Hz auditory click train stimuli (500 ms) during 129 channel electroencephalograph (EEG) recording. A double-blind crossover placebo-controlled design was used to test within groups effects of oral dextroamphetamine (0.5 mg/kg) on the auditory steady state response. Placebo and amphetamine visits were separated by a minimum of 5 days. We evaluated CFC at a region of interest (N = 10 electrodes) surrounding and including FCz estimated as the mutual information between gamma(40 Hz ± 14 Hz) band amplitudes and delta (2-4 Hz), theta (4-8 Hz), and alpha (8-14 Hz) phases during the stimulation period. Mutual information scores were normalized by Z-transformation using the distribution of 100 surrogate coupling values.
Results
In the placebo condition coupling was significantly lower in patients than controls for the theta-gamma comparison (p = .009). The net effect of amphetamine was to increase theta-gamma coupling in patients (p = .034) and to decrease theta-gamma coupling in controls (p = .031), with the overall change between conditions being significantly greater in patients (p = .003). Despite reduced control CFC there was no significant difference between groups in the amphetamine condition. No effects were detected for alpha-gamma and delta-gamma comparisons
Conclusions
Our findings suggest that dopamine modulation in schizophrenia can improve impaired CFC but in healthy controls can impair intact CFC. This pattern is similar to our prior findings of dopamine modulation of gamma power in patients vs. healthy controls (Komek et al, 2012), and consistent with prior reports of an inverted-U relationship between dopamine levels and cortical function (Williams & Castner, 2006). This suggests that dopamine modulation in patients not only can remediate gamma oscillatory activity in cortical circuits, but also help in restoring the CFC of such gamma activity with lower frequency rhythms.

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Poster

337. Schizophrenia: Circuits and Systems

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Data was downloaded from the Collaborative Informatics and Neuroimaging Suite Data Exchange tool. Data was collected at the Mind Research Network, funded by a Center of Biomedical Research Excellence grant 5P20RR021938/P20GM103472 from NIH.

Title: Resting state functional connectivity abnormalities in schizophrenia

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Abstract: Functional connectivity (FC) is a measure of the temporal correlation among anatomically distinct brain regions underlying large-scale brain networks. It has been widely demonstrated that patients with schizophrenia (SZ) show FC abnormalities throughout the brain. Yet, it is not clear from the current literature whether resting state dysconnectivity continues to deteriorate with disease progress.
Methods: We first investigated FC differences between healthy controls (HC) (n=18) and SZ patients (n=25), with high demographic selectivity: males with a strict SZ diagnosis, stable medication adherence and a similar age of disease onset. Second, we probed the effect of disease progress on FC in SZ subjects between two age groups: early (n=8) versus late 20s (n=8). Finally, in order to isolate the effects of disease progress from normal aging, we investigated FC differences in HCs between two age groups: early (n=6) versus late 20s (n=6). Seed based and parcellation based analysis techniques were used to calculate the Pearson's correlation between the time-courses of each brain region of interest (ROI).
Results: We identified significant FC differences in 365 ROI-pairs between SZ and HC, 135 ROI-pairs between old and young SZ, and 40 ROI-pairs between old and young HC. Results showed dysconnectivity in SZ across the entire brain, primarily in the default mode network (DMN), thalamo-cortical and cerebello-cerebral connectivity. Specifically, the DMN showed hyperconnectivity in SZ patients. Additionally, we found interhemispheric FC abnormalities in SZ, primarily in somato-motor regions, the cingulate gyrus and the inferior parietal lobe. Taken together, our findings demonstrate inter-regional and inter-hemispheric FC abnormalities in SZ. We further found a disease-progress driven exacerbation of FC in as short a period of time as early versus late 20s. This exacerbation was mostly evident in PFC connectivity to thalamus,

cerebellum, precuneus and limbic regions. Hyperconnectivity of the DMN was significantly higher in older patients. This effect was insufficiently explained by aging related factors alone. **Conclusion:** These results extend prior literature indicating that brain networks measured by resting state fMRI are abnormally organized in SZ, with a disease progress driven exacerbation. Higher FC abnormalities seen in older patients -despite stabilization on antipsychotic treatment- may be evidence of the inefficacy of currently available pharmacologic interventions in treating negative and cognitive symptoms. Our findings further demonstrate the clinical potential of resting state FC as a biomarker for early diagnosis and treatment of SZ.

Disclosures: E. Sefik: None. **A. Abbas:** None. **S. Keilholz:** None.

Poster

337. Schizophrenia: Circuits and Systems

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Topic: H.03. Schizophrenia

Support: NIH Grant MH100820

Title: The prefrontal cortex follows the respiration-coupled rhythm during waking and REM-sleep, but not during slow-wave sleep

Authors: *R. MOFLEH, B. KOCSIS
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Abstract: Breathing in rodents normally appears in a wide range of frequencies, overlapping with delta and theta oscillations in brain activity. Recent studies reported that the respiratory rhythm, mediated by monitoring nasal air movement by the olfactory bulb (OB), may promote synchronous oscillations globally in the brain including higher-order brain networks, such as prefrontal cortex (PFC) and hippocampus (rev. Tort et al., 2018). It remains important to clarify, however, what these networks use respiratory synchrony for—as well as when, how, and why. In the present study we investigated the relationship between respiratory rhythm and PFC oscillations, and the contribution of OB to it, in rats during two different stages of sleep, REM-sleep and slow-wave sleep (SWS), as well as two awake states, quiet (QW) and active waking (AW), also identified as non-theta and theta states. Local field potential (LFP) was recorded from OB, PFC, and hippocampus along with neck muscle EMG in undisturbed freely behaving rats while respiratory rhythm was monitored by direct recording of diaphragmal activity (EMG). We found that the prominent PFC oscillations in the delta range synchronize with respiratory rhythm in a state-dependent manner. Coherence between diaphragmal EMG and PFC (dia-PFC) was significantly ($p<0.04$) lower in SWS (0.12+0.03) than in any other state (between 0.37 and 0.68 in AW, QW, REM). Respiratory-OB coherence (dia-OB) did not necessarily show this

relationship, it was not significantly different for example between SWS and REM sleep (p=0.34). Furthermore, within states, dia-PFC did not significantly correlate with dia-OB (R2 between 0.0005 and 0.2534 in SWS, QW, AW and 0.675 only in REM) indicating that OB transfer of respiratory rhythm to PFC was strongly modulated by inputs mediating the level of arousal. Accordingly, dia-PFC and OB-PFC strongly correlated in theta states (0.87 in REM and 0.57 in AW) and less in non-theta states (0.03 in SWS, 0.37 in QW).The prefrontal cortex (PFC) contributes to different cognitive functions and is highly interconnected with various cortical and subcortical structures. Specifically we have shown the importance of a 2-5 Hz rhythm in this communications (Roy et al., 2017). The results of this study indicate that respiratory synchronization may also be involved in generating state- and task-dependent PFC outputs.

Disclosures: R. Mofleh: None. **B. Kocsis:** None.

Poster

337. Schizophrenia: Circuits and Systems

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Title: Loss of dendritic inhibition in pharmacological and genetic mouse models related to schizophrenia

Authors: *F. ALI, D. M. GERHARD, R. S. DUMAN, A. C. KWAN
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Abstract: Schizophrenia (SZ) is a major psychiatric disorder, generally thought to involve an imbalance in excitation and inhibition. However, the precise circuit mechanisms underlying such imbalance are unclear. Here, we uncovered a cortical dendritic disinhibition phenotype involving deficits in somatostatin-positive interneurons (SOM-IN) in two different mouse models related to schizophrenia. We first injected adult mice with systemic ketamine (KET model), an NMDA receptor antagonist that is also a psychotomimetic drug widely used as an acute pharmacological model related to SZ. Combining this with *in vivo* two-photon calcium (GCaMP6) imaging, we found elevated spontaneous calcium transients in layer 1 apical dendritic spines of excitatory neurons (EXC) in dorsomedial portion of prefrontal cortex (dmPFC - Cg1/M2). The same hyperactive spine calcium phenotype was also observed in dmPFC of *Shank3*-R1117X (*Shank3* model) mice with a rare, highly penetrant SZ-related mutation in the *Shank3* gene important for

glutamatergic synapses. We further found that this EXC spine hyperactivity was associated with reduced activity of dendrite-targeting SOM-IN in layer 2/3 and their layer 1-projecting axons in both the KET and *Shank3* models. Together, our convergent results in mouse models suggest reduced SOM-IN activity that releases the dendritic spines from inhibition i.e., disinhibition. Because layer 1 is an important site of cortico-cortical processing, we further examined the consequences of dendritic disinhibition on long-range cortical information processing via two experiments in the KET model. First, we electrically stimulated the retrosplenial cortex (RSC), which sends dense projections to dmPFC layer 1 while imaging the dendritic spines in layer 1 of dmPFC. We found that ketamine increased the response of EXC dendritic spines to long-range RSC inputs, particularly at high stimulation frequency regimes. In the 2nd experiment, we recorded local field potentials (LFP) simultaneously in RSC and dmPFC, finding an increased field-field coherence between the two areas after ketamine injections. Overall, our imaging experiments provide a potential circuit basis for the widely-found hyperconnectivity phenotype in SZ: a hypofunction in dendrite-targeting SOM-IN associated with disinhibition of dendritic spines, leading to long-range hyperconnectivity. We hypothesize that loss of SOM-IN activity is due to a deficit in NMDAR function, reducing excitatory drive to SOM-IN. We are currently testing this hypothesis using viral strategies and pharmacological manipulations in both KET and *Shank3* models during *in vivo* imaging and behavior.

Disclosures: F. Ali: None. **D.M. Gerhard:** None. **R.S. Duman:** None. **A.C. Kwan:** None.

Poster

337. Schizophrenia: Circuits and Systems

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Title: Maternal immune activation alters cortical catecholaminergic function and induces cognitive impairment in offspring

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Abstract: Schizophrenia is a chronic and disabling mental disorder with an early onset. Cognitive deficits start early and are present together with classical schizophrenia symptoms. The dorsolateral prefrontal cortex (DLPFC) is the main anatomical pathway modulating cognitive activities and is critical for executive function. Interestingly, the postsynaptic alpha-2 adrenoceptors located on pyramidal cells of the DLPFC, that maintain basal cognitive activity, seem to be underactive in schizophrenic patients. Importantly, one of the most significant environmental risk factors for the development of schizophrenia is prenatal exposure to infection. Indeed, maternal immune activation (MIA) in animals produces behavioral and neurochemical aberrations considered relevant in models of schizophrenia. The aim of this study was to evaluate a MIA model mimicking prenatal viral infection by the administration of poly(I:C) to pregnant dams (7.5 mg/kg ip, gestational day 9.5). We evaluated cognitive impairments of adult offspring by the novel-object recognition test (NORT) in the presence and absence of either the alpha-2 agonist (guanfacine 0.1 mg/kg ip) or the alpha-2 antagonist (MK-912 0.05 mg/kg ip). In addition, we measured extracellular dopamine and norepinephrine (NE) concentrations in prefrontal cortex (PFC) by microdialysis. Poly (I:C) mice showed decreased novel object discrimination in the NORT compared with controls, demonstrating a cognitive deficiency. Interestingly, both the alpha-2 agonist (guanfacine) and the alpha-2 antagonist (MK-912) were able to reverse that deficiency in the Poly (I:C) offspring. Therefore, the cognitive impairment produced by MIA in offspring could be related to alterations in the noradrenergic pathways of the PFC that control cognitive processes. To determine the sufficiency of increased PFC noradrenergic tone in reversing the MIA-induced cognitive impairment, we sought to selectively manipulate this projection in vivo. To do so, we genetically targeted channelrhodopsin-2 to only locus coeruleus noradrenergic (LC-NE) neurons used local photostimulation to increase LC-NE terminal activity in the PFC following MIA. Together these results suggest that noradrenergic tone is important for regulating cognitive function in the Poly (I:C) model of maternal immune activation. This approach provides a promising translational animal model for the study of cognitive dysfunctions present in schizophrenia.

Disclosures: B. Perez-Palomar: None. **J.E. Ortega:** None. **J.J. Meana:** None. **J.G. McCall:** None.

Poster

337. Schizophrenia: Circuits and Systems

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 337.10/JJJ45

Topic: H.03. Schizophrenia

Support: NIH Grant MH057440

Title: Adolescent stress during critical periods alters the developmental trajectory of hippocampal parvalbumin (PV) interneurons and recapitulates circuit dysfunction implicated in schizophrenia

Authors: *X. ZHU[1,2], F. V. GOMES[1,2], A. A. GRACE[1,2]
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Abstract: Adolescence is characterized by enhanced neuroplasticity and responsivity to external events. While this period facilitates many beneficial learning processes, it is also a vulnerable period with respect to detrimental environmental impacts. Indeed, our prior studies indicated that unregulated stress during adolescence is able to induce long-term behavioral deficits and circuit dysregulation leading to an adult condition analogous to schizophrenia (SCZ). Based on these observations, we evaluated the hypothesis that adolescence is both a sensitive period and a critical period for environment to modulate pathophysiological process of SCZ. Specifically, male Sprague-Dawley rats were submitted to a 10-day combined footshock (FS) and restraint stress (RS) during two stages (PD21-30 or PD31-40) during adolescence or at adulthood (>PD75). Using *in vivo* electrophysiology, the long-term effects (>PD75 and 5-6 weeks post-stress) on dopamine (DA) neuron activity in the ventral tegmental area (VTA) were evaluated. Parvalbumin (PV) intensity and PV neuron number were also evaluated in prefrontal cortex (PFC) and ventral hippocampus (vHipp) subregions 1, 10, 20 days post-stress and in adulthood. Our results showed that adolescent stress during PD21-30 or PD31-40 resulted in comparable DA system hyperresponsivity in the adult, and produced persistent PV cell loss in the ventral subiculum of vHipp and transient (only at 1 day post-stress) PV loss in the prelimbic regions of PFC. These effects were not observed for groups exposed to the same 10-day stress paradigm in adulthood. To examine whether adolescence may also be a critical period for attenuating pathophysiology, we used the methylazoxymethanol acetate (MAM) developmental disruption model of schizophrenia, and tested whether environmental enrichment (EE) during PD21-40 could ameliorate or prevent DA circuit dysregulation and structural abnormalities in adults. Our preliminary results suggested that adolescent EE is able to ameliorate the structural deficits in the vHipp and the DA hyperresponsitivity in the VTA, an effect not detected with adult EE (>PD75) groups. Altogether, this study suggests that early adolescence is perhaps both a sensitive and a critical period for deleterious as well as protective effects of the environment on schizophrenia.

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Poster

337. Schizophrenia: Circuits and Systems

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 337.11/JJJ46

Topic: H.03. Schizophrenia

Title: M4 muscarinic acetylcholine receptor leads to antipsychotic and precognitive efficacy in rodents

Authors: M. POPIOLEK[1], A. ROSSI[2], *Y. MANDELBLAT-CERF[3], D. YOUNG[4], S. LOTARSKI[2], L. ZHANG[2], C. BUTLER[2], R. KOZAK[4]
[1]Sage Therapeut., Cambridge, MA; [2]Pfizer, Cambridge, MA; [3]Biogen, Belmont, MA; [4]Biogen, Cambridge, MA

Abstract: Preclinical and clinical data suggest that muscarinic acetylcholine receptor activation may be therapeutically beneficial for the treatment of psychosis and cognitive impairment. This is best exemplified by clinical observations with xanomeline, whose efficacy is thought to be mediated through co-activation of the M1 and the M4 muscarinic acetylcholine receptors (mAChRs). Here we examined the impact of treatment with a novel M4 mAChR selective activator on striatal dopamine terminals in vivo. Through fiber photometry we observed attenuation of striatal dopamine activity. Outcome of the striatal mechanistic study was consistent with antipsychotic-like efficacy in behavioral assays including reversal of amphetamine locomotor activity and amphetamine prepulse inhibition. In addition to antipsychotic efficacy, we also found M4 mAChR to enhance rodent performance on attentional and cognitive readouts including the sustained attentional task under distractor condition (d/SAT/SAT) and the continuous trial-unique to nonmatching-to-location task (cTUNL). Taken together we concluded that xanomeline's clinical efficacy may, at least in part, be attributable to activation of the M4 mAChR.

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Poster

337. Schizophrenia: Circuits and Systems

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Topic: H.03. Schizophrenia

Support: NIH Grant NS50355
NIH Grant MH115188
FSU CRC Planning Grant

Title: Adeno-associated virus mediated inhibition of 14-3-3 proteins in the hippocampus induces schizophrenia-like behaviors in mice

Authors: *J. ZHANG[1], K. GRAHAM[1], H. QIAO[2], Y. WU[1], Y. ZHOU[1]
[1]Florida State Univ., Tallahassee, FL; [2]Shaanxi Univ. of Chinese Med., Xianyang Shi, China

Abstract: The 14-3-3 family of proteins is involved in a number of neuronal processes, and is genetically linked to several psychiatric disorders such as schizophrenia. Existing 14-3-3 knockout models, including our 14-3-3 functional knockout (FKO) mice that express an isoform-nonspecific 14-3-3 inhibitor primarily in the forebrain, exhibit behavioral endophenotypes corresponding to the core symptoms of schizophrenics. Prior human studies have implicated key forebrain regions, such as the prefrontal cortex (PFC) and the hippocampus (HP), in the pathophysiology of schizophrenia. However, 14-3-3 deficiency in these specific brain regions has not been examined in mouse models as a potential cause of schizophrenia-associated behaviors. In this study, we used an adeno-associated virus (AAV) which delivered shRNA to knock down the expression of the 14-3-3 inhibitor transgene in the 14-3-3 FKO mice, thus selectively restoring the function of 14-3-3 within targeted brain regions. We found that expression of the shRNA in both the PFC and HP is necessary to attenuate psychomotor agitation of the 14-3-3 FKO mice. Furthermore, to determine whether regional inhibition of 14-3-3 is sufficient to induce schizophrenia-associated behaviors, we constructed an AAV to express the 14-3-3 inhibitor. We found that AAV-mediated 14-3-3 inhibition in both the PFC and HP can trigger psychomotor agitation in wild type mice. Interestingly, when assessing the two brain regions separately, we determined that AAV-mediated 14-3-3 inhibition is sufficient to induce several behavioral and cognitive deficits including hyperactivity, impaired associative learning and memory, and reduced sensorimotor gating. In addition, we found that acute 14-3-3 inhibition results in decreased post-synaptic NMDA receptor levels and dendritic spine density. Together, findings from this study directly link 14-3-3 inhibition in the HP to certain schizophrenia-associated endophenotypes. Further study is underway to investigate how 14-3-3 deficiency in the HP induces these behavioral deficits.

Disclosures: J. Zhang: None. **K. Graham:** None. **H. Qiao:** None. **Y. Wu:** None. **Y. Zhou:** None.

Poster

337. Schizophrenia: Circuits and Systems

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Topic: H.03. Schizophrenia

Support: NSF Grant GRFP 1449440
NIH Grant MH115188

Title: *In vivo* electrophysiology in the 14-3-3 functional knockout mouse model of schizophrenia

Authors: *Z. B. JONES, J. ZHANG, Y. WU, Y. ZHOU
Biomed. Sci., Florida State Univ., Tallahassee, FL

Abstract: Schizophrenia is a chronic and disabling psychiatric disorder that affects approximately 1% of individuals worldwide. Patients with schizophrenia exhibit diverse cognitive and behavioral deficits, yet the neurobiology underlying these deficits remains poorly understood. In particular, elucidating the circuit and network level changes that occur in schizophrenic brains may provide crucial insights into the development and treatment of this highly intractable disorder. Several psychiatric disorders, including schizophrenia, feature perturbations in rhythmic oscillations at various frequencies as part of their pathophysiology. In addition, defects in both local and long-range neural synchrony have long been observed in schizophrenic individuals. To further examine altered network activity in an animal model of schizophrenia, here we use a 14-3-3 functional knockout (FKO) mouse line that our lab has recently developed. These mice transgenically express a 14-3-3 peptide inhibitor with a neuronal-specific promoter to disrupt the endogenous functions of 14-3-3 proteins in an isoform-independent manner. We have previously shown that these 14-3-3 FKO mice recapitulate several schizophrenia-related behavioral phenotypes and exhibit impairments in learning, memory, synaptic activity and plasticity. This study aims to determine whether this FKO model also recapitulates the oscillatory and neural synchrony defects that manifest in patients with schizophrenia. To begin addressing this question, we implanted monopolar electrodes into prefrontal and hippocampal areas of our 14-3-3 FKO mice and their wild-type littermates and recorded local field potentials under resting state conditions. Through comparisons of these two groups in specific measures such as band power (particularly in the gamma frequency range), coherence, and phase synchrony, we expect to identify specific 14-3-3 mediated electrophysiological defects and correlate those defects to schizophrenia-associated behavioral endophenotypes. Future work will seek to determine the mechanisms driving these network changes in the brain as well as the temporal and regional specificity of 14-3-3 mediated dysfunctions at the cellular, network, and behavioral levels.

Disclosures: Z.B. Jones: None. **J. Zhang:** None. **Y. Wu:** None. **Y. Zhou:** None.

Poster

337. Schizophrenia: Circuits and Systems

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 337.14/JJJ49

Topic: H.03. Schizophrenia

Title: Brain morphological abnormality in schizophrenia: Voxel-based morphometry and surface-based morphometry using CAT12

Authors: *Y. KYURAGI, N. ORIBE, S. FUKUSHIMA, N. NAKAYAMA, R. HAYASHIDA, Y. MIYAKE, K. OTA, T. UENO
Natl. Hosp. Organization Hizen Psychiatric C, Saga, Saga, Japan

Abstract: Introduction: Previous brain image studies and postmortem brain studies have reported that gray matter volume decreases mainly in frontal lobes, temporal lobe, and limbic system in schizophrenia. By using the Voxel-based morphometry (VBM) method, abnormal brain structure volume can be detected by searching the whole brain. Moreover, by using the Surface-based morphometry (SBM) method, the form of the cerebral cortex can be evaluated in more detail. We examined gray matter volume and morphological abnormality of the cerebral cortex in schizophrenia using Computational Anatomy Toolbox (CAT12) which became newly available in Statistical Parametric Mapping (SPM12).Methods: We covered 30 patients with schizophrenia hospitalized and treated at our hospital and 30 healthy, age and sex matched individuals. We compared the gray matter volume using the 3D T1-weighted images by the VBM method, and detailed structure evaluation was performed on the cerebral cortex region, which showed the gray matter volume decrease in schizophrenia, by SBM method. We calculated the cortical thickness, gyrification index and sulcal depth in the target cerebral cortex region and its surrounding structures using Aparc.a2009s atlas and compared between groups.Results: In the VBM analysis, there was a decrease in gray matter volume in schizophrenia in left superior temporal gyrus, right frontal operculum, left middle occipital gyrus, right thalamus, both side calcarine cortex, left anterior cingulate gyrus, left frontal operculum (p&lt0.05, FDR corrected; whole brain). In the SBM analysis, the surrounding structures of the left superior temporal gyrus showed a decrease in gyrification index in the left planum polare and a decrease in sulcal depth in the left transverse temporal sulcus, the left posterior limb of the lateral fissure, and the left superior temporal fissure (p&lt0.05). Abnormality in the SBM analysis could be confirmed for the other volume decrease regions seen in the VBM analysis.Conclusion: Decreased gray matter volume and morphological abnormality of the cerebral cortex were observed in schizophrenia. These abnormalities may be involved in the pathology of schizophrenia.

Disclosures: N. Oribe: None. **S. Fukushima:** None. **N. Nakayama:** None. **R. Hayashida:** None. **Y. Miyake:** None. **K. Ota:** None. **T. Ueno:** None.

Poster

337. Schizophrenia: Circuits and Systems

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 337.15/JJJ50

Topic: H.03. Schizophrenia

Support: Kakenhi MEXT 25240019

Title: Severe symptomatic schizophrenia showed smaller local gray matter volume

Authors: *T. UENO[1], Y. KYURAGI[1], R. HAYASHIDA[2], N. ORIBE[2], N. NAKAYAMA[2], K. KAWAKAMI[2], M. ONOUE[2], H. KUGA[3], S. FUKUSHIMA[4], Y. MIYAKE[1], T. YUZURIHA[1]
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Abstract: Introduction; Several studies investigated that the gray matter volume in schizophrenia patients were reduced than the normal control subjects. However, the location of the reduction is not clearly understood. Neckelmann et al. showed that the hallucination score was related to the gray matter volume in the temporal lobe. They used Brief Psychiatric Rating Scale (BPRS) to access the clinical feature. Although they accessed the clinical impairments, the group consisted of severe symptom and not so severe symptom. This study aimed to investigate the gray matter volume reduction in severe symptomatic schizophrenia patients. Methods; One hundred and twenty one schizophrenia patients were recruited from Hizen Psychiatric Center. They met to the DSM-5 criteria diagnosed by two independent psychiatrists. All participants signed informed consent forms according to the ethical committee of the Hizen Psychiatric Center. The exclusion criteria were alcohol/drug abuse, brain hemorrhage/ infarction, or thyroid dysfunction.BPRS (24 factors) was used to assess the clinical condition of each patient. Sixteen schizophrenia patients were chosen out of this group by symptomatic state with the scale of Unusual thought, Bizarre behavior, and Conceptual disorganization in the BPRS scale. They had 6(severe) or 7(very severe) points rated. Sixteen normal age matched normal control were recruited from Hizen Psychiatric Center by Ads . All participants were scanned by 1.5T MRI machine (Philips) to get the T1 weighted structural brain images in 6 minutes. Resolution was 1mm x 1mm x 1.2 mm. All the images were segmented to the gray matter images and converted to the normalized images with the canonical brain image in MNI coordinate with the DARTEL method in SPM software (Ashburner 2007). General linear model was used to investigate a gray matter volume reduction rather than normal control. General linear model has covariates of age and sex. Cutoff was under 0.001 (P value) of each point of brain, and 0.01 (P value) of spatial extent with Gaussian random field model to exclude the type 1 error.Results; Schizophrenia patients showed smaller volume in right medial temporal lobe, left anterior cingulate, and left orbitofrontal lobe. No voxels were survived in the analysis of volume excess rather than normal control.Discussion; Severity in schizophrenia patients might be related to temporal lobe and anterior cingulate, and orbitofrontal lobe. However, left temporal lobe were not detected in this study. Further investigation would be needed.References: Neckelmann G, Specht K, et al(2006) , Int J Neurosci 116(1):9-23Ashburner, J. (2007). Neuroimage 38(1): 95-113.

Disclosures: T. Ueno: None. **Y. Kyuragi:** None. **R. Hayashida:** None. **N. Oribe:** None. **N. Nakayama:** None. **K. Kawakami:** None. **M. Onoue:** None. **H. Kuga:** None. **S. Fukushima:** None. **Y. MIyake:** None. **T. Yuzuriha:** None.

Poster

337. Schizophrenia: Circuits and Systems

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 337.16/JJJ51

Topic: H.03. Schizophrenia

Support: Simons Foundation Autism Research Initiative 177638
NICHD HD055748

Title: Abnormal diffusion across the brain in schizophrenia compared to autism

Authors: *S. M. HAIGH[1], S. M. EACK[2], T. KELLER[1], N. J. MINSHEW[3], M. BEHRMANN[1]
[1]Psychology, Carnegie Mellon Univ., Pittsburgh, PA; [2]Sch. of Social Work, Univ. of Pittsburgh, Pittsburgh, PA; [3]Professor of Psychiatry and Neurol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Autism and schizophrenia share many behavioral characteristics such as social and communication problems and sensory abnormalities, despite the differences in diagnostic criteria. This has led to investigations into the underlying pathophysiology that may help differentiate between the two conditions. In the current study, we used Diffusion Tensor Imaging (DTI) to investigate the integrity of white matter tracts across the brain. We directly compared 23 adults with Autism Spectrum Disorder (ASD) to 15 adults with schizophrenia, and to 14 healthy age- and gender-matched controls. Measures of fractional anisotropy (FA) were similar across the three groups, but the adults with schizophrenia showed greater mean diffusivity (MD) in both radial and axial directions compared to the adults with ASD and controls. There were no significant group differences in head motion and brain volume, and even when these factors were included in the analyses, the effects in MD still held. The results suggest that although the integrity of white matter tracts as measured by FA is similar in the three groups, the microstructure of white matter in schizophrenia has fewer barriers to restrict water diffusion overall, compared to that in autism and in typically developing individuals. Together, this indicates that white matter tracts may be subtly impaired in schizophrenia, and may be helpful in differentiating the pathological differences between these two conditions.

Disclosures: S.M. Haigh: None. **S.M. Eack:** None. **T. Keller:** None. **N.J. Minshew:** None. **M. Behrmann:** None.

Poster

337. Schizophrenia: Circuits and Systems

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 337.17/JJJ52

Topic: H.03. Schizophrenia

Support: NIH Grant P50 MH103222

Title: The effects of oral tryptophan challenge on blood kynurenines, cerebral blood flow, and cognition in schizophrenia

Authors: *L. M. ROWLAND, R. W. BUCHANAN, D. L. KELLY, C. F. KILDAY, F. M. NOTARANGELO, M. A. R. THOMAS, R. SCHWARCZ
Psychiatry, Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Elevated brain levels of kynurenic acid (KYNA), a metabolite of the kynurenine pathway of tryptophan (TRYP) degradation, are observed in schizophrenia (SZ) and are thought to be causally involved in the cognitive deficits observed in the illness. Increases in brain KYNA levels cause behavioral impairments in rodents reminiscent of SZ, but this effect has not been investigated in humans. Therefore, we administered oral TRYP to increase production of brain KYNA in patients with SZ and healthy controls and assessed blood kynurenines, brain blood flow, and cognition. Thirty-one participants (14 controls and 17 patients) consumed a slurry of 6 g TRYP or placebo and completed blood draws, a neuroimaging session consisting of arterial spin labeling (ASL) for cerebral blood flow measures, and neuropsychological tests of verbal and visual memory, attention, and working memory. Results revealed a robust increase in blood kynurenine and KYNA following TRYP but not placebo administration in both groups ($p<0.05$). With respect to cerebral blood flow, there was a significant drug by group interaction such that prefrontal cortical blood flow during TRYP versus placebo was higher in healthy controls and lower in patients ($p < 0.05$). This is important since we and others have shown that lower cortical blood flow is related to poorer cognitive function in patients with schizophrenia. Our results suggest that an increase in KYNA may be causally involved in this phenomenon. Finally, verbal learning performance was significantly poorer during TRYP compared to placebo in the healthy control group. These results provide strong support for the hypothesis that increased KYNA may be related to the pathophysiology of cognitive impairments in SZ. The results also highlight the methodological utility of a TRYP challenge to increase the production of kynurenines in humans.

Disclosures: L.M. Rowland: None. **R.W. Buchanan:** None. **D.L. Kelly:** None. **C.F. Kilday:** None. **F.M. Notarangelo:** None. **M.A.R. Thomas:** None. **R. Schwarcz:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.01/JJJ53

Topic: I.04. Physiological Methods

Support: NEI (DP1EY024503, R01EY011787)
NIMH (R01MH101218, R01MH100561)
U. S. Army Research Office under contract number W911NF-12-1-0594 (MURI)
S. H. is a Howard Hughes Medical Institute International Student Research fellow
W. Y. holds a career award at the scientific interface by Burroughs Wellcome Fund

Title: Dual-color volumetric imaging of neural activity of cortical columns *in vivo*

Authors: *S. HAN[1], W. YANG[1,2], R. YUSTE[1]
[1]Biol. Sci., Columbia Univ., New York, NY; [2]Dept. of Electrical and Computer Engin., Univ. of California, Davis, Davis, CA

Abstract: To capture the emergent functional properties of neural circuits, high-speed volumetric imaging of neural activity at cellular resolution would be ideal. Although two-photon calcium imaging is a powerful tool to study population activity *in vivo*, conventional two-photon microscopes only image two-dimensional planes. Expanding it to three-dimensions while maintaining a high spatiotemporal resolution appears necessary. We developed a novel two-photon microscope with dual-color laser excitation that can image neural activity in a 3D volume in mice cortex *in vivo*. We use 920 nm and 1064 nm lasers to image, at the same time, neurons labeled with GCaMP6 in layer 2/3, and with jRGECO in layer 5, respectively. To enable volumetric scanning, an electrically tunable lens or a spatial light modulator was implemented in the beam path to enable fast sequential or simultaneous scanning of different focal planes. Using this beam multiplexing strategy, we image the neuronal activity of cortical circuits at high speed in primary visual cortex from awake mice (600 μm deep volumes at 10 vol/s). Using these data, we analyze the orientation tuning properties of cells in cortical columns, as well as the spatial structures of visually-evoked neuronal ensembles. We also demonstrate fast volumetric calcium imaging of layer 1 apical dendrites and layer 2/3 somata in local V1 circuits, as well as long-range projections from PFC and layer 2/3 somata in V1. We are optimizing our system to image functional neural circuits through the entire depth of a cortical column.

Disclosures: S. Han: None. **W. Yang:** None. **R. Yuste:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.02/JJJ54

Topic: I.04. Physiological Methods

Support: CZ.02.1.01/0.0/0.0/15_003/0000476

Title: Improving quality of optical fiber-based endoscopy for *in vivo* brain imaging

Authors: *T. TUCKOVA, M. HONS, P. JAKL, M. SILER, E. DRAZANOVA, L. KRATKA, J. TRÄGÅRDH, T. PIKALEK, S. SIMPSON, T. TYC, H. UHLIROVA, T. CIZMAR
Inst. of Scientific Instruments of the CAS, Brno, Czech Republic

Abstract: Optical fibers have been used in the past to image in locations deep in the scattering tissue which are not accessible through optical microscopy. Recently, the endeavor to minimize tissue damage has motivated the use of multi-mode fibers which allowed for high-resolution imaging with significantly smaller cross-section than single-mode fibers or GRIN lenses. Only recently the first successful functional imaging of neuronal calcium in vivo has been demonstrated in the mouse brain [1, 2]. These efforts represent a huge leap forward in MMF-based endoscopy, yet the quality of the detected functional calcium signals in vivo is still far from the state-of-the-art standards set by confocal and multi-photon microscopy. We introduce here computational and technological advancements to improve the quality of fiber-based imaging potentially important for brain endoscopy.
1. Ohayon, S., et al., *Minimally invasive multimode optical fiber microendoscope for deep brain fluorescence imaging.* Biomedical Optics Express, 2018. **9**(4): p. 1492-1509.
2. Vasquez-Lopez, S.A., et al., *Minimally invasive deep-brain imaging through a 50 μm-core multimode fibre.* bioRxiv, 2018.

Disclosures: T. Tuckova: None. **M. Hons:** None. **P. Jakl:** None. **M. Siler:** None. **E. Drazanova:** None. **L. Kratka:** None. **J. Trägårdh:** None. **T. Pikalek:** None. **S. Simpson:** None. **T. Tyc:** None. **H. Uhlirova:** None. **T. Cizmar:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.03/JJJ55

Topic: I.04. Physiological Methods

Title: A new method for measuring GABA using enzymatic reactors and fluorometric detection

Authors: *C. M. PÉREZ[1], A. A. RUÍZ-GARCÍA[1], A. MORALES-VILLAGRÁN[2], J. C. SALAZAR-SÁNCHEZ[2]
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Abstract: γ-Aminobutyric acid (GABA) is a non-proteic amino acid recognized as the major inhibitory neurotransmitter in the mammalian central nervous system. GABA has been a widely studied molecule, despite the difficult that its measurement represents. Several methods have been developed for this purpose; most of them use HPLC and with minor frequency fluorescence methods. We present a methodology to quantify GABA in micro and sub-micro molar range using fluorometric detection coupled to a customized flow system developed in our laboratory to allow continuous measurements. In this methodology GABA standards and samples were treated with an enzymatic reactor that contained GABAse to convert the GABA to glutamate, and glutamate oxidase to produce hydrogen peroxide which reacts with Amplex^{TM} Red and horseradish peroxidase (HRP) producing resorufin as a fluorescence derivate. The detection system uses a laser beam of 532 nm to excite the resorufin, which produces fluorescence at 590nm, which is proportional to GABA concentration. The light emitted was captured in a silicon photomultiplier coupled to an Arduino data acquisition system, afterwards, numerical values were recorded. GABA standards concentrations were also measured with an HPLC with electrochemical detection to validate this new method. The lower concentrations tested with this technique was 500nM, obtaining linear R^2 coefficient values higher than 0.95. This method provides the alternatives for detecting both low and high quantities of GABA present in fluid samples, such as in tissue extract or microdialysates. It offers the possibility to run a large number of samples in a single trial due to its immediate detection and the short time needed between individual readings.

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Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.04/JJJ56

Topic: I.04. Physiological Methods

Title: Cortex wide, multi-modal, cellular resolution neural interfacing via transparent polymer prostheses

Authors: *L. GHANBARI[1], R. E. CARTER[2], M. RYNES[3], J. DOMINGUEZ[1], J. HU[3], N. MOSSAZGHI[2], M. LAROQUE[1], T. J. EBNER[2], S. B. KODANDARAMAIAH[1,3]
[1]Mechanical Engin., [2]Neurosci., [3]Biomed. Engin., Univ. of Minnesota, Minneapolis, MN

Abstract: The brain mediates our interaction with the external world by performing complex computations undertaken by highly interconnected regions spread across several centimeters. To understand how computations occurring globally mediate behavior, we need tools to measure and manipulate the activities of these widespread brain regions at the single cell resolution, and at multiple timescales. Currently, appropriate tools to access large brain regions while simultaneously sampling information at high rates are not available. The ability to perform such multi-scale imaging in the context of neural perturbation of localized regions of the brain would be very powerful. To this end, we have developed “See-Shells”, digitally generated transparent polymer skulls, that enable wide-field sub-cellular resolution optical access to the whole dorsal cortex in mice. We used a motorized stereotax to map the skull surface of a 9-week old C57/BL6 mouse at 85 points to generate a 3D point cloud. We used this point cloud to interpolate a general 3D surface that accurately mimicked the morphology of the skull and subsequently used the interpolated surface as a template to digitally design skull replacements using computer aided design (CAD, SolidWorks) software. The See-Shells consist of a 3D printed PMMA frame bonded to a transparent, thin and flexible polymer, Polyethylene terephthalate (PET) using an adhesive epoxy. See-Shells were implanted on 16 C57/BL6 mice, 2 Thy1-YFp mice, and 27 Thy1-GCaMP6f mice by adapting previous window implantation protocols. See-Shells were chronically implanted and allowed optical access for over 100 days. We demonstrate the ability to image sub-cellular structures such as dendrites and dendritic spines at depth *in vivo* using two-photon (2P) microscopy. We also performed wide-field imaging of mesoscale activity in awake head-fixed animals, as well as imaged the activity of individual neurons in localized cortical regions spread across several millimeters using 2P microscopy. Perforating the PET allowed us to introduce probes for intra-cortical stimulation of the motor cortex while performing cortex wide imaging. We observed that localized stimulation of the motor cortex causes global activation of the whole cortex in both anesthetized and awake animals. Thus, See-Shells enable us to chronically interface with the cortex at high spatial and temporal resolution, at both mesoscale and cellular levels, in the awake animal.

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Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.05/JJJ57

Topic: I.04. Physiological Methods

Support: Human Frontiers Science Program
NIH grant R01MH080047
NIH grant 1DP1NS096787
Max Planck Florida Institute

Title: *In vivo* imaging of experience dependent CREB activity in the mammalian brain

Authors: *T. LAVIV[1], B. SCHOLL[1], P. PARA BUENO[1], B. FOOTE[1], C. ZHANG[2], L. YAN[1], D. FITZPATRICK[1], J. CHU[2], R. YASUDA[1]
[1]Max Planck Florida Inst., Jupiter, FL; [2]Inst. of Biomed. and Hlth. Engineering, Shenzhen Inst. of Advanced Technology, Chinese Acad. of Sci., Shenzen, China

Abstract: Regulation of gene transcription is essential for long-term plasticity in the brain. However, it has not been possible to monitor *in vivo* the dynamics of neuronal transcription and to correlate them to the activity patterns in a large ensemble of cells over time. To address this, we developed a technique to image *in vivo* the activity of cAMP response element binding protein (CREB), an activity-dependent transcription factor important for synaptic plasticity, using 2-photon fluorescence lifetime imaging (2pFLIM) in combination with new FRET biosensors. This technique allowed for a long-term simultaneous imaging of CREB and neuronal activity in layer 2/3 cortical neurons in awake animals. We found that, on average, CREB activity is positively correlated with behavioral performance in a motor learning task. Further, we performed chronic dual-imaging of CREB and neuronal activity in the primary visual cortex and identified a correlation between CREB and neuronal activity dynamics following sensory deprivation. This approach will allow researchers to unravel transcriptional dynamics underlying experience-dependent plasticity in the brain.

Disclosures: T. Laviv: None. **B. Scholl:** None. **P. Para Bueno:** None. **B. Foote:** None. **C. Zhang:** None. **L. Yan:** None. **D. Fitzpatrick:** None. **J. Chu:** None. **R. Yasuda:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.06/JJJ58

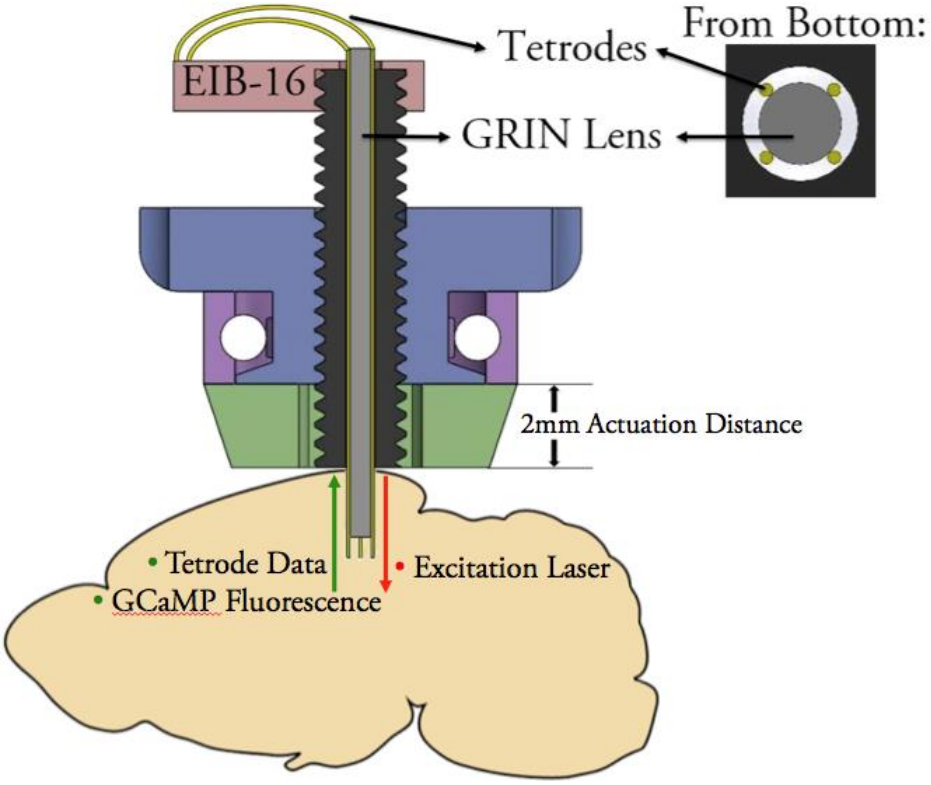
Topic: I.04. Physiological Methods

Support: NSF Grant NCS:FO CBET-1631912
NIH Grant NS099577

Title: Design and demonstration of a GRINtrode: A movable GRIN lens & tetrode drive for head-mounted microscopy

Authors: *C. M. MCCULLOUGH[1], D. RAMIREZ-GORDILLO[2], E. GIBSON[3], D. RESTREPO[4]
[1]Univ. of Colorado, Denver, CO; [3]Bioengineering, [4]Cell & Dev. Biology, Neurosci. Program, [2]Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: Single neuron and local field potential electrophysiological tetrode recordings of fast dynamic electrical activity and large ensemble neural oscillations have enabled researchers to begin deciphering functional aspects of deep brain regions where optical methods struggle due to scattering effects. This lack of optical access prevents imaging single cell calcium dynamics and spatial localization of cells. Methods exist to increase optical imaging depth, but even with 3-photon excitation imaging beyond 2mm is difficult. To overcome this limitation, it is possible to image through implanted GRIN lenses: rod shaped glass lenses of small diameter. Here, we describe a GRINtrode, a deep brain implant that combines optical and electrophysiological recording in a single, compact design.
The GRINtrode is designed for dual imaging/electrical recording in the hippocampus but can be modified using different length GRIN lenses for a variety of deep brain regions. The device includes a drive to allow manual vertical translation for fine-tuning the recording location.



Disclosures: D. Ramirez-Gordillo: None. **E. Gibson:** None. **D. Restrepo:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.07/JJJ59

Topic: I.04. Physiological Methods

Support: Leverhulme Trust

Title: Light in the dark! Shedding light on the suitability of novel BOPIDY dyes for voltage sensitive imaging of neurons in the stomatogastric ganglion of cancer pagurus

Authors: *J. BUTCHER[1], J. A. TICKLE[2], D. SIRBU[4], A. C. BENNISTON[4], P. E. ANDRAS[3]
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Abstract: Voltage sensitive dyes (VSDs) allow the activity of 100s-1000s of neurons to be monitored simultaneously providing fast temporal dynamics, making single action potential events observable. However, VSDs suffer from poor signal to noise ratio (SNR), where typically it is ~10 times less than that of calcium sensitive dyes. This work aims to improve the SNR of VSDs while maintaining their temporal dynamics by building on previous work using a new generation of VSDs derived from BOPIDY dyes. These dyes were recently shown to be viable alternatives to standard VSDs [1] such as Di4-ANEPPS [2].
The stomatogastric ganglion (STG) of *Cancer pagurus*, which controls the movement of muscles in the gastric system, produces a robust and stable pyloric rhythm (PR), making it well-suited for testing VSDs. As a result, optical imaging of the STG using VSDs is well documented (e.g. [3]). The toxicity (indicated by the increase in PR frequency) of several novel dyes was assessed and compared to Di4-ANEPPs. The STG was removed and desheathed to allow for optical recording followed by a 20 minute bath application of each dye and a 20 minute washout. For each dye, the duration of light shone onto the STG ranged from 20s to 5 minutes in increments of 20s as described before [1]. Each of the dyes tested showed low toxicity when measuring the change in the PR frequency. The SNR of each dye, measured by the change in fluorescence of a cell when intracellularly injected with a current of 0.1 nA, showed that the new dyes offered a similar SNR when compared to Di4-ANEPPS.
Future work involves the further validation of these dyes, assessing toxicity and SNR in crab and mammalian tissue, the results of which will feedback into the refinement of the structure of suitable novel dyes in the future.
[1] Sirbu, D., Butcher, J.B., Waddell, P.G., Andras, P. and Benniston, A.C., 2017. Locally Excited State–Charge Transfer State Coupled Dyes as Optically Responsive Neuron Firing Probes. *Chemistry-A European Journal*, 23(58), pp.14639-14649.

[2] Bai, D., Benniston, A.C., Clift, S., Baisch, U., Steyn, J., Everitt, N. and Andras, P., 2014. Low molecular weight Neutral Boron Dipyrromethene (Bodipy) dyads for fluorescence-based neural imaging. *Journal of Molecular Structure*, *1065*, pp.10-15.
[3] Städele, C., Andras, P. and Stein, W., 2012. Simultaneous measurement of membrane potential changes in multiple pattern generating neurons using voltage sensitive dye imaging. *Journal of neuroscience methods*, *203*(1), pp.78-88.

Disclosures: J.A. Tickle: None. **D. Sirbu:** None. **A.C. Benniston:** None. **P.E. Andras:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.08/JJJ60

Topic: I.04. Physiological Methods

Support: ERC Grant 677683
ERC Grant 692943
Simons Collaboration on the Global Brain Grant 543037SPI
NIH Grant U01NS094190

Title: Light collection properties of flat-cleaved optical fibers measured with a two-photon microscopy approach

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Abstract: In recent years fiber photometry [1, 2] gained popularity among neuroscientists as a method for causal investigation of neural circuitry *in vivo* [3, 4]. The knowledge of the spatial characteristics of the light collected by the implanted waveguide is a key aspect for the analysis of data related to calcium or voltage dynamics. Here we present a method to measure light collection properties of flat cleaved optical fibers based on laser scanning two photon microscopy (LS2PM). The setup is shown in Fig 1(a): one facet of the optical fiber is immersed into a fluorescent medium, while the light emitted by the distal facet is conveyed on a PMT. Via a volumetric raster scanning of the fluorescence excitation, the light collected from the optical fiber is measured point by point. By combining the two images acquired from the system, the fraction of light collected from the optical fiber can be assessed. A meridional section of the light collection diagram of a 0.39NA/200µm core fiber in PBS:fluorescein solution is shown in Fig.

1(b), and the respective three dimensional reconstruction is shown in Fig. 1(c) (isosurfaces at 10%, 20%, 40%, 60% and 80% of the maximum). In typical *in vivo* experiments, fluorescence is excited and detected through the same waveguide; hence, the signal gathered from a specific position depends on the intensity of excitation. The pinhole detection path in the optical setup allows to measure the distribution of the light emitted by the waveguide. Fig. 1(d) depicts a meridional section of the light emission diagram (Fig. 1(d1)), the light collection diagram (Fig. 1(d2)), and their combination in a photometry efficiency parameter (Fig. (1d3)), obtained as a pixel by pixel product) of a 0.39NA/200µm core fiber in a fluorescent mouse brain slice.
The method proposed here potentially represents a rapid tool for the performances characterization of various photometry devices.

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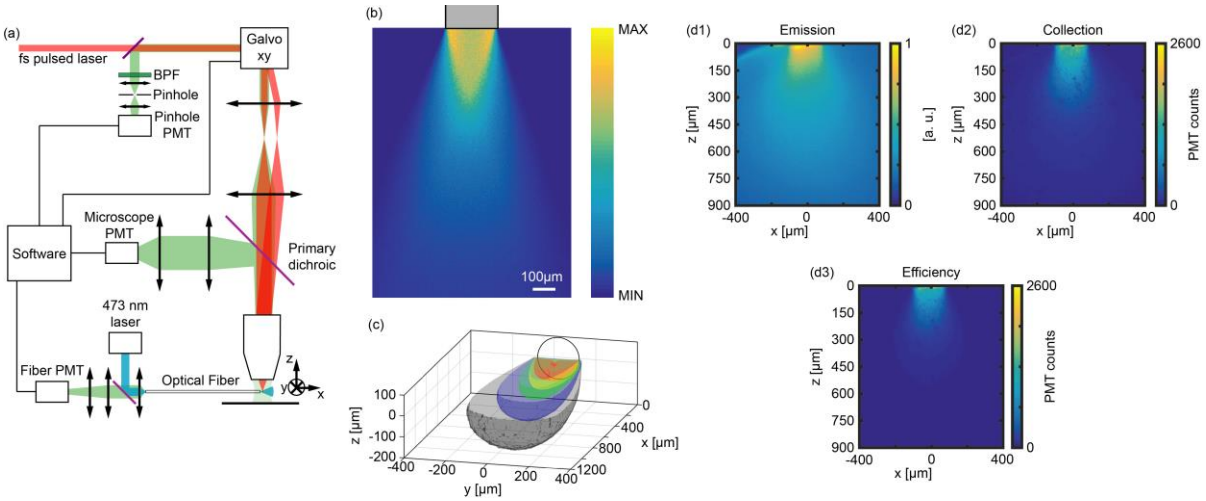
[4] A.L. Falkner (2016). *Nat. Neurosci.*, **19**, 596-604.



Disclosures: M. Pisanello: None. **F. Pisano:** None. **M. Hyun:** None. **E. Maglie:** None. **A. Balena:** None. **B. Spagnolo:** None. **E. Bellistri:** None. **L. Sileo:** None. **M. De Vittorio:** None. **F. Pisanello:** None. **B.L. Sabatini:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.09/JJJ61

Topic: I.04. Physiological Methods

Title: Dynamic ratio-metric imaging of cytosolic free Ca^{2+} in skeletal muscle cells using 340/380 nm light emitting diode illuminators

Authors: *M. CHENCHILIYAN[1], A. DEUTSCH[2], E. PEWZNER[2], D. FIXLER[1]
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Abstract: Calcium-sensitive fluorescent indicator falls broadly into two categories, ratio-metric (dual-wavelength) or single-wavelength indicators based on their response to a calcium elevation. Ratio-metric indicators shift either their excitation or their emission wavelengths in response to calcium, allowing the concentration of intracellular calcium to be determined from the ratio of fluorescence emission or excitation at distinct wavelengths. Fura-2 is one of the most common ratio-metric fluorescent Ca^{2+} indicator, which has an emission maximum at 510 nm whereas its excitation maxima change from 380 nm to 340 nm in response to calcium binding. Historically, a combination of arc lamp and monochromators have been used as the light source for Fura-2 ratio-matric fluorescence microscopy. In recent years different combinations of LEDs such as 350/380 nm or 360/380 nm have been used to excite Fura-2. To precisely match the Fura-2 excitation, in this study we built a fast switchable 340/380 nm LED (Prizmatix Ltd., Israel) excitation light source. The newly constructed light source has been exploited in Fura-2 ratio-metric calcium imaging of skeletal muscle cells. The spontaneously elicited Ca^{2+} transients in the cells were recorded with a high temporal resolution (1 ms). The light source utilized for the demonstrated instrumentation in this report optimally matches the excitation wavelengths of either calcium-free or bound states of Fura-2. The high-intensity stability and fast switching of the 340/380 nm LED illuminator indicates their potential as a preferred light source for Fura-2 ratio-metric calcium imaging over the existing light sources.

Disclosures: M. Chenchiliyan: None. **A. Deutsch:** None. **E. Pewzner:** None. **D. Fixler:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.10/JJJ62

Topic: I.04. Physiological Methods

Support: CHIR Foundation Grant
Leducq Fondation
Brain Canada Neurophotonics Platform

Title: Improved automated imaging of mouse mesoscale cortical circuits and behavioral analysis

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Abstract: We have reported a system to voluntarily head fix (autoheadfixation) and images cortices of adult group-housed mice (Murphy et al. 2016 Nature Comm) that are identified using RFID tags (Bolanos et al. 2017). We replaced noisy solenoids with servo fixation which results in > 10-fold higher head fixation rates and use both male and female mice C57bl6. Mice are water restricted and can complete as many trials of head fixation per day as they desire to obtain water. Any mouse not performing the task will be given supplemental water. To facilitate a behavioral task, we have added automated lick detection and synchronization of the head fixation system with multiple behavioral cameras using an internet-based UDP trigger. This triggering system ensures that animal specific time stamp information is passed between different Raspberry PIs controlling head fixation or video imaging clearly associating videos with a specific mouse RFID tag and time stamp. To train animals for future head fixation and behavioral tests we employ multiple stages. The first stage, which typically lasts about a week involves an animal entering the head fixation tube (only ~35 mm) and receiving what are called "entrance rewards" from an elongated water spout. The water spout is shortened over the next 3-6 days. The animal then proceeds further down the tube and trips an IR sensor which will initiate a program of brain imaging or behavioral task, but is not associated with head fixation (3-6 days). We then gradually add head fixation over the next week. We then sequence the animals to full voluntary head fixation (not >2 min in duration) and integration with a licking based reward task (over an additional 3 days). Stages of task engagement first involves auditory feedback for inappropriate licking. We find that animals will tend to lick spontaneously while head fixed. We give auditory feedback if licking occurs at too high a frequency and in the absence of rewards. This imposes a condition where the lick rate needs to subside before rewards are delivered. Once the licking rate subsides for period of 1-2 seconds we then present a vibration stimulus and they need to lick within a time window to receive a reward. 18 mice were trained in this manner and greater than 50% were able to respond with tone-based lick suppression and then licked when given a go-trial vibrational cue leading to reward. While the integration between behavior and brain imaging is still being done (and analysis pipeline developed), we anticipate that improved training regimens and behavior readouts will facilitate more complex and automated homecage tasks leading to robust longitudinal animal models of human disease.

Disclosures: T.H. Murphy: None. **J. Boyd:** None. **J. Ledue:** None. **F. Bolanos:** None. **M. Balbi:** None. **M.P. Vanni:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.11/DP14/JJJ63

Topic: I.04. Physiological Methods

Support: HHMI

Title: Brainwide optical circuit interrogation at the cellular level guided by online analysis of neuronal function

Authors: *C. WANG[1], N. VLADIMIROV[1], B. HOECKENDORF[1], Y. MU[1], M. TANIMOTO[1], J. WITTENBACH[1], J. FREEMAN[1,2], S. PREIBISCH[1,3], P. KELLER[1], M. AHRENS[1]
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Abstract: Understanding the brain requires measuring and perturbing neuronal activity. Tools for this have advanced rapidly, and are typically applied locally, but behavior is generated by the coordinated activity of neurons widely distributed across the brain. Thus, ideally we want to measure activity patterns of all neurons in the brain during behavior, use this information to decide which neurons to perturb, and record the brainwide effects of the perturbation. We developed an experimental and computational system that enables such experiments at the brainwide scale. In behaving larval zebrafish, we measure neuronal activity in the entire brain during behavior using light-sheet imaging. Concurrently, through fast distributed computational analysis, we generate whole-brain functional maps relating neuronal activity to stimuli/behavior. Any subset of neurons can be selected from the maps and then optically ablated/activated with a two-photon laser. Deleting specific functional neuron types from any of these nuclei has profound, distinct effects on brainwide responses consistent with a distributed implementation of the sensorimotor transformation. We extend the method to cellular-resolution targeted optogenetic activation during whole-brain imaging. These open-source methods allow for concurrent whole-brain activity and causality mapping in the same animal, which will enable delineating the contributions of neurons to brainwide circuit dynamics and behavior.

Disclosures: C. Wang: None. **N. Vladimirov:** None. **B. Hoeckendorf:** None. **Y. Mu:** None. **M. Tanimoto:** None. **J. Wittenbach:** None. **J. Freeman:** None. **S. Preibisch:** None. **P. Keller:** None. **M. Ahrens:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.12/JJJ64

Topic: I.04. Physiological Methods

Support: NIH Grant U01-NS103518
Simons Foundation Grant; 325548, Pesaran

Title: Stable, flexible positioning for *in vivo* imaging of neural activity in the awake macaque monkey

Authors: *J. CHOI[1], V. GONCHAROV[3], J. KLEINBART[2], A. L. ORSBORN[2], B. PESARAN[2]
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Abstract: Two photon imaging of neural activity in the awake monkey has the potential to offer important insights into the cellular organization of neuronal population dynamics during complex cognitive behaviors. However, large-scale cellular resolution imaging in macaques is complicated by large movement artifacts and the expansive curvature of the cortical surface, spanning 80 degrees of angle and centimeters. Automatically positioning a microscope objective to multiple areas of the macaque cortical surface remains an unsolved problem. Doing so accurately and repeatably is necessary for localizing neurons across days and reducing aberrations due to poor alignment with glass cranial windows. Additionally, physiological pulsations and bodily movements can cause artifacts on the order of millimeters if left unstabilized. To address these concerns, we designed an implant and robotic positioning system to optically align the objective lens with a set of defined imaging sites, specifically in the visual and somatosensory cortices. The positioner adds five motorized degrees of freedom providing enough flexibility to move the objective into precise optical alignment with any target on the dorsal convexity of cortex. To track the moving elements, a set of computer vision markers attached to the microscope and the imaging chamber implant(s) allow their relative pose to be monitored and adjusted. Stability is ensured by a set of lockable reinforcing posts that rigidly fix the implant in relation to the microscope's optical table when a suitable imaging position has been found. A novel custom designed skull ring implant rigidly fixes the implant in three places to the head fixation apparatus. In addition to providing stability, this provides a watertight enclosure for imaging chambers placed within the ring. An easily replaceable two-photon chamber insert provides a sealed, incompressible interface between the brain and glass window, limiting pulsation artifacts. While testing the system to image a patch of cortex expressing GCaMP6s in an awake macaque, the resulting motion from all sources was measured to have a maximum deviation of 5 μm in the imaging plane and less than 1 um during periods of quiet wakefulness. The marker tracking error was measured to be less than 0.5 mm in position and less than 0.11 degrees in rotation. These results demonstrate stable and repeatable functional imaging of cellular activity in the awake macaque monkey sufficient for the analysis of large-scale neural population dynamics.

Disclosures: J. Choi: None. **V. Goncharov:** None. **J. Kleinbart:** None. **A.L. Orsborn:** None. **B. Pesaran:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.13/JJJ65

Topic: I.04. Physiological Methods

Support: UNAM PAPIIT # IA206417

Title: Simple low cost system for optical intrinsic signal imaging of the mouse cortex

Authors: *H. E. LOPEZ-VALDES[1,2], C. NOLLA-SALTIEL[2], H. MARTÍNEZ-CORIA[1,3], M. X. MENDOZA-ROJAS[2], J. F. MENDOZA-VICTORINO[2]
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Abstract: Optical intrinsic signal imaging (OISI) is a technique to map brain activity by measuring intrinsic activity-related changes in tissue reflectance. Main related changes detected are increased in cerebral blood flow and hemoglobin oxygenation changes. OISI have been commonly used to map the visual, olfactory and somatosentory cortices under physiologic and pathological condition. We develop our system taking advantage of open source hardware and software. Our OIS system was made with inexpensive electronic, mechanical and optical parts available from commercial suppliers and some custom-made components. A solid aluminum optical breadboards was used to set a stage for surgery with inhaled anesthetic, a stereo microscope, a homoeothermic blanket system, a CCD monochrome camera with a tandem lens, a three color led ring and a stimulus isolator. Male mice (28-32 g) were anesthetized with isoflurane and temperature maintained at 37℃. Images were obtained through the intact skull under red light using a 8-12 bit CCD camera connected to a tandem lens (50 mm, mounted front-to-front). To generate forepaw functional maps, electrical stimulation (50 Hz, 0.001 seconds pulse width, 0.14 to 0.22 mA) was generated by a custom-made pulse stimulator, connected to a custom-made stimulus isolator, and delivered to the tissue through a pair of subdermal needle electrodes (27 GA; Rochester Electro-Medical, Tampa, FL, USA), which were inserted 2mm apart under the proximal and distal walking pads of the right forepaw. 1 second stimulation was delivered 5 seconds after the start of each trial and the total duration of one trial was 25 seconds. For image analysis, a square region of interest of 2.00 mm was centered 2.12 mm lateral and 0.04 mm anterior to bregma. Maps were generated by thresholding at 50% of the maximal response. All the significant pixels in the region of interest were summed and then converted to millimeter to obtain the activated area. The control of electrostimulation and data acquisition was written in Visual Studio 2010. Image analysis was performed using either plugins or custom routines written for ImageJ 1.5.1A (NIH, Bethesda, MD, USA).

Disclosures: H.E. Lopez-Valdes: None. **C. Nolla-Saltiel:** None. **H. Martínez-Coria:** None. **M.X. Mendoza-Rojas:** None. **J.F. Mendoza-Victorino:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.14/JJJ66

Topic: I.04. Physiological Methods

Title: Single-step implants for microendoscopic calcium imaging - enabling higher yield experiments with more consistent and standardized imaging performance

Authors: *J. J. NASSI, D. CHENG, M. J. SCHACHTER, M. TRULSON, S. MALANOWSKI, A. TAJIK, K. VISSCHER, S. L. OTTE
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Abstract: Head-mounted, single-photon miniature microscopes coupled to implanted microendoscopic GRIN lenses enables unprecedented access to large-scale neural circuit calcium dynamics in behaving rodents. In order to accelerate mass adoption of this powerful technology, there is a need for a simple and reliable surgical workflow associated with preparation of animals for imaging, which currently requires three separate surgeries to inject virus, implant a GRIN lens and attach a microscope baseplate to the skull. Here we present a single-step solution for surgical preparation in mice which entails GRIN lenses coated at their distal end with GCaMP-expressing AAV coupled to the latest miniature microscopes featuring liquid lens based electronic focusing (nVista 3.0; Inscopix, Inc.). This solution reduces the number of required surgeries from three to one, reducing the time, cost and risks associated with the standard surgical workflow. We have additionally developed a suite of cellular calcium metrics that allows for the quantification of GCaMP performance and overall imaging quality longitudinally for a given animal and across animals at specified time-points. Serial dilution studies utilizing these in-vivo performance metrics, along with histological analysis, aid in determining the optimal number of viral particles with which to coat the lens and thereby allow for the standardization of AAV-coated lenses and the in-vivo imaging performance they enable. These single-step implants, along with key improvements to the focusing and docking mechanisms of the miniature microscope, should significantly increase experimental yield and enable more consistent and standardized imaging performance within and across labs, thereby lowering the barriers for mass adoption of this technology and rapidly advancing breakthrough discoveries in the brain sciences.

Disclosures: J.J. Nassi: A. Employment/Salary (full or part-time):; Inscopix, Inc. **D. Cheng:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **M.J. Schachter:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **M. Trulson:** A. Employment/Salary (full or part-time):;

Inscopix, Inc. **S. Malanowski:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **A. Tajik:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **K. Visscher:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **S.L. Otte:** A. Employment/Salary (full or part-time):; Inscopix, Inc..

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.15/JJJ67

Topic: I.04. Physiological Methods

Support: BMBF Grant RAPID3D

Title: Z-scanning in volumetric 2P-microscopy with a fast voice coil driven remote focus system

Authors: F. HUHN[1], C. SCHULZE[2], *T. G. OERTNER[2], G. RAPP[1]
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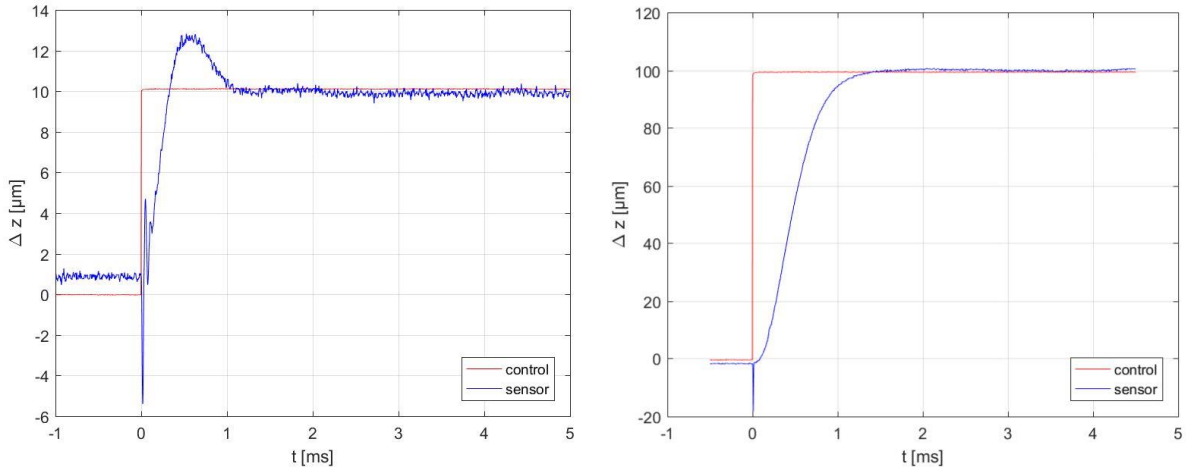
Abstract: Fast volumetric sampling of biological specimens with laser scanning microscopes is required in many fields of neurobiology and medicine. When image acquisition in the lateral (x,y) plane reaches frame rates up to 100 Hz by means of resonant scanner systems, a jump between two z-layers in the image stack should also be performed in a few milliseconds, a time scale that cannot be reached by moving the objective or the specimen. Several proposed remote focusing systems only translate a small mirror with a mass below 1g and therefore rely on fast linear positioners.
We present measurements with a fast remote focusing system on a two-photon-microscope using a voice coil driven linear stage that we developed. The voice coil stage has a travel range of 1000 µm, a 10 µm step response time of 1ms and position accuracy better than 1 µm (Fig. 1). We characterize the dynamic properties of the voice coil stage and describe the remote focus system. As proof of concept, we show its applicability for 2-photon calcium imaging of neuronal activity in the CA1 region of rat hippocampus. The remote focusing system is compatible with the open-source software ScanImage (HHMI Janelia Research Campus / Vidrio Technologies, LCC).



Disclosures: **F. Huhn:** A. Employment/Salary (full or part-time):; Rapp OptoElectronic GmbH. **C. Schulze:** None. **T.G. Oertner:** None. **G. Rapp:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rapp OptoElectronic GmbH.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.16/JJJ68

Topic: I.04. Physiological Methods

Support: Wellcome Trust DBT India Alliance Fellowship
IIT KGP SRIC Challenge Grant
IIT KGP Institute Fellowship
DST INSPIRE faculty fellowship
IITB Seed Grant

Title: Reconstruction of single neuron resolution spiking activity from simulated diamond nitrogen-vacancy center vector magnetometric maps

Authors: ***M. PARASHAR**[1], K. SAHA[3], S. BANDYOPADHYAY[2]
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Abstract: Spikes, each a rapid (1-2 millisecond) neural membrane potential fluctuation, need to be detected in neurons at single cell resolution, possibly from any structure of the brain, in order to advance microscale understanding of brain structure and function. Currently, no technique

(fMRI, MEG, Electrophysiology) other than in-vivo two-photon calcium imaging achieves the desired resolution, however only within <1mm from the brain surface. Nitrogen-Vacancy centers (NVC) in diamond allow biomagnetic field (like action potential associated magnetic field; APMF) imaging, due to its ultrahigh magnetic field sensitivity, microscale spatial and temporal resolution and room temperature operation. We perform theoretical and computational analysis to find achievable spatial and temporal resolution in 2-Dimensional (2D) vector magnetic field measurements obtained from widefield diamond NVC imaging of mammalian cortical pyramidal neurons. We simulate AP propagation in cortical pyramidal neuron, taking into account detailed neuronal geometry and ion channel densities. Magnetic field vector has been calculated from voltage propagation simulations. We find ~1pT peak-to-peak magnitude of APMF of cortical pyramidal neurons. Different values of mammalian APMF magnitude have been reported in the range of 1pT-1nT in other studies. Therefore, we simulate magnetic field values by application of Biot-Savart law on a cable-theory based multi-compartment neuronal model, with minimal assumptions. The above framework has been used to simulate 2D NV magnetometric maps (NVMMs). Our results show that AP propagation through different regions of the pyramidal neuron, like axon hillock, action initial segment, myelinated regions and nodal regions, form different and computationally identifiable signatures in the 2D NVMMs. Further, we solve the inverse problem of reconstructing location of spiking neurons by developing a reconstruction algorithm. We find that APMF from different neurons, present in the plane parallel and perpendicular to the 2D diamond NV layer, can be separately identified in 2D NVMMs, even in case of simultaneous firing. These results suggest that the inverse problem in diamond NVC based images can be solved using the algorithm developed here. The expected resolution depends on occupancy of the 3D volume of interest, sparseness of activity, pixel scan size of diamond NV widefield imager, acquisition time and sensitivity of the imaging setup. Therefore, we show that diamond NV magnetometry is a realistic and promising tool for detecting single neuron resolution spiking activity in mammals.

Disclosures: M. Parashar: None. **K. Saha:** None. **S. Bandyopadhyay:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.17/JJJ69

Topic: I.04. Physiological Methods

Support: R24NS092986
R01NS091230

Title: Facilitating the adoption of oxygen partial pressure imaging with two-photon microscopy

Authors: *S. SAKADZIC[1], T. V. ESIPOVA[2], M. A. YASEEN[1], A. DEVOR[1,3], S. A. VINOGRADOV[2], D. A. BOAS[1,4]
[1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Univ. of California San Diego, La Jolla, CA; [4]Boston Univ., Boston, MA

Abstract: The assessment of brain oxygenation on the microscopic level has the potential to transform our understanding of important clinical problems, such as stroke, Alzheimer's disease, dementia, chronic hypertension, and brain cancer, facilitating the development of new therapies and helping to improve clinical imaging and treatment protocols. Until now, no technology has been capable of microscopic oxygen imaging in the brain with high spatial and temporal resolution. Over the past several years we have developed a method, termed two-photon phosphorescence lifetime microscopy of oxygen (2PLM), which has the unique capability of fulfilling this niche. This is the only imaging method that allows high resolution mapping of brain oxygenation in real time.
2PLM of oxygen is a combination of state-of-the-art two-photon enhanced phosphorescent probes and a unique variant of two-photon laser scanning microscopy. The transformative power of 2PLM of oxygen has been demonstrated in several high-impact publications [1-7], producing great interest in the neuroscience community. With the help of NIH R24-NS092986 grant, we are in a process of setting up a self-sustaining resource that promotes widespread use of the two-photon oxygen imaging technology, making this new powerful method available to a broad group of neuroscience researchers.
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Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

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Program #/Poster #: 338.18/JJJ70

Topic: I.04. Physiological Methods

Support: 5U01NS094296
Simons Foundation Collaboration on the Global Brain
MURI, W911NF-12-1-0594
Kavli Foundation
R01 NS069679

Title: Diverse applications and extensions of SCAPE microscopy for high-speed volumetric neuroimaging

Authors: *E. M. HILLMAN[1], W. LI[2], V. VOLETI[2], H. YU[2], K. PATEL[3], C. PEREZ-CAMPOS[3], G. LEE[3], Y. CHEN[3], W. B. GRUEBER[4], R. VAADIA[3], S. J. FIRESTEIN[5], L. XU[6], E. S. SCHAFFER[3], N. MISHRA[7], R. BEHNIA[8], S. BENEZRA[8], R. M. BRUNO[8], D. SCHOPPIK[9], D. E. EHRLICH[10], E. S. BOYDEN[11], D. M. COSIO[12], E. HOSSEINI[13], O. T. CELIKER[14], E. PNEVMATIKAKIS[15], L. PANINSKI[3], T. ZHENG[3]
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Abstract: Swept confocally aligned planar excitation (SCAPE) microscopy is a light-sheet based imaging technique that permits very high speed volumetric imaging of cellular structure and function through a single, stationary objective lens. We have developed second generation SCAPE microscopes that further extend the capabilities of this approach to cover sub-cellular and very high speed (>100 VPS) imaging, meso-scale field of view volumetric imaging, two-photon excitation for fast volumetric imaging deeper into the mammalian brain, and a system optimized for high throughput imaging of cleared tissues. Working with collaborators, we have applied SCAPE to imaging a wide diversity of samples relevant to modern neuroscience including the freely crawling Drosophila larvae, awake behaving flies, larval zebrafish, C. Elegans worms, intact olfactory epithelium, awake behaving mice and cleared and expanded brain tissues. In these samples, we have used SCAPE to address a range of biological questions, made accessible by SCAPE's unique features, for example characterizing the sequential firing patterns of proprioceptive neurons throughout the crawling Drosophila larva. In turn, these

applications have highlighted the data analysis challenges of datasets exceeding 100's of Gbs. We will also report on progress towards dimensionality reduction and denoising, 4D registration and cell tracking and the application of big-data analysis techniques for information extraction and modeling of activity in the context of real time behavior.

Disclosures: E.M. Hillman: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Leica Microsystems. F. Consulting Fees (e.g., advisory boards); Leica Microsystems. **W. Li:** None. **V. Voleti:** None. **H. Yu:** None. **K. Patel:** None. **C. Perez-Campos:** None. **G. Lee:** None. **Y. Chen:** None. **W.B. Grueber:** None. **R. Vaadia:** None. **S.J. Firestein:** None. **L. Xu:** None. **E.S. Schaffer:** None. **N. Mishra:** None. **R. Behnia:** None. **S. Benezra:** None. **R.M. Bruno:** None. **D. Schoppik:** None. **D.E. Ehrlich:** None. **E.S. Boyden:** None. **D.M. Cosio:** None. **E. Hosseini:** None. **O.T. Celiker:** None. **E. Pnevmatikakis:** None. **L. Paninski:** None. **T. Zheng:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.19/LLL1

Topic: I.04. Physiological Methods

Support: NIH Grant EY028395
NSF Grant 1354015

Title: SLM-based rapidly configurable light sheet microscopy platform

Authors: *B. A. MADRUGA[1,2,4], J. CARMONA, Jr.[1], S. MENDOZA[1], L. BENTOLILA[4,3], K. ARISAKA[1,2,4]
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Abstract: Sheet Illumination microscopy is a well developed tool in the bio-imaging community due to its many inherent advantages. Increased photonic efficiency allows for lower power light sources to be used, which in turn reduce phototoxic damage at the sample over time. High fidelity, high SNR data can be collected from these systems due to their optical sectioning capabilities, and as such, many have been designed to operate within a limited parameter space. These instruments often follow traditional design logic, for specialization in a single imaging condition, for the observation of a single type of neuroscientific data. This mentality yields high resolution results for a particular type of data, yet is limited in terms of flexibility. Here, the design and development of a user-configurable light sheet microscope is discussed, which uses a spatial phase modulator to dynamically shape and optimize the incident light sheet to perform

highly in a number of temporal and spatial scales. Optical performance and stability is assessed using fluorescent microspheres for PSF evaluation before conducting calcium imaging experiments on *C. elegans* and *Danio rerio.* The result is a general purpose microscopy platform that can adapt to the observation of many neuroscientific phenomenon in numerous spatial and temporal scales.

Disclosures: B.A. Madruga: None. **J. Carmona:** None. **S. Mendoza:** None. **L. Bentolila:** None. **K. Arisaka:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.20/LLL2

Topic: I.04. Physiological Methods

Support: NIH Grant R24NS098536

Title: An expanded open-source toolbox for widefield calcium imaging in freely behaving animals

Authors: *D. P. LEMAN[1], I. A. CHEN[2], W. W. YEN[1], A. CRUZ-MARTIN[1], N. PERKINS[3], W. A. LIBERTI[5], T. J. GARDNER[1], T. M. OTCHY[3], I. G. DAVISON[4]
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Abstract: The combination of genetically encoded Ca^{2+} indicators and miniaturized, head-mounted fluorescence microscopes ("miniscopes") now offers the ability to record the activity of large neural populations in freely moving animals such as mice, rats, and songbirds. The freedom of movement afforded by miniscopes has enabled imaging during a wide range of naturalistic behaviors. However, current systems are limited to single-color imaging, and rely on gradient-index lenses that restrict their field of view to less than ~1mm^2. Here, we present an expanded-capability miniscope toolbox based on our open-source FinchScope project that helps overcome these limitations.
First, we have developed a dual-color system that uses multiplexing of excitation wavelengths to image spectrally distinct fluorescent reporters. This approach should enable identification of genetically specified cell types within circuits broadly labeled with single-wavelength activity sensors, as well as imaging of different cell classes labeled with different activity reporters, including specific subpopulations identified by retrograde labeling from different target areas. Tools for dual-color imaging will allow improved access to the activity of functionally distinct ensembles within heterogeneous neural circuits.
Second, we have developed an enlarged field-of-view system capable of imaging brain areas up

to 3 X 4 mm^2 in behaving mice. Using a 3D printed housing and off-the-shelf components, our optical design provides resolution of approximately 10μm and field curvature of less than 200μm. Combined with a high-resolution 5MP sensor, this resolution should be sufficient for single neuron imaging. Our large-area system is well suited for capturing distributed neural representations, such as sensory maps within olfactory bulb or single cortical areas. It should also allow visualization of functional interactions across multiple sensory and motor cortical regions. Methods for large-area imaging in freely moving animals will offer further insights into sensory coding, navigation, and sensory-motor coupling.
Overall, our low-cost, easily modifiable open-source system provides new imaging capabilities that complement advances in genetically encoded Ca^{2+} indicators, creating further opportunities for neural circuit imaging in naturalistic environments.

Disclosures: D.P. Leman: None. **I.A. Chen:** None. **W.W. Yen:** None. **A. Cruz-Martin:** None. **N. Perkins:** None. **W.A. Liberti:** None. **T.J. Gardner:** None. **T.M. Otchy:** None. **I.G. Davison:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

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Program #/Poster #: 338.21/LLL3

Topic: I.04. Physiological Methods

Support: NIH Grant R01 MH109685
One Mind Institute
Rita Allen Foundation
Klingenstein-Simons Foundation

Title: OpenCortex: An integrated platform of cortex-wide imaging and deep-brain modulation for measuring cellular functional connectivity in behaving mice

Authors: *B. S. HUANG[1], L. GROSENICK[2,3], T. SPELLMAN[1], N. YADAV[1], A. TOADER[1], C. LISTON[1]
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Abstract: Cognitive functions, such as memory encoding/retrieval, involve distributed functional connectivity networks spanning the cortex, with concurrent interplay with subcortical structures such as the hippocampus. Past work has largely focused on separate brain regions in isolation, while mechanisms of large-scale cortical-subcortical interactions as an integrated functional network remain unclear. Current barriers in acquiring cortex-wide cellular-resolution activity in mice include: 1) limited chronic whole-cortex recording access with cellular

resolution, 2) difficulties in capturing the multiple spatial and temporal scales involved, and 3) lack of techniques for concurrent cortical and subcortical recording/manipulation, which could facilitate the interpretation of cortical network activity. To overcome the first challenge, we have developed an *open-skull cortex-wide cranial window* in mice that provides optical access to the entire dorsal cortical surface, by surgically replacing the skull with a 10-mm-diameter glass coverslip. In addition, these windows can be fused with micro-prism implants for imaging deep medial cortical regions, such as the medial prefrontal and retrosplenial cortices. For the second challenge, we took a multiscale imaging approach (combining one-photon widefield imaging and 2-photon microscopy at different magnifications in the same brain) to acquire multi-level dynamic functional connectivity at both global and single-neuron levels. For the third challenge, we combined the cortex-wide window with chronically-implanted multi-functional fiber-probes and deep-imaging optical elements within the same brain, using newly-developed lateral-entry strategies to gain access from the side of the skull, while preserving the dorsal surface for cortex-wide imaging access. Here we demonstrate how the *OpenCortex* platform enables cortex-wide recording of cellular-resolution network activity with simultaneous monitoring and modulation of subcortical inputs in head-fixed behaving mice engaged in higher-order cognitive tasks. Long-term stability of the cortex-wide windows and implanted devices allows repeated recordings from the same animal-subject over days and months, thus enabling longitudinal studies of changing cellular circuits and networks across learning and development, in addition to supporting continuous iterations between theory and experimentation to test causal models of network mechanisms underlying cognition.

Disclosures: B.S. Huang: None. **L. Grosenick:** None. **T. Spellman:** None. **N. Yadav:** None. **A. Toader:** None. **C. Liston:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.22/LLL4

Topic: I.04. Physiological Methods

Support: NIH Research Project Grant Program RO1

Title: Visualization of neuromodulation action at single synapse resolution

Authors: *S. KRUESSEL[1], D. LEE[2], J. HYUN[1], H.-B. KWON[1]
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Abstract: Neuromodulators influence characteristics of cells and circuits. They change intrinsic properties of neurons by modulating ionic channels and also change plasticity threshold by altering ionotropic receptor functions. However, most of previous studies analyzed changes via

recording at cell body, which lacks the precise origin of neuromodulation-induced changes. In this study, we develop a synapse version of iTango2, named “Syn-iTango2”, and test whether the neuromodulation action can be monitored in real-time in local dendritic regions. Proof of principle was performed in HEK cells using Western Blot analyses, in vitro organotypic mouse slices applying dopamine agonist quinquirole and in acute slices of the nucleus accumbens activating dopaminergic terminals arising from the VTA via channelrhodopsin. This innovative technique will open the feasibility of studying neuromodulation circuits at subcellular resolution in behaving animals.

Disclosures: S. Kruessel: None. **D. Lee:** None. **J. Hyun:** None. **H. Kwon:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

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Program #/Poster #: 338.23/LLL5

Topic: I.04. Physiological Methods

Support: Allen Institute for Brain Science

Title: Volumetric imaging of neural activity using a fast-switching spatial light modulator

Authors: *R. LIU, N. BALL, J. BROCKILL, J. ZHUANG, L. KUAN, C. WHITE, A. LEON, D. SULLIVAN, C. SLAUGHTERBECK, C. FARRELL, P. SAGGAU
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Abstract: Large-scale *in vivo* recording of neural dynamics from mammalian brains at physiologically relevant temporal resolution is essential for our mechanistic understanding of brain function and its disorders. Multi-plane imaging is a conceptually straightforward approach to achieve volumetric recording of neural activity by utilizing the laminar structure of neocortical columns. However, the scanning trajectory and speed for traditional PZT-based multi-plane imaging is limited by mechanical inertia. Here, we report our recent advances in developing a microscope platform using a high-speed liquid crystal spatial light modulator. This novel imaging system allows for inertia-free multiplane functional imaging of awake and behaving animals at physiologically relevant frame rates. Using our approach, we recorded neural activity from the neocortex of awake and behaving mice at a volume of $500 \times 500 \times 200$ μm^3 at a rate of ~7 Hz (i.e., 500×500 μm^2 at each plane and a separation of ~40 μm between planes). In addition, imaging planes can be arbitrarily arranged at different depth within a column of neocortex, allowing us to record from multiple cortical layers (i.e., layer II/III, layer IV, and layer V) in a quasi-simultaneous manner during the same behavioral state.

Disclosures: R. Liu: None. **N. Ball:** None. **J. Brockill:** None. **J. Zhuang:** None. **L. Kuan:** None. **C. White:** None. **A. Leon:** None. **D. Sullivan:** None. **C. Slaughterbeck:** None. **C. Farrell:** None. **P. Saggau:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.24/LLL6

Topic: I.04. Physiological Methods

Support: BRAIN Initiative U01NS094232
BRAIN Initiative R01MH111359
NIH NS057198
NIH S10RR029050

Title: Non-degenerate 2-photon microscopy for deep tissue imaging

Authors: *S. SADEGH[1], M.-H. YANG[2], C. G. L. FERRI[2], M. THUNEMANN[3], P. H. L. NGUYEN[2], P. SAISAN[5], E. RODRIQUEZ[4], S. R. ADAMS[4], S. VINOGRADOV[7], Y. FAINMAN[2], A. DEVOR[6]
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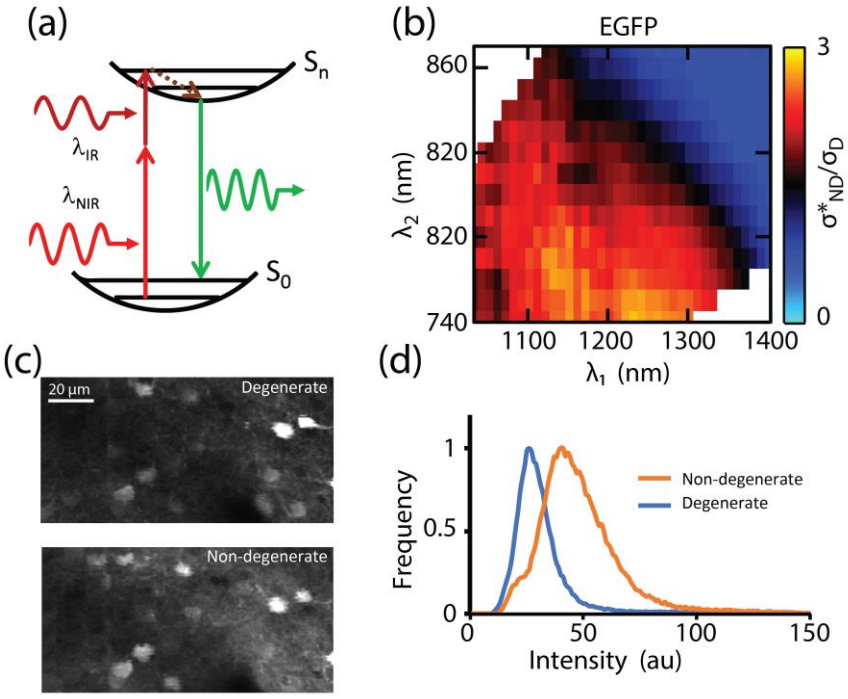
Abstract: In non-degenerate two-photon excitation (ND2PE) microscopy the required energy for transition from the ground state to the excited state is delivered via absorption of two photons of different energies - NIR and IR - from two pulsed laser beams (Fig1(a)). ND2PE microscopy has the following advantages: (i) an increase in the IR power can be used to compensate for the loss of NIR power due to scattering and absorption; (ii) under ND2PE, fluorophores exhibit an increase in the absorption cross section; (iii) ND2PE can be used to mitigate out-of-focus excitation, which limits depth penetration of two-photon microscopy, when the NIR and IR wavelengths are chosen outside of the fluorophore excitation spectrum and are spatially displaced outside the focal plane. First, for each considered fluorophore, we obtained a 2D map of the absorption cross-section. Figure 1 shows a Jablonski diagram for ND2PE (a) and a cross-section map for EGFP (b); each value was normalized to the maximum degenerate absorption cross-section. Based on these results, we selected the combination of NIR and IR wavelengths that gave us significant cross-section enhancement and implemented these wavelengths for imaging of neurons in mouse cerebral cortex *in vivo*. As predicted, we observed an increase in the image brightness (Figs 1(c-d)). Finally, by spatially displacing the beams outside of the focal plane, we reduced the out-of-focus fluorescence, in phantoms and *in vivo*, while achieving high spatial resolution comparable to that of conventional two-photon microscopy.



Disclosures: S. Sadegh: None. **M. Yang:** None. **C.G.L. Ferri:** None. **M. Thunemann:** None. **P.H.L. Nguyen:** None. **P. Saisan:** None. **E. Rodriquez:** None. **S.R. Adams:** None. **S. Vinogradov:** None. **Y. Fainman:** None. **A. Devor:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.25/LLL7

Topic: I.04. Physiological Methods

Support: NSF STC CBET 0939511 (EBICS)
NSF DGE 1735252 (NRT UtB)

Title: Gradient light interference microscopy for label-free quantitative assessment of brain slices

Authors: *M. E. KANDEL[1], S. JOUNG[2], G. NASERI KOUZEHGARANI[3], M. U. GILLETTE[4], C. A. POPESCU[6], G. POPESCU[5]
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Abstract: We developed Gradient Light Interference Microscopy (GLIM) as a label-free method for studying thick, strongly scattering specimens, such as acute brain slices. GLIM combines DIC microscopy with phase-shifting interferometry to suppress multiple scattering and attaches as an upgrade module to an existing microscope. GLIM enables quantitative studies of mesoscale structures that are hundreds of microns thick. Nevertheless, many such biological samples are not transparent, or otherwise incompatible with transmitted light imaging (e.g., high well count microplates). Thus, we designed a new epi-illumination GLIM microscope (epi-GLIM), which is now compatible with bulk tissues, including mm-thick brain slices and model organisms (e.g., zebrafish). We present the principle of operation, performance in terms of resolution and contrast and proof of concept applications to imaging thick specimens and tomographic reconstructions.

Disclosures: M.E. Kandel: None. **S. Joung:** None. **G. Naseri Kouzehgarani:** None. **M.U. Gillette:** None. **C.A. Popescu:** None. **G. Popescu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Phi Optics Inc.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.26/LLL8

Topic: I.04. Physiological Methods

Title: Virtual manipulation of model organisms with rapid volumetric and neural activity feedback

Authors: *J. CARMONA, JR[1], B. A. MADRUGA[2], A. C. ROBERTS[3], K. ARISAKA[1]
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Abstract: Surveillance of environmentally unaware organisms is the primary objective of neuro-fields. The unconstrained mobility of organisms is the best possible method to solving questions in regards to how and why brains operate in their enigmatic manner. For this reason, rapid cellular resolution volumetric imaging and macro behavioral tracking of animals can be decoded and translated from complex static connectomes to sequential and theoretically defined processes. This was achieved using a line scanning confocal microscope operating at user discretion volumetric rates from ultra fidelity volumes (450 um x 450 um x 100 um) to rapid > 30 volumes/second (200 um x 100 um x 100um) and a low magnification tracking microscope. In addition, various virtual environments are created using spatiotemporally controlled electromagnetic sources (electric fields, magnetic fields, near ultraviolet, 405 nm, and infrared, 1490 nm) and chemical sources (salt concentrations) to which organisms have developed sensors for including, chemical, photoreceptors and thermoreceptors as cardinal for survival. Furthermore, optogenetic applications and laser ablation techniques were embedded into the

system for manipulation of neural networks with closed loop control. The system was applied to nematode Caenorhabditis elegans (C. elegans) and the more complex vertebrate Danio rerio (Zebrafish) and observed behaviorally and neuronally (via the GCaMP6 calcium dependent fluorescent protein) while mobile and immobilized; confirming previous research and yielding novel results.

Disclosures: J. Carmona: None. **B.A. Madruga:** None. **A.C. Roberts:** None. **K. Arisaka:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

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Program #/Poster #: 338.27/LLL9

Topic: I.04. Physiological Methods

Support: NSF CBET-1631912
NIH NS099577

Title: Multi-plane two-photon imaging of the piriform cortex in freely-behaving mice

Authors: *B. OZBAY[1], G. L. FUTIA[2], M. MA[3], D. RESTREPO[4], E. A. GIBSON[2]
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Abstract: Two-photon microscopy is used as a common technique for acquiring neuronal data from multiple neuronal layers in head-fixed mice. As the miniaturization of electronics and optics improve, it is becoming more feasible to use advanced microscopy techniques in head-mounted devices for the imaging of naturally-behaving mice. In this work, we show deep-brain imaging of the piriform cortex in a mouse using a two-photon fiber-coupled microscope (2P-FCM). A coherent imaging fiber-bundle is used for lateral imaging and an electrowetting tunable lens is used for rapid axial focusing with no mechanically moving parts. The 2P-FCM weighs 2.5 g, with a lateral resolution of 1.5 µm and an axial resolution of 10 µm. We show imaging of a cylindrical volume of ~150 µm diameter by ~150 µm depth. The 2P-FCM is coupled to a GRIN lens implanted in the anterior piriform cortex for the imaging of GCaMP6s-expressing neurons. Behaviorally relevant neuronal activity is observed in multiple neuronal layers as female mice explore an environment with both their own bedding and unfamiliar male bedding. We show that the overall level of neuronal activity in the piriform cortex increases with decreasing distance to unfamiliar bedding. We could identify the responsiveness of specific neurons to each type of bedding. This setup can potentially be used for the multi-plane single-neuron imaging of high-level olfactory processing as mice track odorant plumes, which is currently not feasible under head-fixed conditions.

Disclosures: B. Ozbay: None. **G.L. Futia:** None. **M. Ma:** None. **D. Restrepo:** None. **E.A. Gibson:** None.

Poster

338. Physiological Methods: Optical Methodology: Development I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 338.28/LLL10

Topic: I.04. Physiological Methods

Support: Simons Foundation SCGB

Title: Two-photon calcium imaging of the hippocampus in transgenic rats under voluntary head fixation

Authors: *P. D. RICH[1], B. B. SCOTT[1], S. Y. THIBERGE[1,2], A. SONG[1,3], C. GUO[4], D. G. TERVO[4], C. D. BRODY[1], A. Y. KARPOVA[4], N. D. DAW[1], D. W. TANK[1,2]
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Bezos Ctr. for Neural Circuit Dynamics, Princeton, NJ; [3]Physics, Princeton Univ., Princeton, NJ; [4]HHMI/ Janelia Res. Campus, Ashburn, VA

Abstract: Optical access to cortical and subcortical structures in task-performing animals has become an essential tool in neuroscience. Large ensembles of neurons can be recorded simultaneously and subsets of those can be silenced or stimulated. In rodents, this approach has been mainly been used in mice, however rats are often the first choice for the study of cognitive functions. Our goal was to record calcium dynamics from the hippocampus of awake rats; large ensembles of simultaneously recorded cells will help advance our understanding of how neural activity relates to the hippocampus' proposed role in navigation and planning.
Multiphoton imaging in rodents requires stability and optical access to brain; one such approach is to use voluntary head restraint with a table-top microscope (Scott et al., 2013, 2017). Voluntary head restraint also enables precise stimulus presentation whilst allowing free spatial behaviour during other periods of a behavioural task.
We visualized calcium dynamics of dorsal CA1 neurons in transgenic rats expressing GCaMP6f under the control of Thy-1 promoter with 2-photon microscopy (Dombeck 2010). Furthermore we developed a new head positioning system that is entirely passive and allows rats to engage and break fixation instantly, at any point, at will. We incorporated a magnetic bearing mechanism to the existing kinematic alignment system. In the new system, magnets retain the headplate with sufficient force to ensure stable imaging, whilst still allowing the animal to pull away at any point during imaging.
We trained animals to initiate and retain head fixation for brief periods (1-5s) before a reward was delivered. Stability within and registration accuracy across fixations allowed the imaging of calcium dynamics of large populations of hippocampal neurons across multiple trials and between sessions. We altered the task to present rewards continuously at a random rate of 0.2/s

for as long as the animal held fixation. We were able to achieve fixations, with recorded calcium dynamics, for up to 1 minute.
We are currently developing tasks that combine the controlled conditions of head fixation with free spatial behaviour in order to investigate the hippocampal contributions to navigation and planning.

Disclosures: P.D. Rich: None. **B.B. Scott:** None. **S.Y. Thiberge:** None. **A. Song:** None. **C. Guo:** None. **D.G. Tervo:** None. **C.D. Brody:** None. **A.Y. Karpova:** None. **N.D. Daw:** None. **D.W. Tank:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.01/LLL11

Topic: I.06. Computation, Modeling, and Simulation

Support: Prior support from MH068012,
MH057153,
NS11555,
and N00014-90-J-1490 from ONR

Title: Neuromorphic neural networks: Converging globally, acting locally

Authors: *D. GARDNER
Physiol. & Biophysics, Joan and Sanford I Weill Med. Col. of Cornell Univ., New York, NY

Abstract: In 1993, The Neurobiology of Neural Networks (Gardner, D., MIT Press) presented parallels between artificial neural networks (ANN) and neuronal circuitry and offered neuromorphic implementations or extensions. In the following 25 years, advances in both neurobiology and ANNs extend parallels and possibilities. Current computationally capable ANNS include not only classic perceptron-derived feed-forward parvo-layered nets, but also magno-layered convolutional ‘deep learning’ ANNs and recurrent nets including LSTMs. ANNs evolve function by tuning synaptic weights across layers, including hidden layers; two years ago at SfN Gardner and Gardner (2016) noted hidden-layer-like responses in several systems. Contemporary synaptic physiology offers multiple mechanisms for plastic alteration of synaptic strength compatible with useful ANNs. Such models also need selective propagation of information along and across network levels in order to alter specific synapses. Neurobiology offers examples of global modulation as well as biophysically-plausible mechanisms to use transmitted information to adjust local plasticity. Transported signals from neuronal somas can selectively alter locally-tagged synapses, providing sites for convergence of cell-wide and synapse-local information. Presynaptic inhibition and facilitation can use remotely-originating

information to alter specific synapses. Two very general properties of nervous systems offer potential molecular mechanisms for supervised control of local plasticity. Many synapses are spanned by protein-protein links including membrane-spanning cell-adhesion molecules with cytoskeletal connections. Astrocytes and microglia may mediate both short-term and long-term actions specific to individual synapses, potentially controlled by both local and global factors. Invertebrates offer additional examples of neuromorphic mechanisms. Aplysia buccal ganglia provide a simple, well-characterized example of a minimal yet functional hidden layer, a narrow channel consisting of two neurons (B4 and B5) with identical structural connectivity but with different neuromodulatory co-transmitters, signals, and potential for differential programmability. This network also offers evidence for postsynaptic, and therefore retrosynaptic, specification of transmitter release. Fly olfaction relies on ANN-like organization and synaptic modulation. Enhanced communication and collaboration by neuroscientists and ANN developers has great potential both for new and neuromorphic ANN designs and also for analyses of the computations performed by neural networks formed by real neurons.

Disclosures: D. Gardner: None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.02/LLL12

Topic: I.06. Computation, Modeling, and Simulation

Support: National Key Research and Development Program of China （2017YFA0105203）
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Title: Achieving context-dependent processing in neural networks through human-level continual learning

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Abstract: One of the hallmarks of high-level intelligence is flexibility. Humans can respond differentially to the same stimulus according to contexts, such as different goals, environments, and internal states. The prefrontal cortex (PFC), which is highly elaborated in primates, is pivotal for such an ability. The PFC can quickly learn "rules of the game" and dynamically apply them to map the sensory inputs to different actions in a context-dependent way. This is quite different compared to the current artificial deep neural networks (DNNs). DNNs are powerful for recognition and classification tasks as they learn sophisticated mapping rules between the inputs and the outputs. However, the rules that current DNNs can learn are typically stereotyped. This limits the network's ability to work in more complex and dynamical situations in which the mapping rules themselves are not fixed but constantly change according to contexts, such as different environments and goals. Inspired by the role of the prefrontal cortex (PFC) in mediating context-dependent processing in the primate brain, we propose a novel approach, involving a learning algorithm named orthogonal weights modification (OWM) with the addition of a PFC-like module, that enables networks to continually learn different mapping rules in a context-dependent way. We demonstrate that with OWM to protect previously acquired knowledge, the networks could sequentially learn up to thousands of different mapping rules without interference, and needing as few as ~10 samples to learn each, reaching a human level ability in online, continual learning. In addition, by using the PFC-like module to properly mix sensory and contextual information, a network could sequentially learn different, yet context-specific mapping rules for identical sensory inputs. Taken together, these approaches allow us to teach a single network numerous context-dependent mapping rules in an online, continual manner. This enable highly compact systems to gradually learn myriad of regularities of the real world and eventually behave appropriately within it. Our model would offer an alternative option to explain how new information are integrated into neural systems, shed light on the potential role of replay of experiences in the learning process and show how sensory information can be modulated by context signals in PFC.

Disclosures: Y. Chen: None. **G. Zeng:** None. **B. Cui:** None. **S. Yu:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.03/LLL13

Topic: I.06. Computation, Modeling, and Simulation

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Beyond Moore's Law project (DOE ASCR at LANL)

Title: A mechanism for synaptic copy between neural circuits

Authors: *L. TAO[1], B. WANG[2], Y. SHAO[2], A. T. SORNBORGER[3]
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Abstract: Cortical oscillations are central to information transfer in neural systems. Experimental evidence supports the idea that coincident spike input can allow the neural threshold to be overcome, and spikes or firing rates to be propagated downstream in a circuit. Therefore, an observation of oscillations in neural circuits would be an indication that repeated synchronous spiking is enabling information transfer and processing. However, for memory transfers, in which synaptic weights must be being transferred from one brain region to another, the underlying dynamical and circuit mechanisms remain unclear. Here, we present a synaptic transfer mechanism whose structure provides some understanding of the phenomena that have been implicated in memory transfer, including nested hippocampal, thalamo-cortical and slow cortical oscillations. We construct a circuit that uses pulse-gating to guide graded information through Hebbian synapses to learn (encode) a covariance matrix from input data. Using pulse-gating we then copy the synaptic strengths encoding the covariance to a second set of Hebbian synapses. The dynamics that emerges is similar to those observed experimentally, i.e., nested oscillations at various frequencies, that accompany memory consolidation and memory transfer. We show that there are a number of gating schemes capable of performing the transfer, all based on generating bases and basis transforms that may be gated between sets of synapses.

Disclosures: L. Tao: None. **B. Wang:** None. **Y. Shao:** None. **A.T. Sornborger:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.04/LLL14

Topic: I.06. Computation, Modeling, and Simulation

Title: Hierarchical selective recruitment: A control-theoretic framework for goal-driven selective attention

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Abstract: The ability to prioritize relevant over irrelevant sensory information according to endogenous desires (and not stimulus salience) is commonly referred to as goal-driven selective attention (GDSA). A long lasting debate in the study of GDSA concerns the point in the thalamocortical information-processing hierarchy at which the selection occurs, culminating in

the idea that the locus of selection is task-dependent and distributed along the hierarchy [1]. Nevertheless, a full understanding of how this distributed multi-level selection arises from network dynamics is still lacking.
Using a model-based approach, we provide a unified framework to explain GDSA termed hierarchical selective recruitment (HSR). In HSR, the sensory hierarchy is decomposed into discrete layers with inter-layer timescale separation and intra-layer dynamics described by recurrent networks with nonlinear rate dynamics. The network at each layer is further decomposed into a subnetwork representing relevant information and another representing distractions which are, respectively, recruited and inhibited by the layer above. This results in a multiple-timescale, arbitrarily large, complex nonlinear dynamical system that is remarkably flexible and capable of explaining the principles of GDSA across different modalities.
These properties, however, depend on the network structure, i.e., the pattern and efficacy of synaptic connections. Using linear-threshold nonlinearities for intra-layer dynamics and tools from systems and control theory, we derive several necessary and sufficient conditions on network structure that guarantee HSR. These conditions have in turn direct implications for thalamocortical networks that support selective attention. For instance, we show that the effective size of the recruited subnetwork at each layer has to remain bounded, posing restrictions on the stimuli that can be simultaneously attended to. We apply our framework to a case-study of selective audition in rats, using simultaneous recordings of prefrontal cortex and primary auditory cortex from [2]. We show that our proposed network structure with only 4 nodes per region and less than 20% of possible synaptic connections can explain more than 85% of the rate dynamics in both regions, which is significantly higher than random structures with the same number of nodes and sparsity level. These analytical and computational results thus support HSR as a generic mechanism for GDSA.
[1] J. T. Serences, S. Kastner, The Oxford Handbook of Attention, 76 (2014).
[2] C. C. Rodgers, M. R. DeWeese, Neuron 82, 1157 (2014).

Disclosures: J. Cortes: None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.05/LLL15

Topic: I.06. Computation, Modeling, and Simulation

Title: A roadmap for multi-scale and multi-subject analysis of human functional brain networks

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[1]Dept. of Bioengineering, [2]Dept. of Physics and Astronomy, [3]Dept. of Electrical & Systems Engin., [4]Dept. of Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Brain networks can be partitioned into sub-networks known as “modules.” Modules expose patterns in the brain’s wiring, delineate groups of functionally related brain areas, and serve as biomarkers of development and disease [1]. Despite this, principled methods for characterizing inter-individual variation in the brain’s modular structure remain elusive. Most current approaches make strong assumptions about the scale at which modules are defined (their number and size) or their stability across individuals. These assumptions go against prevailing beliefs that brains exhibit multi-scale and hierarchical modules and weaken the generalizability of module-based biomarkers. Developing a deeper understanding of how modules are organized within individuals and how they vary across individuals requires new analytic tools and approaches. Here, we present a novel approach for module detection that allows for assumption-free comparisons across subjects. Based on advances in multi-layer network analysis, our method represents individual’s networks as single layers in a multi-layer ensemble, whose layers are clustered simultaneously [2]. Separate parameters allow users to interrogate modules at different topological scales and to flexibly accommodate different hypotheses about the stability of modules across individuals. Critically, because module labels are preserved across layers, inter-individual comparisons can be carried out with no additional heuristics, facilitating inter-individual module comparisons with unprecedented straightforwardness and certainty. We apply this approach to connectivity data from the Human Connectome Project (HCP) and the Midnight Scan Club (MSC). We find evidence across datasets that modules vary along different modes with distinct spatial patterns and topological scales. We further examine each mode at the level of individual subjects in the HCP dataset, observing that the correlation of module similarity across subjects is differentially associated with subjects’ performances on tasks requiring working memory, language, social, and relational processing. Finally, using MSC data, we find that intra-individual module variability exhibits distinct modes but is subject-specific. In summary, we propose a novel, assumption-free method for module detection and comparison. We demonstrate this method’s utility by applying it to two datasets, uncovering novel brain-behavior associations, and revealing the multi-scale nature of functional brain networks.
References:[1] Sporns & Betzel (2016). Annual review of psychology, 67, 613-640. [2] Mucha et al. (2010). S*cience*, *328*(5980), 876-878.

Disclosures: R. Betzel: None. **M.A. Bertolero:** None. **D.S. Bassett:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.06/LLL16

Topic: I.06. Computation, Modeling, and Simulation

Support: National Science Foundation Award IIS-1302125

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Korean Institute for Science and Technology

Title: A neural network model of predictive smooth pursuit eye movement in primates

Authors: *H. J. KASHYAP[1], G. DETORAKIS[2], N. DUTT[1], J. L. KRICHMAR[2], E. NEFTCI[2]
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Abstract: Primates utilize smooth pursuit eye movement to track a moving target. Due to sensory and processing delays of 80-100 milliseconds in the primate visual pathway, zero lag smooth pursuit is not achievable solely using retinal slip (RS) as feedback. Instead, the brain uses a predictive mechanism to calculate eye velocity from the delayed RS input, which allows zero lag pursuit and tracking of a target during occlusions. If a target’s motion is predictable, the primate vision system rapidly learns the spatiotemporal sequence of target velocity. Herein, we propose a recurrent neural network (RNN) based model that rapidly learns a visual target’s velocity on-the-fly and demonstrates the predictive behaviors of the primate smooth pursuit system. The proposed model is able to i) gradually eliminate the initial lag between eye and target velocities, ii) track a target with nonlinear velocity during occlusions, iii) adapt to unpredictable perturbation and phase shift in target velocity, and iv) qualitatively reproduce the typical initial pursuit acceleration observed in experiments. Although pursuit experiments on primates suggested that an internal model of target motion may be used for pursuit prediction, the neural mechanism to create and maintain such an internal model was not known. Our work shows how the internal model of target velocity is learned and updated rapidly by a neuron population using a delayed RS signal as the error. We propose that the frontal eye fields area of the primate brain is comparable to our RNN, based on their common predictive activities during smooth pursuit and location on the pursuit pathway.

Disclosures: H.J. Kashyap: None. **G. Detorakis:** None. **N. Dutt:** None. **J.L. Krichmar:** None. **E. Neftci:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.07/LLL17

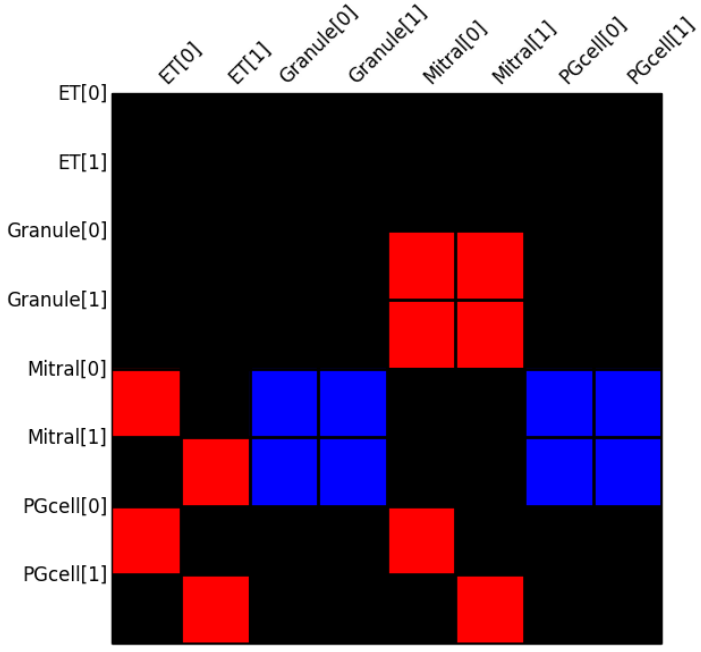
Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01 DC009977

Title: Enhancing computational model discovery via network visualization and analysis

Authors: *T. M. MORSE[1], R. A. MCDOUGAL[2]
[1]Neurosci., Yale Univ. Sch. Med., New Haven, CT; [2]Neurosci., Yale Univ., New Haven, CT

Abstract: ModelDB, a database for sharing and discovering computational neuroscience work, contains the source code for over 1300 published computational models including over 400 network models. To facilitate assessing these models for research relevance and potential reuse, we are expanding ModelDB's search and ModelView visualizations with data obtained from semi-automated network model analysis. To ensure simulator independence, we assume the availability of a specification of the network's inhibitory, excitatory, and gap junction connections in the NeuroML standard.For NEURON models using common naming conventions, a semi-automated analysis tool uses simulator introspection to identify inhibitory, excitatory and gap junctions between pre- and post-synaptic neurons and encodes this information in the NeuroML standard. A separate script reads the connectivity information from the NeuroML file to generate summary statistics which are stored and made searchable in the database. ModelView for network models is extended to support displaying the default connectivity information in various formats such as is shown in the figure for Short et al., 2016 (modeldb.yale.edu/183300, red excitatory, blue inhibitory). Note that each model may support being run in multiple configurations; for Short et al., for example, in other configurations the model has more cells and connects the ET cells. Our initial development focuses on NEURON network models because NEURON has a semi-automated analysis tool that uses simulator introspection to extract network connectivity from models that follow common naming conventions. In principle, developers of other simulators could add such analysis tools to their own software.Our first-stage work initially focuses on supporting NEURON network models because that is the most commonly used simulator for ModelDB entries and because we previously had single-cell model visualization for these models. Since the remaining steps use data stored in NeuroML, they are simulator-independent.



Disclosures: T.M. Morse: None. **R.A. McDougal:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.08/LLL18

Topic: I.06. Computation, Modeling, and Simulation

Title: Drift-diffusion balance generates asynchronous irregular activity in networks of conductance-based neurons

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Abstract: In the balanced model, the irregular firing observed in cortical neurons is explained through a cancellation of mean excitatory and inhibitory inputs to the cells of the network, which lead to a `balanced state' in which firing is due to fluctuations in synaptic inputs. In current-based models, where inputs do not depend on membrane potential, such state emerges dynamically in the strong coupling limit (large number of synaptic connections per cell K), provided that synapses are of order 1/sqrt(K), so to produce fluctuations large enough for the membrane potential to cross threshold. While these models have successfully reproduced a number of experimental observations in cortex, it is still unclear to what extent they apply to real cortical networks, in which synaptic inputs are due to conductance changes and are therefore voltage dependent. In particular, in networks of conductance-based neurons, the balanced state does not produce irregular firing because, in the large K limit, mean excitatory and inhibitory synaptic inputs are constrained to remain at finite distance from threshold, while fluctuations become negligible. Using a mean field approach, we show that asynchronous irregular activity emerges in these networks thanks to a new mechanism: rates dynamically adjust to balance the contributions of input mean, which suppresses firing, and fluctuations, which facilitates firing. As in the classical balanced-state model, the state is characterized by a linear network transfer function, CV of the inter-spike intervals close to one, and an approximately lognormal distribution of firing rates. The different operating mechanism manifests itself, as the coupling strength increases, in two ways. First, to preserve firing, synaptic efficacy should scale as 1/log(K), i.e. synapses are stronger than the 1/sqrt(K) found in current-based models. Second, compared to the current-based model, the operating regime of networks of conductance-based neurons is significantly more robust to heterogeneities in input connectivity.

Disclosures: A. Sanzeni: None. **M.H. Histed:** None. **N. Brunel:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

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Program #/Poster #: 339.09/LLL19

Topic: I.06. Computation, Modeling, and Simulation

Support: CHDI Foundation #A-8427

Title: The role of striatal tonically active neurons in reinforcement learning: A modeling study

Authors: *I. A. RYBAK[1], T. KIM[2], K. C. HAMADE[1], W. H. BARNETT[4], R. A. CAPPS[5], E. M. LATASH[6], S. N. MARKIN[3], Y. I. MOLKOV[4]
[1]Dept. of Neurobio. and Anat., [3]Dept. Neurobio. and Anat., [2]Drexel Univ. Col. of Med., Philadelphia, PA; [4]Dept. of Mathematics and Statistics, [5]Mathematics & Statistics, [6]Mathematics and Statistics, Georgia State Univ., Atlanta, GA

Abstract: The striatum is an important part of the basal ganglia which is critical for reinforcement learning. Cholinergic tonically active neurons (TANs) in this structure are thought to gate the dopaminergic input to medium spiny neurons for action selection and reinforcement learning. TANs exhibit a context-dependent pause in their activity. During the pause, the dopamine (DA) concentration in the striatum varies to encode the reward prediction error (RPE), i.e. the difference between the expected and actual reward. Despite multiple previous experimental studies, the role of TANs in reinforcement learning remains poorly understood. In the present study, we used computational modeling to investigate the possible role of TANs in reinforcement learning and their involvement in the control of DA release in the striatum. Our model is based on the following concepts synthesized from existing literature data. During tonic firing, TANs control the level of DA by releasing acetylcholine (ACh) onto nicotinic receptors at the axon terminals of dopaminergic neurons (DANs) projecting to the striatum. Via this mechanism in presence of cholinergic input, the striatal DA concentration stabilizes at a baseline level. In response to an excitatory stimulus, putatively originating in the thalamus, TANs generate a short burst followed by a prolonged pause in their activity lasting for several hundred milliseconds. During this pause, the cholinergic input to the DANs disappears, and DA release is solely controlled by DAN activity that encodes the RPE thus enabling the reinforcement learning. In the model, the mechanism of the pause in TAN activity is defined by the electrophysiological properties of TANs. Specifically, the short burst in TAN activity is followed by a slow after-hyperpolarization (sAHP) current lasting for several seconds. Another current, the hyperpolarization-activated h current, allows quick recovery from sAHP. The h-current in these neurons is suppressed by DA via D2 receptors. In summary, the TAN pause is produced by the sAHP current, and the pause duration is controlled by the h-current which in turn depends on DA concentration. Our model predicts that the RPE encoding depends on dynamic interactions

between DA release and TAN activity in the striatum. To evaluate the behavioral consequences of this interaction, we have incorporated our proposed striatal micro-circuitry into a previously published model that performs reward-based motor learning. The model allowed us to investigate the effects of the striatal DA deficiency on non-error-based motor adaptation as observed in Parkinson's disease (PD) and the effects of L-DOPA treatment for PD patients.

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Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.10/LLL20

Topic: I.06. Computation, Modeling, and Simulation

Support: NRF-2017M3C7A1049051

Title: A computational analysis of the voltage sensitive dye imaging data of the rodent hippocampus

Authors: *J. KANG[1,3], K. JUNG[1,3], H. BAHNG[1,3], H.-J. PARK[1,3,2]
[1]Dept. of Nuclear Med., [2]Brain Korea 21 PLUS Project for Med. Sci., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [3]Ctr. for Systems and Translational Brain Sciences, Inst. of Human Complexity and Systems Sci., Yonsei Univ., Seoul, Korea, Republic of

Abstract: Voltage-sensitive dye imaging (VSDI) reflect the membrane potentials of ensembles of neurons. Since the VSDI technique provides us high temporal and spatial resolution data in both of in vitro and in vivo, this technique is an important neurophysiological technique to investigate the dynamics of the brain. However, due to the complexity of the VSDI signal, to analyze the connectivity across neural populations, computational analysis is essential.
In this study, we applied the dynamic causal modeling (DCM) [1] to analyzed VSDI data of the hippocampal slices of mice in the open dataset [2]. In this framework, the computational model consisted of two parts; neural activity and observation models, and all these model parameters were simultaneously estimated to minimize prediction errors with observed VSDI data by Bayesian inferences.
In the experiment, the temporoammonic pathway was stimulated four times with 100 ms intervals. The VSDI data was recorded for 10 and 8 brain slices of the wild type and the epileptic Arx conditional knock-out mutant mouse, respectively. In the wild type, hyperpolarization after the stimulation was observed in CA1 region for the first stimulation, and this inhibition was reduced for the latter stimuli. On the other hand, in the mutant, reduction of the hyperpolarization was suppressed.

To describe adaptive properties of the neural spikes, we employed extended Jansen and Rit model with an additional memory term for the neural model. For the observation model of VSDI signals, we used a weighted sum of three sub-populations. To construct DCM, we extracted VSDI signals at the Hilus, CA1, and CA3 regions of the hippocampus, and systematically explored 512 patterns of effective connectivity.
As a result, the most fitted DCM successfully reproduced VSDI signals in both wild type and mutant mouse. Our results suggested that the adaptive parameter of the DCM plays an essential role to understand different responses in the mutant from those of the wild type. In this way, the DCM for the VSDI could be used for the investigation of the mesoscale brain dynamics.
[1] Friston, K. J., et al. Neuroimage 19(2003) 1273. [2] Bourgeois, E. B., et al. Plos One 9(2014) e108686.

Disclosures: J. Kang: None. **K. Jung:** None. **H. Bahng:** None. **H. Park:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.11/LLL21

Topic: I.06. Computation, Modeling, and Simulation

Support: HHMI Award #: 55108520

Title: An optimization principle for the emergence of the grid cell system

Authors: *T. MA, I. FIETE
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Abstract: Individually, grid cells are defined by their periodic responses as a function of animal location in 2D spaces. Collectively, the grid cell system is defined as a collection of individual cells that can be grouped into a small number of disjoint sets (modules) with different spatial periods across sets and the same spatial periods within sets [Stensola12]. Grid cell tuning can spontaneously emerge through unsupervised learning using spike-time dependent plasticity in recurrent circuits [Widloski14] or using Hebbian-like learning on feedforward weights from a set of place cell inputs [Derdikman16, Kropff08]. These are mechanistic models of how plasticity could lead to the self-organization of a single grid cell module, but do not consider the functional reasons for the emergence of grid cell tuning. On the other hand, there are models of grid cell emergence based on training a network to learn a spatial task; however, the cells exhibit a single spatial period [Cueva18]. Theoretically, it has been hypothesized and demonstrated through analytical methods [Fiete08, Fiete11, Fuhs06, Herz12] that the multi-periodic structure of the grid cell system enables exponentially high capacity coding in the number of grid modules. At the same time, models show that grid cells can function as path integrators [Burak09,Burgess07],

and experimental results are consistent with the low-dimensional continuous attractor dynamics hypothesized for path integration in some of these models [Fyhn07, Yoon13]. What has remained unclear, however, is what combination of functional and biological constraints are sufficient to give rise to the grid cell system. To address this question, we define cost functions and set up neural network training schemes to optimize these constraints. We find that maximizing the number of unique coding states while fulfilling the path integration requirement with simple mechanisms are essential elements for the emergence of periodic single-neuron responses and the emergence of multiple discrete modules.

Disclosures: T. Ma: None. **I. Fiete:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.12/LLL22

Topic: I.06. Computation, Modeling, and Simulation

Support: IMSD Grant Number GM055052

Title: Converting correlation codes into firing rate codes via nonlinear dendritic integration

Authors: *R. GRGURICH[1], H. T. BLAIR, IV[2]
[1]Psychology, [2]Dept Psychology, UCLA, Los Angeles, CA

Abstract: A population of spiking neurons can encode information about a stimulus using a *firing rate code*, which maps values of the stimulus onto patterns of neural firing rates, or using a *correlation code*, which maps values of the stimulus onto patterns of temporal correlations among spike trains. Here, we show how a correlation code can be converted into a firing rate code by a single layer of neurons that performs nonlinear integration of synaptic inputs onto its dendrites. To demonstrate this, we simulated spike trains generated by a population of head direction (HD) cells, where each individual HD cell fired maximally when a rat's head faced toward that cell's preferred azimuth angle. As the rat turns its head, the dynamics of head movement induce temporal correlations among HD cell spike trains which depend upon the angular head velocity; so in addition to storing a firing rate code for head angle, the population of HD cells also generates a correlation code for the angular head velocity. We show that this correlation code for velocity can be converted into a firing rate code for velocity by a single layer of neurons that uses nonlinear dendritic integration to compute "co-firing rates" between pairs of HD cell spike trains. We used the NEURON simulator to show how this process of nonlinear dendritic integration can be performed by NMDA receptor currents in a multicompartmental neuron model with morphology similar to a pyramidal or stellate cell. Based upon these results, we propose that dendritic mechanisms for converting correlation codes into firing rate codes may

underlie the brain's ability to perform a variety of useful computations such as neural differentiation (that is, extracting velocity signals from position signals, which may account for some firing properties of "speed cells" in hippocampal networks), measuring phase alignments between neural oscillators to decode information encoded within patterns of neural synchrony, and encoding different spatial contexts by detecting spike train correlations among hippocampal place cells that arise from the unique adjacency relationships among place fields in each context.

Disclosures: R. Grgurich: None. **H.T. Blair:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.13/LLL23

Topic: I.06. Computation, Modeling, and Simulation

Title: Deriving binocular spontaneous neural activity by optimizing depth perception in an innate learning model of visual development

Authors: *S. SENDELBACH[1,2], M. V. ALBERT[1,2]
[1]Dept. of Computer Sci., [2]Neurosci. Program, Loyola Univ. Chicago, Chicago, IL

Abstract: Spontaneous, patterned neural activity occurs prenatally in the early visual system. This work tests the results of alternate neural activity patterns on simulated animal visual performance using the efficient coding paradigm. The goal was to better understand the precise nature of correlated binocular spontaneous activity in the LGN and V1 by observing the derived ability of an animal to perform an ecologically relevant visual task - depth discrimination. Spontaneous neural activity in the retina presents as amorphous, spatiotemporal patterns that have been directly observed; although LGN and V1 spontaneous activity is only partially observable, our results qualitatively match with what is known about correlated activity between eye layers. But the question remains, why these patterns? Why so similar across distinct species? This work is a continuation of an "innate learning" paradigm in which spontaneous neural activity prepares an animal for adult vision in a similar way to learning that occurs after the eyes open. To study this activity, we implemented a two eye-layer percolation model for activity generation. The parameters of the model resemble abstractions from retinal wave modeling: fractions of recruitable cells, dendritic field sizes, surrounding activity thresholds, and additionally a probability of transmitting activity between eye-specific layers. Simulated neural activity in a range of candidate parameter choices were tested. These activity images were provided as inputs to a V1 efficient coding strategy to derive candidate receptive fields. These derived binocular V1-like receptive fields were then used in a series of depth perception tasks on autostereograms, and scored accordingly. For each set of activity parameters, 2000 binocular filters were generated from the derived images and used for depth estimation and scoring.

Optimal parameters for depth perception produced simulated activity that closely resembled spontaneous activity measured in vivo. This work demonstrates how an ecologically relevant goal, like binocular depth estimation, can be used to directly estimate properties of binocular visual development.

Disclosures: S. Sendelbach: None. **M.V. Albert:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

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Program #/Poster #: 339.14/LLL24

Topic: I.06. Computation, Modeling, and Simulation

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Title: A software framework for simulating large-scale population dynamics of growth transform spiking neural network

Authors: *D. MEHTA, A. GANGOPADHYAY, J. HA, K. AONO, S. CHAKRABARTTY
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Abstract: The process of neural spike generation and transmission expend relatively large amounts of energy; therefore, neurobiological systems have evolved to use neural codes that are energy optimized for different information processing tasks. Current spiking neural network models, however, do not capture the process of spike generation and encoding from the perspective of energy-minimization; instead treat the energy costs as a constraint. In contrast, we study spike generation and neural coding in a network of spiking neurons by designing an energy functional (fig. a), which when minimized under realistic physical constraints, produces emergent spiking dynamics (Gangopadhyay & Chakrabartty, TNNLS '17, fig. b). At the core of this formulation is a growth transform (GT) based neuron model that follows a trajectory in a dual optimization space, while the network follows a trajectory in a high-dimensional primal space (fig. c). These high-dimensional trajectories are guaranteed to be stable, interpretable and have been found to be consistent with population dynamics that have been observed in neurobiology (Saha & Raman, NatNeuro '13).
For disseminating this concept to the scientific community, we have developed two versions of open source software for simulating an arbitrary network of GT neurons. The network is capable of handling asymmetrical excitatory and inhibitory connections between neurons. The MATLAB^{TM} based provides an intuitive introduction to the GT Neuron Network. Input currents, objective function parameters and the connection matrix can be dynamically updated, and the

neuronal responses can be continuously visualized. An optimized C++ code that can simulate more than million neurons, can be used as a tool for large-scale simulation using sparse matrix representations and libraries. The software can be mapped onto GPU based computational platforms. Users can create hierarchical network models and present different forms of complex stimuli. These toolboxes are available through the web-portal https://aimlab.seas.wustl.edu/.

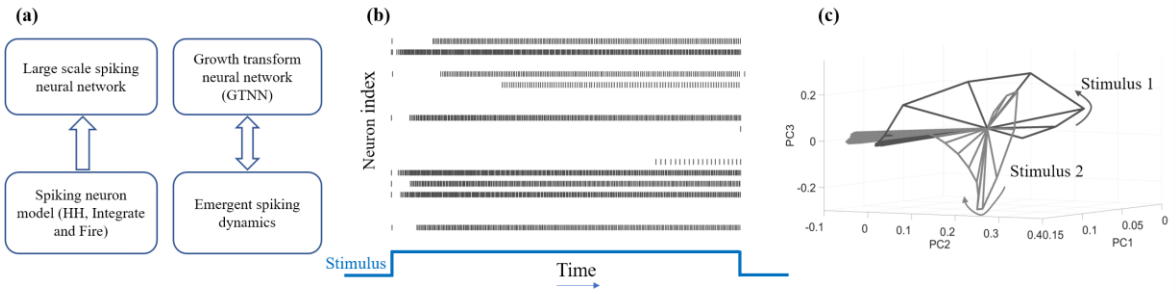

Fig 1. a) Conceptual description of growth transform neural network (GTNN) b) Raster plot of spiking dynamics for a given stimulus c) Trajectories of population responses projected onto principal components for different stimuli

Disclosures: D. Mehta: None. **A. Gangopadhyay:** None. **J. Ha:** None. **K. Aono:** None. **S. Chakrabartty:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.15/LLL25

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH

Title: Addressing analysis questions for a nonlinear synaptic system as a model for ictogenesis

Authors: *S. KARAMINTZIOU, K. J. STALEY
Harvard Med. School/Mgh, Charlestown, MA

Abstract: Seeking to understand and control the conditions that lead to seizure initiation, we simulate the hippocampal CA3 region as a network of integrate-and-fire neurons with an anatomical synaptic topology that is modulated by use-dependent synaptic depression and recovery. The network exhibits high-dimensional, third-order nonlinear dynamics. The cornerstone of the modeling approach is short-term synaptic plasticity, that is, the modification in transmitter release probability, a process demonstrated experimentally to exhibit first-order depression and recovery kinetics. This type of synaptic plasticity may also underlie elements of activity-dependent disinhibition arising from depression of excitatory glutamatergic inputs to interneurons. Using this model we look for parameters that are within experimentally described

ranges and that generate both stable interictal network activity and occasional ictal transitions. A preliminary analysis is performed within a system-theoretical framework.

Disclosures: S. Karamintziou: None. **K.J. Staley:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.16/LLL26

Topic: I.06. Computation, Modeling, and Simulation

Support: ONR N000141812114-P00002
NIH T32 AG00096-34

Title: Models of recurrent networks in hippocampus encode temporal order

Authors: *C. D. COX, B. G. GUNN, G. LYNCH
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Abstract: There has been considerable discussion about the possible contributions of the hippocampus in the encoding of sequential and temporal information. Relatedly, a great deal of evidence indicates that the structure plays a central role in the organization of the flow of experience into episodic memories. Field CA3 is a component of hippocampus including a dense collateral system that is seemingly appropriate for processing temporal information. To evaluate the properties of the hippocampal CA3 across biologically relevant timescales to ordering within episodes, we developed a realistic simulation composed of ~1000 simple biophysical neurons. Based on previous studies, the model was wired to create neighborhoods, favoring local over global connectivity; CA3 interneurons provided local feedback and global feed-forward connections. We previously showed that simulations of this type generate sharp waves with properties comparable to those found in field recording of slices. This previous model was updated in several ways, including stronger neighborhood linkages. A brief (100ms) physiologically realistic activation led to continual firing lasting 10 seconds. The activity was eventually terminated by slowly building effects of local inhibition. The firing was found to be extremely vulnerable to disruptions: small increases in inhibition or loss of 5-10% of excitatory synapses caused model collapse. Increases in connectivity or reduction of inhibition produced runaway activity. By adding multiple inputs, a plasticity rule, and sparse long range connections the model was found to be capable of storing and retrieving the proper order of a sequence of cues over biologically relevant timescales. Essential elements of this model were verified with in vitro physiological preparations.

Disclosures: C.D. Cox: None. **B.G. Gunn:** None. **G. Lynch:** None.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.17/LLL27

Topic: I.06. Computation, Modeling, and Simulation

Title: A method of online learning with neuromorphic computing network

Authors: *R. SCORCIONI, Q. JANG, S. SKORHEIM, N. STEPP, V. DE SAPIO, P. PILLY
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Abstract: One of the most challenging issues in online learning is to learn from a small set of training samples because it is difficult to have a large set of training samples for an online learning system, which is generally required to achieve real-time computing and in many applications, a large set of training samples may not be available or too expensive to obtain. Another challenge in online learning is to learn new things without fully retraining the learning system because the requirement of real-time computing prevents online learning systems to fully retrain the system when they have to learn new things. In our approach, our learning system is able to perform unsupervised learning automatically in real-time; different objects in the input data are clustered into different categories by the unsupervised learning; and only a small set of training samples is needed to label the categories in supervised learning. When new objects are input into the system, new categories will be formed by the unsupervised learning process and only a small set of new training samples is needed to label the new categories so that the system is able to learn new categories without fully retraining the system. Since our online learning system is based on neuromorphic computing network, it is computationally much efficient compared to deep learning based methods.

Disclosures: R. Scorcioni: A. Employment/Salary (full or part-time):; HRL Labs. **Q. Jang:** A. Employment/Salary (full or part-time):; HRL Laboratories. **S. Skorheim:** A. Employment/Salary (full or part-time):; HRL Laboratories. **N. Stepp:** A. Employment/Salary (full or part-time):; HRL Laboratories. **V. De Sapio:** A. Employment/Salary (full or part-time):; HRL Laboratories. **P. Pilly:** A. Employment/Salary (full or part-time):; HRL Laboratories.

Poster

339. Computation, Modeling, and Simulation: Network Models: Theory I

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 339.18/LLL28

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH grant R01NS079774
US Army grant W911NF-17-1-0534
NSF ABI Innovation grant 1564736
Shanghai Youth Science and Technology Sail Project 16YF1415200

Title: Neural coding via spike-timing self-information

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[1]Harvard Univ., Cambridge, MA; [2]Augusta Univ., Augusta, GA; [3]Dept. of Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Cracking brain's neural code is of general interest. Here, we examine the "Neural Self-Information Theory" that the interspike-interval (ISI) carries self-information that is inversely proportional to its variability-probability. Specifically, higher-probability ISIs convey minimal information because they reflect the ground state, whereas lower-probability ISIs carry more information, in the form of "positive" or "negative surprisals," signifying the excitatory or inhibitory shifts from the ground state, respectively. These surprisals serve as the quanta of information to construct temporally coordinated cell-assembly ternary codes representing real-time cognitions. Accordingly, we devised a general decoding method and unbiasedly uncovered 15 cell assemblies underlying different sleep cycles, fear-memory experiences, spatial navigation, and 5-choice serial-reaction time (5CSRT) visual-discrimination behaviors. We further revealed that robust cell-assembly codes were generated by ISI surprisals constituted of ~20% of the skewed ISI gamma-distribution tails, conforming to the "Pareto Principle" that specifies, for many events—including communication—roughly 80% of the output or consequences come from 20% of the input or causes. These results demonstrate that real-time neural coding arises from the temporal assembly of neural-clique members via silence variability-based self-information codes.

Disclosures: **M. Li:** A. Employment/Salary (full or part-time):; Harvard University. **K. Xie:** None. **J. Liu:** None. **D. Wang:** None. **G. Fox:** None. **F. Zhao:** None. **J.Z. Tsien:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.01/LLL29

Topic: I.06. Computation, Modeling, and Simulation

Support: National Key Research and Development Program of China (2017YFA0105203)

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Title: Pairwise interactions among different brain regions organize large scale neural networks for information processing

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Abstract: Spatially separated brain areas do not function independently. Instead, they interact with each other to form networks with coordinated activities, supporting various brain functions including perception, motion and cognition. It is well known that higher order interaction (HOI), such as Exclusive Or operation, is necessary for a system to be computation universal, i.e., to be able to perform all possible computations. However, currently it is unclear whether HOI is present in large scale neural networks when these networks are actively involved in information processing. To address this question, we analyzed functional magnetic resonance imaging data collected from human subjects when they were executing various tasks including perception, language, working memory, etc (the HCP data set). Our results demonstrated that the strength of HOIs in large scale neural networks, such as the default mode network, the frontal-parietal network, etc., were very weak, indicating that the computations underlying major brain functions do not rely on HOIs at the level of brain areas. Further, we examined the activities of a neural network model with dynamic features similar to the actual brain. No strong HOI were observed even when the model was stimulated, suggesting that the lack of HOIs is intrinsic for networks with neural dynamics similar to the brain. Our results revealed the dominance of pairwise interactions in organizing coordinated activities among different regions to support key functions of the brain. It also suggest- that human like, highly versatile artificial intelligence system can be built based on pairwise interactions among different functional modules, which greatly simplifies the complexity of the design and training of such systems.

Disclosures: W. Niu: None. **X. Huang:** None. **K. Xu:** None. **T. Jiang:** None. **S. Yu:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.02/LLL30

Topic: I.06. Computation, Modeling, and Simulation

Support: ISI Foundation
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DARPA N66001-14-2-4032

Title: White matter network architecture guides direct electrical stimulation through optimal state transitions

Authors: *J. STISO[1], A. N. KHAMBHATI[1], T. MENARA[2], A. E. KAHN[1], J. M. STEIN[1], S. DAS[1], R. GORNIAK[3], B. LITT[1], K. A. DAVIS[1], F. PASQUALETTI[2], J. TRACY[4], T. H. LUCAS[1], D. S. BASSETT[1]
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Abstract: Electrical brain stimulation is currently being investigated as a potential therapy for neurological disease. However, opportunities to optimize and personalize such therapies are challenged by the fact that the beneficial impact (and potential side-effects) of focal stimulation on both neighboring and distant regions is not well understood. Here, we hypothesize that the effects of simulation will propagate along white matter tracts to affect change in the activity of distal regions. Specifically, we use network control theory to build a formal model of brain network function that makes explicit predictions about how stimulation spreads through the brain's white matter network and influences large-scale dynamics. We test these predictions using combined electrocorticography (ECoG) and diffusion weighted imaging (DWI) data from patients with medically refractory epilepsy undergoing evaluation for resective surgery, and who volunteered to participate in an extensive stimulation regimen. We posit a specific model-based manner in which white matter tracts constrain stimulation, defining its capacity to drive the brain to new states, including states associated with successful memory encoding (as defined by a previously trained and validated classifier). In a first validation of our model, we find that the true pattern of white matter tracts can be used to more accurately predict the state transitions induced by direct electrical stimulation than the artificial patterns of a topological or spatial network null model. We then use a targeted optimal control framework to solve for the optimal

energy required to drive the brain to a given state. We show that, intuitively, our model predicts larger energy requirements when starting from states that are farther away from a target memory state. We then suggest testable hypotheses about which structural properties will lead to efficient stimulation for improving memory based on energy requirements. We show that the strength and homogeneity of edges between controlled to uncontrolled nodes, as well as the persistent modal controllability of the stimulated region, predict energy requirements. Our work demonstrates that individual white matter architecture plays a vital role in guiding the dynamics of direct electrical stimulation, more generally offering empirical support for the utility of network control-theoretic models of brain response to stimulation.

Disclosures: J. Stiso: None. **A.N. Khambhati:** None. **T. Menara:** None. **A.E. Kahn:** None. **J.M. Stein:** None. **S. Das:** None. **R. Gorniak:** None. **B. Litt:** None. **K.A. Davis:** None. **F. Pasqualetti:** None. **J. Tracy:** None. **T.H. Lucas:** None. **D.S. Bassett:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.03/LLL31

Topic: I.06. Computation, Modeling, and Simulation

Title: A circuit-level model of reward learning under uncertainty

Authors: *A. SOLTANI[1], S. FARASHAHI[2], A. IZQUIERDO[3]
[1]Psychological & Brain Sci., [2]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [3]Dept. of Psychology, UCLA, Los Angeles, CA

Abstract: Though neural correlates of expected uncertainty have been found in many species' brains, we still do not know how these signals contribute to or are influenced by volatility in the environment. To accurately estimate volatility of the environment, or how rapidly reward conditions change, decision-makers should take into account estimates of outcome probabilities. However, most normative models of learning under uncertainty assume a hierarchical representation of expected and unexpected uncertainty (volatility) in which the estimation of volatility is independent of estimates of outcome probabilities. Similarly, it is unclear how volatility could influence learning in reinforcement learning models that update reward values based on reward prediction error. Thus, none of the predominant models of value-based learning provides plausible neural mechanisms for or testable predictions about how the computations of expected uncertainty and volatility are performed, and importantly, how they interact with each other. We have recently shown that reward-dependent metaplasticity provides a plausible mechanism for both computation of value under uncertainty and the estimation of volatility. Here we propose a circuit-level model for computation of expected and unexpected uncertainty and how the two interact. The model consists of three areas; two areas that estimate reward

probabilities using plastic and metaplastic synapses, and one area that estimates volatility based on the output of metaplastic synapses. Volatility is estimated using the output of the metaplastic system on a trial-by-trial basis. This signal is then sent back to both plastic and metaplastic systems to make them more adaptable when volatility is high. Based on previous findings, we hypothesized that anterior cingulate cortex (ACC) and striatum compute reward probabilities using metaplastic and plastic synapses, respectively, whereas volatility is computed in basolateral amygdala (BLA). First, we show that feedback using the volatility signal in BLA, based on input from ACC but not striatum, can improve performance in probabilistic reversal learning. Moreover, we show that inhibition of connections from ACC to BLA reduces learning more strongly than inhibition of BLA to ACC connections. Overall, our circuit-level model proposes a plausible mechanism for interactions between computations of expected and unexpected uncertainty. In addition, it provides specific testable predictions about the contributions of different areas and their connections to learning and choice under uncertainty.

Disclosures: A. Soltani: None. **S. Farashahi:** None. **A. Izquierdo:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.04/LLL32

Topic: I.06. Computation, Modeling, and Simulation

Support: MOST

Title: The GABAA receptor binding SCN is more related to ion channel activity-related TBN than cortical thickness SCN

Authors: *F.-T. WONG[1], N. W. DUNCAN[2]
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Abstract: The gamma-aminobutyric acid (GABA) neurotransmitter system plays an important role in our mental function and health. Here we investigate the relationship of multimodal network topologies associated with GABA system. Firstly, a structural covariance network (SCN) from positron emission tomography (PET) measures of GABAA receptor binding was generated based on 23 participants. Secondly, with the same 23 participants plus 4 participants, SCN based on MRI measures of cortical thickness was generated. Thirdly, applying the GABA receptor-related and ion channel activity-related gene expression maps from human adult brain microarray datasets provided by the Allen Institute for Brain Science (AIBS), transcriptomic brain networks (TBN) were definded by estimating gene co-expression between pairs of cortical regions matched to the nodes of the SCN.
The GABAA receptor binding SCN reveals the topological properties such as small worldness,

rich club, and compact modular structure. However, comparisons of the SCN between GABAA receptor binding and cortical thickness show significant differences in the degree of small world propensity and distribution of connection. By thresholding the 85 percent strength of connection, a majority of preserved overlapped connections is observed in visual cortex across the 4 topological structures. In addition, the regional GABAA receptor binding level is negatively correlated with the regional GABA receptor-related gene expression while positively correlated with ion channel activity-related gene expression. Furthermore, the results of a multivariate dimension-reducing technique of partial least squares (PLS) to explore the associated components between all 20,737 genes and PET level at the SCN nodes demonstrates that the second independent partial least squares component (PLS2) represented a significant association with the gene profile related to regulation of neurotransmitter receptor activity, membrane potential, and glutamate receptor signaling pathway.
The evidence suggested that the GABAA receptor binding SCN has stronger topological relationship with ion channel activity-related TBN than cortical thickness SCN.

Disclosures: F. Wong: None. **N.W. Duncan:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.05/LLL33

Topic: I.06. Computation, Modeling, and Simulation

Title: The underlying mechanism of the alteration of il-bla connectivity by stimulation:A computational perspective

Authors: *Z. CHEN[1], F. FENG[1], E. BLACKWOOD[2], M.-C. LO[2], A. S. WIDGE[2], S. NAIR[1]
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Abstract: Synchrony of low-frequency theta (4-8 Hz) oscillations between infralimbic cortex (IL) and basolateral amygdala (BLA) has recently been shown to impact the regulation of fear-behavior and may be a target for brain stimulation paradigms. Open-loop and closed-loop electrical stimulation have been shown to alter IL-BLA connectivity and coherence, implying alteration of inter-area oscillatory synchrony between IL and BLA. However, the underlying mechanisms that cause the these changes are unknown. Such an understanding will also help with the development of improved stimulation schemes to further enhance coherence between the BLA and IL regions. To address these questions and obtain a mechanistic understanding of its functioning, we developed a biophysical 1460-cell computational model of the IL-BLA network using a Hodgkin-Huxley formulation. The network model was developed using the known physiological and anatomical properties of the BLA and IL, specifically different single

cell types and their neurophysiology, synaptic current dynamics, spatially heterogeneous spatial connectivity, short- and long-term plasticity and neuromodulatory inputs. The model replicated several known features of IL-BLA network. The IL region consists of layer II and layer V with 380 pyramidal cells (PNs) and 80 interneurons (ITNs). The BLA region consists of 900 PNs and 100 ITNs. We used realistic connectivity between different types of neurons in IL and BLA and also the inter-area connectivity between IL and BLA. The average firing rates of PNs and ITNs in BLA are 0.5 Hz and 25 Hz respectively, consistent with biological data. Furthermore, the firing rate of PNs and ITNs in IL are 4-6 Hz and 10-20 Hz respectively. Moreover, simulated LFP signals are recorded in model BLA and IL. Single-pulse evoked potential response (ERP) in BLA given current injections into IL neurons was found similar to in vivo recordings. On-going work examines the role of short-term plasticity in connectivity change. Further work will be to investigate how intrinsic and extrinsic theta oscillation are involved in the synchrony alteration.

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Poster

340. Computation, Modeling, and Simulation: Human Network Models

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Program #/Poster #: 340.06/LLL34

Topic: I.06. Computation, Modeling, and Simulation

Support: James McDonnell Foundation

Title: Precision neurology: Cellular mechanisms of Alzheimer's disease

Authors: *A. SOLODKIN[1], J. ZIMMERMANN[2], V. K. JIRSA[3], A. R. MCINTOSH[4], P. RITTER[5], M. J. BREAKSPEAR[6]
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Abstract: Introduction: Brain function can be measured across multiple spatial scales, from individual cells, to large-scale networks. Within each scale, meaningful signals are mixed across several time scales. There is presently no single experimental technique that can acquire data across these scales. The problem is exacerbated by nonlinearities inherent in the brain, where a vast number of spatiotemporal features at one level support emergent features at another. In this work we use our computational framework, ***TheVirtualBrain (TVB)*** that enables us to integrate data across multiple scales and identify general principles of their interactions. Previous results in Alzheimer's disease (AD) based on simulations of rsfMRI showed local changes on the

inhibition/excitation balance and global changes where local dynamics within regions were stronger than between regions. Here, we focus on functional mechanisms at a cellular level by simulating Local Field Potentials (LFP) in limbic regions as they relate to **G** (Global coupling) to understand basic mechanisms of brain synchrony in AD.
Methods: Behavioral data acquired for 79 participants from the Sydney Memory and Ageing study (MAS) were stratified based on cognitive performance in four groups: 16 super normal controls (SNC), 16 healthy controls (HC), 31 amnesic MCI (aMCI), and 16 Alzheimer's Disease. Simulation of LFP with TVB, determined the value of G (G critical) associated with oscillations of the LFPs. We also measured the range of G values associated with the oscillations along their location, frequency and amplitude finally determining their relationship with cognition.
Results: Can be summarized in 4 points: a) Oscillatory signals in the LFP so robust in super normal controls, gradually decreased as cognition decreased; b) Oscillations were found exclusively in the posterior cingulate region; c) Additional metrics derived from the oscillations (e.g., amplitude, frequency and presence of spikes) showed that their relationship with cognition was either linear (increase or decrease), or U-shaped with an increase in NC and MCI before decreasing in AD representing perhaps a compensatory reaction. d) In parallel, there was also a decrease in synchrony between regions;
Summary: This work establishes an essential new capacity for the neuroscience community to merge the wealth of multiscale data acquired in an evolving computational architecture. Our results represent a new generation of biomakers that are related directly to disease mechanisms, are individualized for each patient and are related to clinical phenotype. As they represent brain dynamics, they can be an invaluable tool for developing novel therapies.

Disclosures: A. Solodkin: None. **J. Zimmermann:** None. **V.K. Jirsa:** None. **A.R. McIntosh:** None. **P. Ritter:** None. **M.J. Breakspear:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.07/LLL35

Topic: I.06. Computation, Modeling, and Simulation

Support: BOF UGENT Support to HA and DM

Title: Modeling brain dynamics in brain tumor patients using the virtual brain

Authors: *D. MARINAZZO[1], H. AERTS[2], M. SCHIRNER[3], B. JEURISSEN[4], D. VAN ROOST[2], E. ACHTEN[2], P. RITTER[5]
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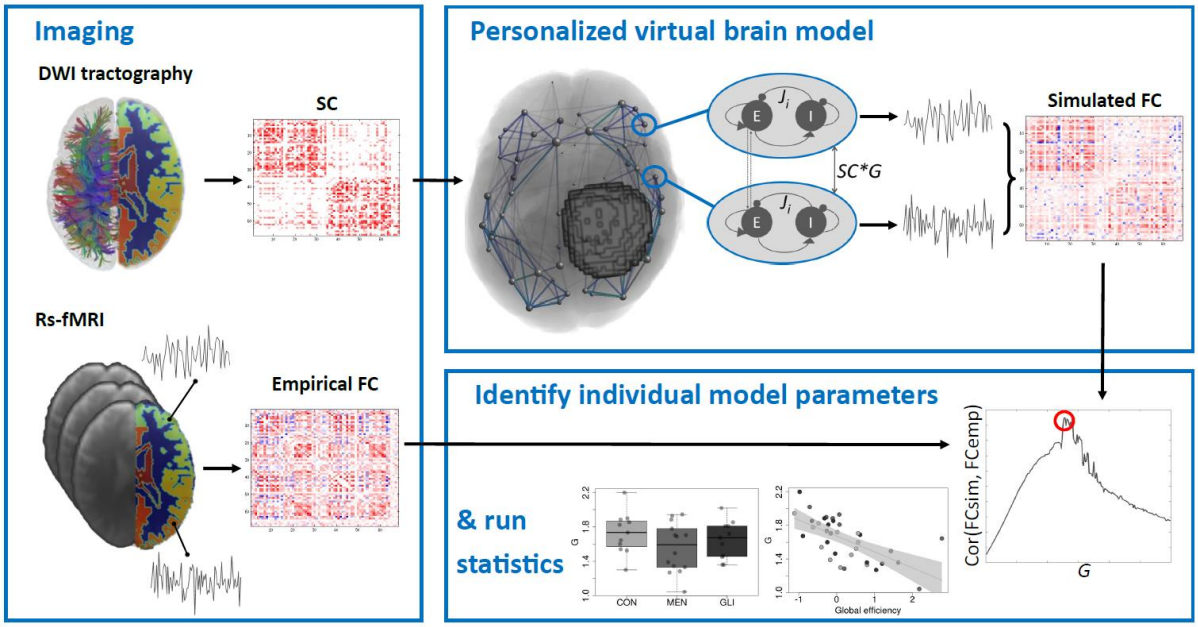
Abstract: Presurgical planning for brain tumor resection aims at delineating eloquent tissue in the vicinity of the lesion to spare during surgery. To this end, non-invasive neuroimaging techniques such as functional MRI and diffusion weighted imaging fiber tracking are currently employed. However, taking into account this information is often still insufficient, as the complex non-linear dynamics of the brain impede straightforward prediction of functional outcome after surgical intervention. Large-scale brain network modeling carries the potential to bridge this gap by integrating neuroimaging data with biophysically based models to predict collective brain dynamics. As a first step in this direction, an appropriate computational model has to be selected, after which suitable model parameter values have to be determined. To this end, we simulated large-scale brain dynamics in 25 human brain tumor patients and 11 human control participants using The Virtual Brain, an open-source neuroinformatics platform. Local and global model parameters of the Reduced Wong-Wang model were individually optimized and compared between brain tumor patients and control subjects. In addition, the relationship between model parameters and structural network topology and cognitive performance was assessed. Results showed (1) significantly improved prediction accuracy of individual functional connectivity when using individually optimized model parameters; (2) local model parameters can differentiate between regions directly affected by a tumor, regions distant from a tumor, and regions in a healthy brain; and (3) interesting associations between individually optimized model parameters and structural network topology and cognitive performance.



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Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.08/LLL36

Topic: I.06. Computation, Modeling, and Simulation

Title: Toward a standard network model of musical improvisation

Authors: *S. E. FABER, A. R. I. MCINTOSH
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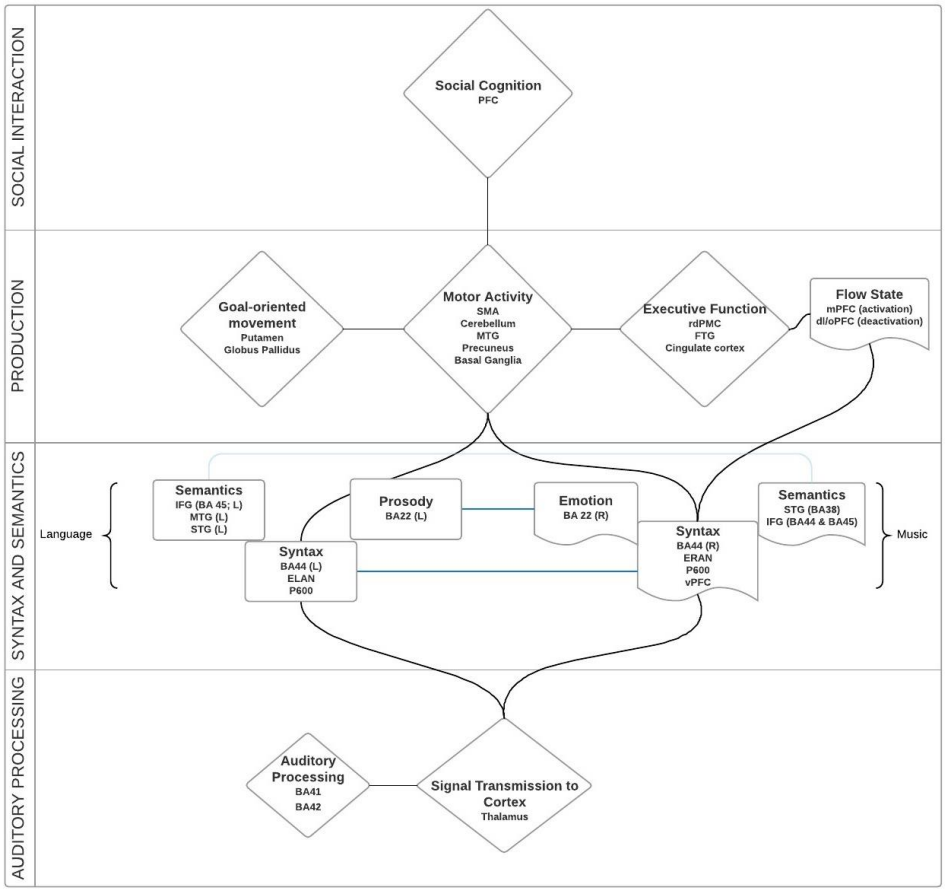
Abstract: Music and language are sophisticated communicative mediums that share many commonalities in the brain. Both rely on acoustic cues, both have form and are bound by culturally-defined rules, and both are social behaviours. The neural correlates of music and speech perception have been extensively quantified. These correlates include an auditory processing network common to both behaviours, and analogous networks for parsing semantic and syntactic content. Researchers have now begun studying productive, spontaneous speech and music-making, adding networks for executive control and goal-directed movement to the perceptual foundation, but the field has yet to reach consensus. This poster will present a new model of social music-making that includes its underlying neural correlates based on previous neuroimaging studies of the perception and production of language and music. I will make recommendations on future directions for the study of social music-making, including research with clinical populations, and discuss the challenges posed by such endeavours.



Disclosures: S.E. Faber: None. **A.R.I. McIntosh:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.09/LLL37

Topic: I.06. Computation, Modeling, and Simulation

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European Commission's Human Brain Project (grant agreement H2020-720270)
French National Research Agency (ANR) as part of the second “Investissements d’Avenir” program (ANR-17-RHUS-0004, EPINOV)
French Institute of Health and Medical Research (Inserm, International Laboratory Associated Program Epi-Surge)
SATT Sud-Est (827-SA-16-UAM)

Title: Characterization of interictal epileptogenic brain networks: Mechanistic insights from large-scale computational modeling using the virtual brain

Authors: *J. COURTIOL[1,2], S. PETKOSKI[1], V. K. JIRSA[1]
[1]Inst. de Neurosciences des Systèmes, Marseille, France; [2]Charité, Univ. Med. Berlin, Berlin, Germany

Abstract: Epileptogenic brain networks are associated with changes in functional connectivity even at rest during the interictal period (i.e., between seizures). Although some algorithms can nowadays robustly detect these changes, findings so far are inconsistent and the mechanism by which these changes occur is still largely unknown. Large-scale computational modeling carries the potential to bridge this gap by investigating the dynamical characteristics of the interictal epileptogenic brain networks during resting-state, in order to study their effects on the resulting functional connectivity. To achieve this, we virtualized 15 individual healthy and epileptic subjects' brain by using the neuroinformatics platform The Virtual Brain. Personalized virtual brain model was built based on a phenomenological neural mass model for resting-state and unfolding over subject-specific brain anatomical connectivity. We investigated how the global brain dynamics leading by the control model parameters (excitability and global coupling) changed between healthy and epileptic subjects by estimating them from functional empirical data and identifying the optimal dynamic working point of each subject's brain. Compared with healthy subjects, epileptic patients showed similar topology of resting-state functional connectivity. Suggesting that brain anatomical connectivity did not differ significantly between the two groups. We then progressively incorporated in the brain model, the patient-specific interictal epileptogenic networks, identified by the pre-surgical evaluation, by systematically altering the underlying local excitability model parameter of the corresponding nodes. The model showed a linear global increase of functional connections and variability along with the increase of excitability parameter and size of the interictal epileptogenic networks. However, the significantly increased were located in the epileptogenic networks followed by a diminished level of complexity. These findings provide a possible underlying mechanism explaining the empirical interictal functional connectivity changes observed in epileptic patients during resting-state, namely a local shift of the brain's dynamic working point of the brain regions involved in the seizure, leading to increased connectivity and decreased complexity.

Disclosures: J. Courtiol: None. **S. Petkoski:** None. **V.K. Jirsa:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

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Program #/Poster #: 340.10/LLL38

Topic: I.06. Computation, Modeling, and Simulation

Support: Ontario Graduate Scholarship
Wiseman Graduate Student Fellowship

Title: Effects of fMRI preprocessing choices on functional connectivity in children and adolescents with and without autism spectrum disorder

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Abstract: Autism spectrum disorder (ASD) is a highly heterogeneous disorder that has been described as a developmental disconnection syndrome. It has been suggested that ASD is characterized by reduced functional connectivity (FC) between frontal and posterior brain regions, increased FC among local regions with concurrent decreases in FC between distant regions, and an atypical trajectory of FC development. However, there has yet to be a framework describing the nature of FC in ASD that is supported consistently. This inconsistency can be attributed, in part, to heterogeneous samples, but also due to heterogeneity of fMRI preprocessing steps across studies.

The aim of this study is to address the heterogeneity of preprocessing methodology by evaluating the effects of different fMRI preprocessing choices on group differences in FC observed between participants with and without ASD.

Resting state fMRI data from 19 participants with ASD (M=10.25 years, SD=1.51 years) and 16 typically developing (TD) participants (M=9.97 years, SD=1.70 years) were obtained from the ABIDE-II database. Participants were matched for age, IQ, and head motion. Using *Optimization of Preprocessing Pipelines for NeuroImaging* (OPPNI; Churchill et al., 2015) software, the following steps were varied: temporal detrending (orders 0-6), lowpass filtering, global signal removal using PCA (GSPC), WM and CSF signal regression (CUSTOMREG), and motion censoring. Time series of 82 cortical ROIs were extracted. FC was defined by Fisher z-transformed Pearson correlations for each ROI pair across all time points. Further, structural connectivity (SC) matrices were constructed from DTI data using The Virtual Brain pipeline. Simulations of resting-state data were performed in TVB. Effects of preprocessing on FC, correlations between each subject's SC and FC matrices, and correlations between simulated and empirical FC, were examined.

CUSTOMREG and GSPC led to diffuse reductions in FC. Further, interactions between pipelines and groups were observed. However, a set of connections showed consistent group differences across all pipelines, with primarily reduced FC in ASD. Across pipelines, there were significant differences in SC-FC correlations and correlations between simulated and empirical FC, which were particularly prominent when GSPC, CUSTOMREG, and lowpass filtering were turned off.

Our results highlight the sensitivity of FC to different preprocessing strategies, especially when comparing groups.

Disclosures: A.K. Easson: None. **S.C. Strother:** Other; VP & Chief Science Officer for ADM Diagnostics, Inc.. **A.R. McIntosh:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.11/LLL39

Topic: I.06. Computation, Modeling, and Simulation

Title: The neurodegenerative virtual brain

Authors: *L. STEFANOVSKI[1,2], P. TRIEBKORN[1,2], A. SPIEGLER[1,2], M. H. MOHAJERANI[3], A. SOLODKIN[4], V. K. JIRSA[5], A. R. MCINTOSH[6], P. RITTER[1,2,7]
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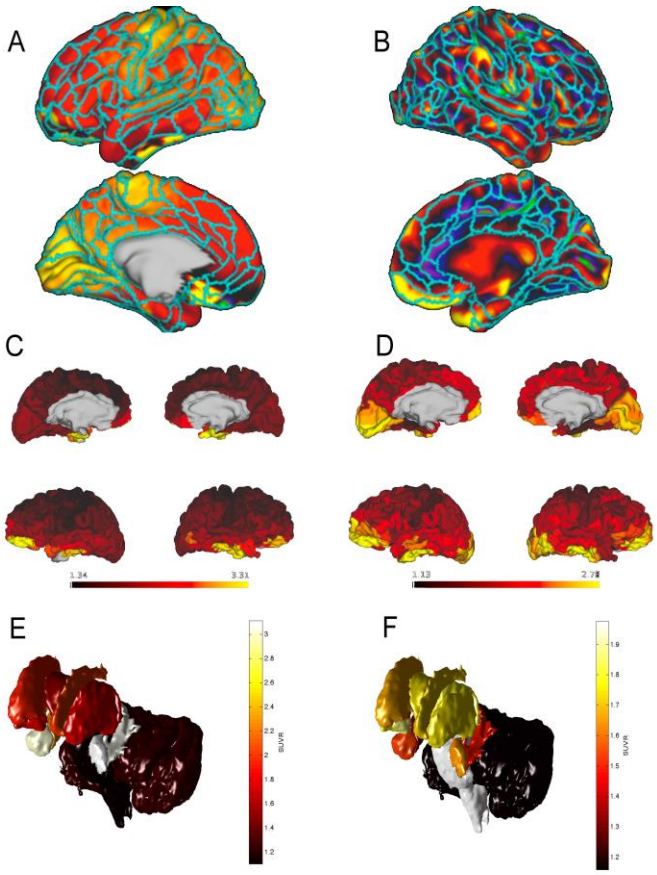
Abstract: We demonstrate how computational multi-scale brain modeling (1) supports revealing potential disease mechanisms in Alzheimer's disease (AD). Central to our research is The Virtual Brain (TVB; thevirtualbrain.org) platform (2,3). TVB allows connectome-based simulation of whole brain dynamics. Recent work with AD patients, healthy controls (HC) and persons with mild cognitive impairment (MCI) from the Sydney Memory and Aging Study confirms the benefit of using the model parameters to characterize cognitive status (4). We here build on this proof of concept and apply advanced methods to a cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI, adni.loni.usc.edu). We used a refined processing pipeline (5) for patients with MCI (n=41), AD (n=17) and HC (n=91). We implemented the processing standards of the Human Connectome Project (HCP, humanconnectome.org) with multimodal parcellation in 379 cortical and subcortical regions (Fig.1). We demonstrate how pathological candidate mechanisms reveal their systems effects in brain network models (BNM's) using TVB. Detailed spatial information derived from person-specific positron emission tomography (PET) with AV-45 and AV-1451 tracing amyloid beta and tau protein was mapped to the individual BNMs (Fig.1). We model the tau burden as a reduced local degree of structural connectivity and the amyloid beta burden as an increased E/I balance. We demonstrate how individual models can explain inter-subject variability of functional activity and cognitive performance.
Figure 1. A,B) MSM parcellation of an ADNI brain showing the right and left pial surfaces. Color: myelin map (A) and cortical folding (B). C,E) Distributions of tau protein and D,F) amyloid beta taken from individual PET data projected to surfaces of cortical/subcortical structures in AD. Registeration to the Glasser group template. Colorbars: SUVR (standardized uptake value ratio).1. Schirner et al. Elife 2018 2. Sanz Leon et al. Front Neuroinform 2013 3. Ritter et al. Brain Connect 2013 4. Zimmermann et al. NeuroImage. Clin. 2018 5. Schirner et al. Neuroimage 2015



Disclosures: L. Stefanovski: None. **P. Triebkorn:** None. **A. Spiegler:** None. **M.H. Mohajerani:** None. **A. Solodkin:** None. **V.K. Jirsa:** None. **A.R. McIntosh:** None. **P. Ritter:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.12/LLL40

Topic: I.06. Computation, Modeling, and Simulation

Support: CIHR

Title: Creating a macaque connectome for large-scale network simulations in TheVirtualBrain

Authors: *K. SHEN[1], S. EVERLING[2], A. R. MCINTOSH[1]
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Abstract: Linking cellular and circuit-level neural activity with signals collected using noninvasive imaging techniques remains a significant challenge to understanding the underlying mechanisms associated with BOLD-fMRI and M/EEG signals. TheVirtualBrain (TVB) is a software platform developed to meet this challenge through simulations of whole-brain network dynamics constrained by multimodal neuroimaging data. TVB models link biophysical parameters at the cellular level with systems-level functional neuroimaging signals. Multi-scale data available from animal models can provide vital constraints for the linkage across spatial and temporal scales. Here, we describe the development of a macaque structural connectome as an initial step towards establishing a comprehensive multi-scale macaque model in TVB. A whole-brain connectivity matrix of 82 ROIs was first generated from the CoCoMac database of tract tracing studies. The resulting matrix included information on the directionality of fiber tracts, but lacked details on fiber tract capacities and tract lengths, variables critical for describing the space-time relationships in large-scale networks. We enhanced this connectome with diffusion-weighted imaging data collected from 10 adult male macaque monkeys (9 *Macaca mulatta*, 1 *Macaca fascicularis*) at 7T. For each animal, probabilistic tractography was performed only for connections specified in the CoCoMac-derived matrix to generate individual estimates of fiber tract capacities and tract lengths. Tractography parameters for each animal were chosen so as to optimize overall accuracy based on an independent tract tracing dataset. Fiber tract capacities were estimated as the probability of detecting streamlines between each ROI pair. Estimates were then averaged across animals to produce 1) a weighted and directed connectivity matrix, and 2) a corresponding tract length matrix. Preliminary simulations of population activity using this macaque connectome yielded networks akin to known resting-state networks in macaques. Further development will allow simulations to be fit to resting-state BOLD-fMRI data collected from the same subjects. This work is a crucial first step to incorporating structural and functional constraints to multi-scale models of brain dynamics in humans.

Disclosures: K. Shen: None. **S. Everling:** None. **A.R. McIntosh:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.13/LLL41

Topic: I.06. Computation, Modeling, and Simulation

Support: James S. McDonnell Foundation JSMF22002082
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John von Neumann Institute for Computing at Jülich Supercomputing Centre
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Stiftung Charité/Private Exzellenzinitiative Johanna Quandt and Berlin Institute of Health
German Research Foundation RI 2073/6-1

Title: Disentangling the effects of aging related network changes for unimanual motor learning - An fMRI/EEG study

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Abstract: Motor learning requires orchestration across sensorimotor networks that can be impaired with age-related neurodegeneration, in particular in the corpus callosum[1]. As a consequence, motor learning may become challenging. We hypothesize that imbalance of inter-hemispheric (excitation) and intra-hemispheric (inhibition) connectivity between PM1 and M1 leads to decreased motor learning capabilities with age[2,3]. We examined 20 young (20-25y) and 20 older (59-70y) healthy right-handed participants who learned to perform a rhythmic perceptual motor task with their right hand, while being monitored with simultaneous EEG-fMRI[4] at Charité Berlin. We quantified behavioral performance by the strength of frequency locking between visual cues and exerted manual force. Improved performance appeared in both groups ($F(4.44,79,96)=2.56$, $p<.05$), but more pronounced in the younger. A 24h follow-up retention test confirmed motor learning in both groups (young $p=.003$, older $p=.007$). Moderate differences occurred in motor-correlated fMRI between groups (peak right cingulum *$T=5.23$ $p<.001$)*. Artifact corrected and motor correlated EEG β-band (15-30Hz) beamformers were lateralized in both groups albeit stronger in the young with left M1 peak ($T=12,95$ $p<.001$). An additional ipsilateral component in the older was found ($T=6,01$, $p<.001$*)*. For both groups motor-task related β-band de-synchronization in left M1 was correlated with behavioral improvement ($r=0.310$, $p<.001$). Our results point at an age-related functional re-organization possibly reflecting an imbalance of inter- and intra-hemispheric pathways. To clarify this further, we will use source-reconstructed EEG in contralateral M1 as regressors for fMRI. This will discern (bilateral) M1 and dorsal PM, which both contribute to motor output[2]. Resulting patterns are expected to differ not only in their lateralization but also in the intra-hemispheric activation. This and future simulations with TheVirtualBrain, will refine our findings that do already support the hypothesis of the need for interhemispheric and intra-hemispheric connectivity for motor performance and learning.

1. Sullivan, Pfefferbaum 2006 *Neurosci & Biobehav Rev*
2. Daffertshofer et al. 2005 *Biolog Cybern*
3. Van Impe et al.2009 *NeuroImage*
4. Ritter, Villringer 2006 *Neurosci & Biobehav Rev*

Disclosures: J. Zimmermann: None. **A. Daffertshofer:** None. **P. Ritter:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.14/LLL42

Topic: I.06. Computation, Modeling, and Simulation

Support: James S. McDonnell Foundation JSMF22002082
Bundesministerium für Bildung und Forschung 01GQ0971-5 & 01GQ1504A
Horizon 2020 ERC Consolidator Grant 683049
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John von Neumann Institute for Computing at Jülich Supercomputing Centre NIC#8344
Stiftung Charité/Private Exzellenzinitiative Johanna Quandt and Berlin Institute of Health
German Research Foundation RI 2073/6-1

Title: How brain oscillations shape perceptual learning - Empirical observations and computational modeling

Authors: *P. TRIEBKORN[1], D. ROY[2], R. SIGALA[1,3], F. FREYER[1,3], A. R. MCINTOSH[4], H. R. DINSE[5,6], P. RITTER[1,3,7]
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Abstract: One of the fundamental functions of our brain is to learn and adapt to our environment, yet little is known about the inter-subject learning variability. In this study we investigate the relation between changes in human electroencephalogram (EEG) oscillations and improvement in tactile acuity. Therefore 26 healthy individuals underwent EEG recordings as well as psychophysical measurements. Perceptual learning was measured via a two-point discrimination task before and after a 30 min repetitive-sensory stimulation of the right index finger. Changes of resting-state upper alpha band oscillations in sensorimotor areas contralateral to the stimulated finger pre versus after stimulation predict the improvement of tactile acuity. This effect sits on top of state-dependent learning outcomes demonstrated previously. In other words, resting state upper alpha (~10-12 Hz) changes over sensorimotor areas contralateral to stimulation are predictors of learning. Using a physiologically-inspired computational model we identify possible neural mechanisms for observed empirical phenomena. Our model combines macro- and microscale characteristics. It simulates cortical activity of primary somatosensory

and motor cortex driven by a thalamic input. Local regions are made of recurrently connected inhibitory and excitatory spiking neurons. Learning is implemented via spike-dependent plasticity kernels and detection rate measured via the phase-locking index of cortical oscillations to thalamic spikes. We systematically explore the effect of the parameters local recurrent inhibition strength and thalamic input frequency on neural frequency changes and learning. An increase in local inhibition and decrease in the thalamic input frequency reproduce the empirical finding of negative correlation between alpha power change and improved tactile acuity.

Disclosures: D. Roy: None. **R. Sigala:** None. **F. Freyer:** None. **A.R. McIntosh:** None. **H.R. Dinse:** None. **P. Ritter:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

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Topic: I.06. Computation, Modeling, and Simulation

Support: Excellence Initiative of the German federal and state governments
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Fondation pour la Recherche Médicale (FRM) (grant number DIC20161236442)

Title: Automatically generating HPC-optimized code for simulations using neural mass models

Authors: *A. PEYSER[1], S. DIAZ[1], M. WOODMAN[2], V. K. JIRSA[2]
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Abstract: High performance computing (HPC) is becoming more accessible and useful as a neuroscientific tool. Simulations of brain networks and analysis of medical data can now be performed at larger scales and with higher resolution. However many current neuroscientific software tools can't utilize yet the full power of supercomputers, GPUs and other computational accelerators.

The Virtual Brain (TVB: Sanz et al 2013) is a validated and popular choice for the simulation of whole brain activity. With TVB, the user can create simulations using neural mass models spanned in 3D space and generate forward solutions for common brain imaging signals (EEG, MEG, fMRI, etc). TVB allows scientists to explore and analyze simulated and experimental signals and contains tools to evaluate relevant scientific parameters over both types of data (Saenz, 2015). Internally, the TVB simulator contains several models for generating neural activity at the region scale. Most of these models are efficiently described using groups of coupled differential equations numerically solved over large spans of simulation time. Currently the models simulated in TVB are primarily written in Python and haven't been optimized for parallel execution or deployment on HPC architectures. Moreover several elements of these models can be abstracted, generalized and re-utilized, but the right abstract description for these models hasn't been implemented yet.Here we present early results from porting several TVB workflows to HPC accelerators. To reduce the required effort to utilize different HPC platforms, we've developed an automatic code generation tool to define abstract models at all stages of simulation, and then translate them to hardware specific code. Our simulation workflows involve different neural mass models (Kuramoto 1997, Wong 2006, etc) as well as pre-processing and post-processing kernels (Balloon model: Buxton 1998, correlation metrics, etc). We discuss strategies used to keep code portable between several architectures yet optimized for each platform, including benefits and limitations. We also show performance comparisons and show what can be achieved with the new code in terms of scalability and simulation times. Implementation of efficient hyperparameter optimization for complex models in TVB such as the epileptic seizure propagation model (Jirsa et al 2017, Proix et al 2018) is a current focus. We discuss implementation of Bayesian Inference techniques used for this purpose and results of initial runs on the HPC infrastructure in Jülich.

Disclosures: A. Peyser: None. **S. Diaz:** None. **M. Woodman:** None. **V.K. Jirsa:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

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Topic: I.06. Computation, Modeling, and Simulation

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European Commission's Human Brain Project (grant agreement H2020-720270)
SATT Sud-Est (TVB-Epilepsy)
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Title: Optimal surgical options considering inoperable zones for epilepsy patients: A computational approach using the virtual brain

Authors: *S. AN[1], F. BARTOLOMEI[1], M. GUYE[2], V. JIRSA[1]
[1]Aix Marseille Univ, INSERM, INS, Inst. Neurosci Sys, Marseille, France; [2]CNRS, CRMBM UMR 7339, Aix Marseille Univ., Marseille, France

Abstract: At present, more than 30% of epilepsy patients suffer from drug-resistant seizures, and surgical intervention is considered as the effective method able to control the drug-resistant seizures. Current studies on epilepsy surgery mostly have focused on localizing the epileptogenic zone (EZ) and effectively removing it. However, in a significant number of patients, EZs are distributed in distinct brain regions and involve eloquent areas that cannot be surgically eliminated due to the risk of neurological complications. Therefore, it is important to develop alternative surgical methods able to induce seizure relief by suppressing seizure propagation to other brain regions, even if they do not prevent the occurrence of seizures in EZs. The method should have no significant impact on normal brain functions. In this study, we propose an in silico surgical approach able to suggest effective and safe surgical options for each patient in case there are inoperable EZs. Our method employs modularity analysis using structural brain connectivity from each patient, which derives target brain regions and target fiber tracts, considering inoperable zones (IZs), for resection and disconnection surgeries, respectively. The effectiveness and the safety of the derived target zones (TZs) are evaluated by brain network simulations using The Virtual Brain (TVB) platform. In a patient-specific network model constructed by a neural mass model, structural brain connectivity and clinical estimation for EZs, characteristics of seizure propagation are simulated. In particular, changes of seizure-recruited regions after removing the TZs are observed in the worst-case where seizures spread to most brain regions. Moreover, the impact of the TZs on normal brain functions has been minimized using a metric developed to assess the integrity of the transient spatiotemporal trajectory following electrical stimulation at certain zones. This approach is aimed at preserving the information transmission capacity before and after eliminating the TZs. We apply this novel feedback approach comprising modularity analysis and network integrity preservation to a total of 7 drug resistant epileptic patients and identify the optimized surgical options for each individual patient. This study demonstrates the possibility of using computational approaches deriving optimal surgical options suitable for each patient and predicting the surgical outcomes.

Disclosures: F. Bartolomei: None. **M. Guye:** None. **V. Jirsa:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.17/LLL45

Topic: I.06. Computation, Modeling, and Simulation

Support: SATT Sud-Est (827-SA-16-UAM)

French National Research Agency (ANR) "Investissements d'Avenir" (ANR-17-RHUS-0004, EPINOV)
French Institute of Health and Medical Research (Inserm, International Laboratory Associated Program Epi-Surge)

Title: Explaining seizure onset patterns by computational modeling of a seizure spread on a cortical surface in The Virtual Brain

Authors: *V. SIP[1], M. GUYE[2,3], F. BARTOLOMEI[1,4], V. K. JIRSA[1]
[1]Aix Marseille Univ, INSERM, INS, Inst. Neurosci Sys, Marseille, France; [2]Aix Marseille Univ, CNRS, CRMBM, Marseille, France; [3]Assistance Publique – Hôpitaux de Marseille, Hôpital de la Timone, CEMEREM, Pôle d'Imagerie Médicale, CHU, Marseille, France; [4]Assistance Publique – Hôpitaux de Marseille, Hôpital de la Timone, Service de Neurophysiologie Clinique, CHU, Marseille, France

Abstract: Among the most commonly observed patterns in intracranial electroencephalography (iEEG) recordings of focal epileptic seizures is the so-called fast activity pattern (FA). This pattern is characterized by fast oscillations (8-30 Hz) and gradually increasing amplitude. Looking through the optics of dynamical system analysis, such onset resembles a nonlinear system going through a supercritical Hopf bifurcation, which may thus be the primary candidate to model the onset dynamics. Here we investigate a different mechanism that can mimic such FA onset pattern through the mechanism of traveling neural fields on a folded cortical sheet. At a given location, the neural field shows a rapid transition via saddle-node bifurcation from silent state to seizure state. The activity of the sheet is observed through the generated local field potential recorded on the contacts of a depth electrode. In this scenario, the gradual amplitude increase on the recorded signals is caused by the translation of the neural field and the subsequent spatial averaging of the source activity. We use The Virtual Brain platform to simulate the spread of the epileptic seizure on a piece of a cortical surface located in the vicinity of the intracranial electrode of interest. The highly resolved triangulated cortical surface is derived from the neuroimaging scans of a patient with a temporal lobe epilepsy. The Epileptor field model is employed to represent the source dynamics, and a dipole model of the cortical surface is used to calculate the iEEG signals from the source activity. Similarly as the iEEG recordings from the real patient, the simulated iEEG signals exhibit the typical feature of the FA onset pattern - slowly increasing amplitude of the oscillations. The comparison of the recorded and simulated signals in terms of the timing of the apparent seizure onset and the duration of the period of amplitude increase show also quantitative consistency, demonstrating the plausibility of the mechanism on the realistic spatial and temporal scales. The results show that it is not necessary that a dynamical model switches to a seizure state through a Hopf bifurcation; other bifurcations may produce the same onset pattern on the electrodes via the here described field effects. Because the choice of the bifurcation type has important consequences for the dynamical behavior of the system (e.g. for the response to stimulation), the obtained results underscore the importance of the appropriate model choice and suggest more dynamic interpretations of the concept of Epileptogenic Zone.

Disclosures: V. Sip: None. **M. Guye:** None. **F. Bartolomei:** None. **V.K. Jirsa:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

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Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.18/LLL46

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French Institute of Health and Medical Research (Inserm, International Laboratory Associated Program Epi-Surge)
SATT Sud-Est (827-SA-16-UAM)

Title: TVB-epilepsy: A software tool extending the virtual brain to predict patient specific seizure propagation

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Abstract: TheVirtualBrain (TVB) is an open source neuroinformatics platform for full brain network simulations using biologically realistic connectivity (see http://www.thevirtualbrain.org). Based on generative model simulation, TVB links the anatomical structure of an individual's brain large-scale networks, obtained via Diffusion Tensor Imaging (DTI), to observable functionality, i.e., neuroimaging signals (functional MRI, EEG, MEG and intracranial EEG) measured experimentally or clinically. Thus, TVB enables the model-based inference of neurophysiological mechanisms across different brain scales that underlie healthy as well as pathological brain function.
One of the most developed and pioneering clinical applications of TVB technology is to be found in epilepsy, a chronic non-communicable disorder of the brain that affects tens of millions of people of all ages worldwide. The current surgery success rate for drug resistant epilepsy (DRE) patients ranges from 30% to 70%, depending on the type of epilepsy, and has remained unchanged in the last fifty years. One of the most daunting challenges of DRE treatment using neurosurgery is the identification of the epileptogenic zone (EZ) responsible for the origin and propagation of an epileptic seizure in the brain.
Here we introduce TVB-epilepsy, a TVB module that extends TVB functionality with statistical inference techniques, aiming at facilitating the use of TVB for epilepsy applications by academic

and clinical researchers alike. Building on recent research on the dynamical mechanisms of seizure onset and propagation via permittivity coupling, TVB-epilepsy uses TVB to construct a dynamical brain network model of seizure energy propagation from patient's (d)MRI data. TVB-epilepsy extends the dynamical brain network model to a probabilistic model and inverts it by contrasting its predictions to (intracranial) EEG clinical data. Thus, TVB users can fit neurophysiologically relevant network parameters, the most important of which, namely the pathological excitability of each brain region, directly points to the EZ. For statistical inference, TVB-epilepsy includes an interface to STAN, a state-of-the-art platform for statistical modelling and high-performance statistical computation (see mc-stan.org). We present TVB-epilepsy's architecture and illustrate its basic workflow along use cases of patients with temporal-lobe DRE.
In summary, TVB-epilepsy enables the clinical and academic researcher to use concepts and state-of-the-art brain network models for patient-specific epilepsy research in a dedicated software environment.

Disclosures: M.M. Woodman: None. **P. Popa:** None. **L. Domide:** None. **J. Mersmann:** None. **V.K. Jirsa:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.19/LLL47

Topic: I.06. Computation, Modeling, and Simulation

Support: Faculty for the Future Fellowship award

Title: Relationship of EEG and music features through low dimensional manifolds

Authors: *S. SHAKIL, S. FABER, A. R. MCCULLOCH, T. M. BROWN, K. SHEN, A. R. MCINTOSH
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Abstract: Background: Music influences mood, and this influence can be associated with musical features. 'Pleasant' music elevates mood and 'sad' music decreases mood. However, the relationship of these features to brain function and states is not well-studied. Here, we explore the relationship between musical features and brain states extracted from EEG data. **Methods**: For this study, we used EEG data from nine healthy subjects (19-35 years old) listening to 40 second excerpts from 25 pieces ranging from Renaissance to contemporary classical. Data was collected using a 64+10 Biosemi Active Two System at a sampling rate of 512 Hz and was preprocessed in EEGLAB. Afterwards, we formed one EEG matrix for each subject by concatenating all music pieces for all electrodes. We also grouped the music pieces in six groups

(very sad, sad, very angry, angry, tender, and happy) based on the valence and arousal features extracted from the musical excerpts. The EEG matrix of each subject was mapped onto a two-dimensional manifold using non-linear dimensionality reduction technique t-Distributed Stochastic Neighbor Embedding (**t-SNE**). Finally, we mapped the music groups onto the t-SNE manifolds. **Results**: Fig. 1, shows the results of the music group mappings on a 2D manifold of EEG data for three subjects. Here, each data point is the brain state at a particular time point based on the EEG data. We observed that the EEG time points for similar music features tend to cluster together (in similar states) as is evident from same color clusters. Furthermore, the sad and very-sad (blue and red) groups extracted from music are close. We do not find such state similarity for very-angry and angry states (yellow and pink), which may suggest that additional musical features should be taken into account in data grouping. **Conclusions**: Different types of music may induce unique brain activity in many states, which may explain music's effectiveness in mood regulation or in therapeutic settings. The relationship between brain states and music features needs to be explored more in order to effectively employ music as a therapeutic tool.

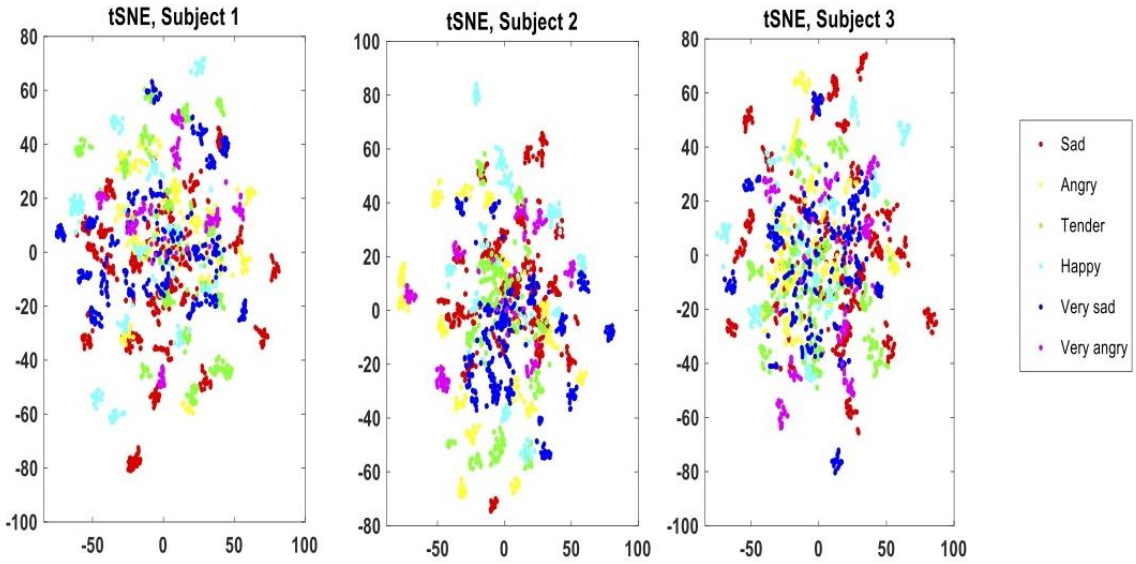

Fig. 1. Music groupings mapped on 2D manifolds of EEG data.

Disclosures: S. Shakil: None. **S. Faber:** None. **A.R. McCulloch:** None. **T.M. Brown:** None. **K. Shen:** None. **A.R. McIntosh:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

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Program #/Poster #: 340.20/LLL48

Topic: I.06. Computation, Modeling, and Simulation

Support: James S. MacDonnell Foundation
The German Ministry of Education and Research
European Union Horizon 2020

Title: Decoding music induced emotions

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Abstract: We study how music alters our emotions on a subjective level. Total 18 subjects (9 females) listened to 30 classical musical excerpts while EEG data was recorded and continuous rating from participants was acquired on a two-dimensional scale of valence and arousal. Data were analyzed a) using PLS[1], b) the source separation framework SPoC[2], and c) classification via cross-frequency coupling features. Results: a) PLS analysis results in two significant variables. Unpleasant- relaxing pieces were related to high alpha-beta 10-20Hz ($p= 0.009$) whereas pleasant -stimulating were related to high gamma 40-80Hz ($p=0$). b) Participants who listen to music to regulate mood have more sensitivity to valence and less to arousal in their EEG ($p<0.05$). Shy and reserved personalities had lesser modulation of EEG ($p<0.01$). c) Two forms of CFC, namely PSI (phase synchronization index) and PAC (phase amplitude coupling) were applied to classify the emotional states, and compared with normally used methods PSD (power spectral density) and DLAT (difference in left-right laterality direction). The results showed that the best performance was obtained by features derived from PAC_4Hz at mean accuracies of 93.49% 92.42% separately for valence and arousal binary classification. Both in valence and arousal level, all the EEG coupling features outperformed the performance of feature types PSD and DLAT. Cross-frequency coupling was more sensitive to characterize the EEG variation in response to emotional states. Since mood is typically described as having either positive or negative valence, our results from b) corroborate that participants who use music to regulate their mood have higher weights for valence compared to arousal, i.e. their EEG is stronger modulated by valence. To capture the interaction of emotion network during musical listening we will combine EEG with fMRI and use the neuro-informatics platform The Virtual Brain (TVB, thevirtualbrain.org) for connectome based multi-scale brain simulations[3]. With TVB we reconstruct the information flow within the brain network and reveal processes that are not directly accessible from brain recordings.
[1]McIntosh et al. Neuroimage 2004
[2]Dähne et al. NeuroImage 2014
[3]Schirner et al. Elife 2018

Disclosures: A. Ghani: None. **J. Zhang:** None. **A. Mclntosh:** None. **K. Müller:** None. **P. Ritter:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.21/LLL49

Topic: I.06. Computation, Modeling, and Simulation

Title: The virtual brain to characterize brain dynamics before and after MR guided interstitial thermal ablation for childhood epilepsy

Authors: *M. M. VANDEWOUW[1], A. G. WEIL[2], G. M. IBRAHIM[3]
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Abstract: Introduction. Epilepsy is a brain disorder characterized by seizures affecting approximately 1-2% of children worldwide, and is associated with significant medical, psychological, and social burdens. Magnetic resonance imaging (MRI)-guided laser-induced thermal ablation has been shown to be an effective and non-invasive treatment for those with refractory epilepsy. Although neuroimaging techniques are used to guide the ablation surgery, the complexity of brain dynamics makes it difficult to predict seizure outcome post-ablation. Whole-brain network modeling combining detailed biophysical information with global dynamics has the potential to better predict changes pre- and post-ablation.
Methods. We obtained data on 12 children with refractory epilepsy. Prior to surgery, while under sedation, the children underwent T1-weighted structural imaging, diffusion-tensor imaging (DTI), and resting-state functional imaging according to site-specific protocols. T1-weighted and resting-state images were also collected immediately after surgery. Post-operative structural T1-weighted images were used to generate ablation volumes. We simulated the pre-ablation large-scale brain dynamics using The Virtual Brain (TVB), inputting each participant's structural connectivity and individually optimizing local and global biophysical parameters according to their pre-ablation functional connectivity. Structural connectomes were then modified according to the ablation volume, and parameters were re-optimized using the post-ablation functional connectivity.
Results. Individualized local and global model parameters were able to accurately simulate pre-ablation brain dynamics. Furthermore, the re-optimized parameters specific to the ablation-modified structural connectome more accurately predicted post-ablation functional connectivity. Each participant's parameters differed between pre- and post-ablation.
Conclusions. Modeling complex brain dynamics with The Virtual Brain can help to further understand the effects of thermal ablation surgery for refractory epilepsy, and the local and global biophysical parameters are altered after ablation.

Disclosures: M.M. Vandewouw: None. **A.G. Weil:** None. **G.M. Ibrahim:** None.

Poster

340. Computation, Modeling, and Simulation: Human Network Models

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 340.22/LLL50

Topic: I.06. Computation, Modeling, and Simulation

Title: Measuring causality in simulations of large scale brain networks using the virtual brain

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Abstract: Inferring causal relations between the nodes of large-scale brain networks can reveal network topology, connectivity, and function, and help uncover the neurobiological basis of cognition. Appropriate methodologies for measuring dynamic causality in large-scale brain networks remain varied and elusive. In this project, we seek to infer causal relations in large-scale brain networks using a nonlinear neural mass model to generate time series data of a local field potential (LFP) signal, and use both the linear autoregressive modeling technique of Granger causality (GC) and the information-theoretic method of transfer entropy (TE), detecting nonlinear relations to analyze the data. Data are generated from two coupled oscillatory neural masses in The Virtual Brain (TVB). We previously provided theoretical and empirical analyses of probabilistic causality in LFP data of a large scale brain network, recovering the causal conditions using a popular variation of GC, in a unique manner. Here we extend the analysis in several ways: 1) we vary the control parameters and thus change the intrinsic dynamics of each node in the model to explore their distinctive effects on causality, 2) we use TE in a unique manner, to remain consistent with the GC results, and 3) we use TE and GC to recover a range of *a priori* parameterized conduction delays set in TVB. TE and GC are widely validated methods in neuroscience, and have been shown to be theoretically equivalent under certain conditions. Here, we empirically validate that equivalency.

Disclosures: M. Mannino: None. **S.L. Bressler:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.01/LLL51

Topic: I.07. Data Analysis and Statistics

Support: NIH grant MH108591
NSF grant BCS1558497

Title: Multivariate distance correlation features of functional connectivity improve the reliability and power of connectome-based predictive modeling

Authors: *K. R. YOO[1], M. D. ROSENBERG[2], S. M. NOBLE[3], D. SCHEINOST[4], R. T. CONSTABLE[5], M. M. CHUN[4]
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Abstract: FMRI studies have shown that multivariate spatial activity patterns across voxels reflect mental states of the brain (Haxby et al. 2014). An open question is whether multivariate voxel-wise timecourses can better characterize region-by-region interactions (functional connectivity) compared to univariate approaches, typically measured with Pearson's correlations (r). We investigated the utility and reliability of multivariate functional connectivity estimated by multivariate distance correlations (dCor; Székely et al. 2007), a measure of multivariate dependency between two sets of variables, estimating both linear and non-linear associations. We examined the utility of multivariate functional connectivity in two ways using data from the Human Connectome Project (S1200 release; n=563 after exclusion; 7 task and 2 rest scans/individual; 160 TRs/scan). First, we assessed the identifiability of individual connectomes (Finn et al. 2015), and second, we used these features to predict an individual's fluid intelligence, using connectome-based predictive modeling methods (Finn et al., 2015; Rosenberg et al., 2016; Shen et al., 2017). Prior work relied on Pearson's r to measure functional connectivity, and basically, this study tested whether dCor features may produce superior performance. Multivariate functional connectivity measures using dCor achieved a higher identification rate (97%; Pearson:82%) between individuals' two resting-state scans. Identification rates with dCor were higher among every pair of fMRI scans (97±2%; Pearson:58±15%;). Predictive models constructed using dCor better predicted individuals' fluid intelligence (correlation between predicted and observed scores: 0.242; Pearson:0.156; $p<0.05$ with 10,000 bootstrap). We then assessed the test-retest reliability of dCor in a dataset previously used to evaluate the reliability of functional connectivity estimated by Pearson correlations (n=12, Noble et al. 2017). Multivariate functional connectivity measured with dCor was more reliable than univariate functional connectivity measures with Pearson correlation. dCor had a higher edge-wise reliability (0.43±0.13 for a single 6-min scan; Pearson:0.18±0.13) and higher connectome-wise reliability (0.45; Pearson:0.22). Furthermore, dCor provided higher perfect separation rate than Pearson's r. In conclusion, our findings suggest that multivariate estimates of functional connectivity are more reliable than univariate estimates, providing more powerful information about an individual's functional brain organization and its relation to cognitive skills.

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Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.02/LLL52

Topic: I.07. Data Analysis and Statistics

Support: VA Merit Review Grants
Marine Resilience Study-II
McDonnel Foundation via Brain Trauma Foundation

Title: Blast-related mild traumatic brain injury in chronic phase: A diffusion tensor imaging study with machine learning

Authors: *P.-Y. HSU[1,2], R. THEILMANN[2], A. ANGELES-QUINTO[2], A. ROBB-SWAN[2], S. NICHOLS[2], D. HARRINGTON[2], A. DRAKE[4], T. SONG[2], M. DIWAKAR[5], R. CLIFFORD[2], R. LEE[2], C.-K. CHENG[2], A. MANDELL[2], D. BAKER[2], M. HUANG[3]
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Abstract: Individuals exposed to blast-related mild traumatic brain injury (bmTBI) often experience long-term neurological and cognitive disorders. Yet no optimal treatments have been developed specifically for bmTBI, owing in part to the heterogeneity of injuries. In this regard, sensitive neuroimaging techniques combined with multivariate statistical analyses might help elucidate the mechanisms underlying bmTBI and ultimately, potential treatment targets. In the present study, deployed service members with combat exposure were recruited, including 19 healthy controls (HC) and 20 individuals with chronic bmTBI. Participants underwent diffusion tensor imaging (DTI) and neuropsychological (NP) testing. Voxel-wise statistical analyses of DTI data were carried out using Tract-Based Spatial Statistics (TBSS), and regions that showed significant group differences in various diffusion metrics were then utilized as variables in a support vector machine (SVM) analysis to identify the linear combination of aberrant diffusion metrics that optimally distinguished bmTBI patients from HC participants. The TBSS analysis revealed significantly increased fractional anisotropy (FA) and reduced radial diffusivity (RD) in bmTBI compared to HC participants, but no group differences in mean diffusivity or axial diffusivity (AD). The SVM model achieved 94% classification accuracy of bmTBI and HC participants in cross-validation experiments based on FA and AD/RD ratio. Regions in the genu and body of the corpus callosum and bilateral anterior corona radiata, anterior and posterior limb of the internal capsule, and the superior corona radiata were identified as potential markers of bmTBI. These results provide important evidence that persistent neurological and cognitive

symptoms associated with a history of blast-exposure sustained during combat is related to subtle, yet long-term changes in the underlying neuropathophysiology of the brain.

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Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.03/LLL53

Topic: I.07. Data Analysis and Statistics

Title: Scan path modeling using marked point processes

Authors: *R. SHIBUE, M. YONEYA
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Abstract: A scan path is a time series of where the eye is looking. When modeling a scan path, it is necessary to consider the strong non-linearity arising from saccades. Without considering such non-linearity, estimation errors may occur and the estimate may become unreliable. This non-linearity also makes it difficult to model scan path distribution. Previous studies focused on partial features extracted from scan paths, such as the fixation map, saccade shapes and saccade transitions. These approaches disregard the relationships between partial features of scan path and it may result in loss of information.
In this presentation, we propose a new probabilistic generative model for scan paths. In our model, we use a marked point process determined by the superior colliculus structure to express a saccade occurrence and give a new definition of the saliency map. The marked point process is a stochastic process that is used for modeling series of events. It enables us to handle the non-linearity due to saccades without any preprocessing procedure and specify the scan path distribution directly.
We assume that the observed scan path is generated from the model and calculate the posterior of hidden variables by using variational inference approach. Distributions of partial features of a scan path can be obtained by marginalizing the estimated scan path distribution; our method can detect saccades, denoise a scan path measured by an eye tracker, estimate saccade shapes and calculate a fixation map simultaneously. Previous studies carried out these procedures in separate steps, which may cause errors and loss of information. On the other hand, our method avoids such problems by expressing these elements in a unified generative model.

Disclosures: R. Shibue: None. **M. Yoneya:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.04/LLL54

Topic: I.07. Data Analysis and Statistics

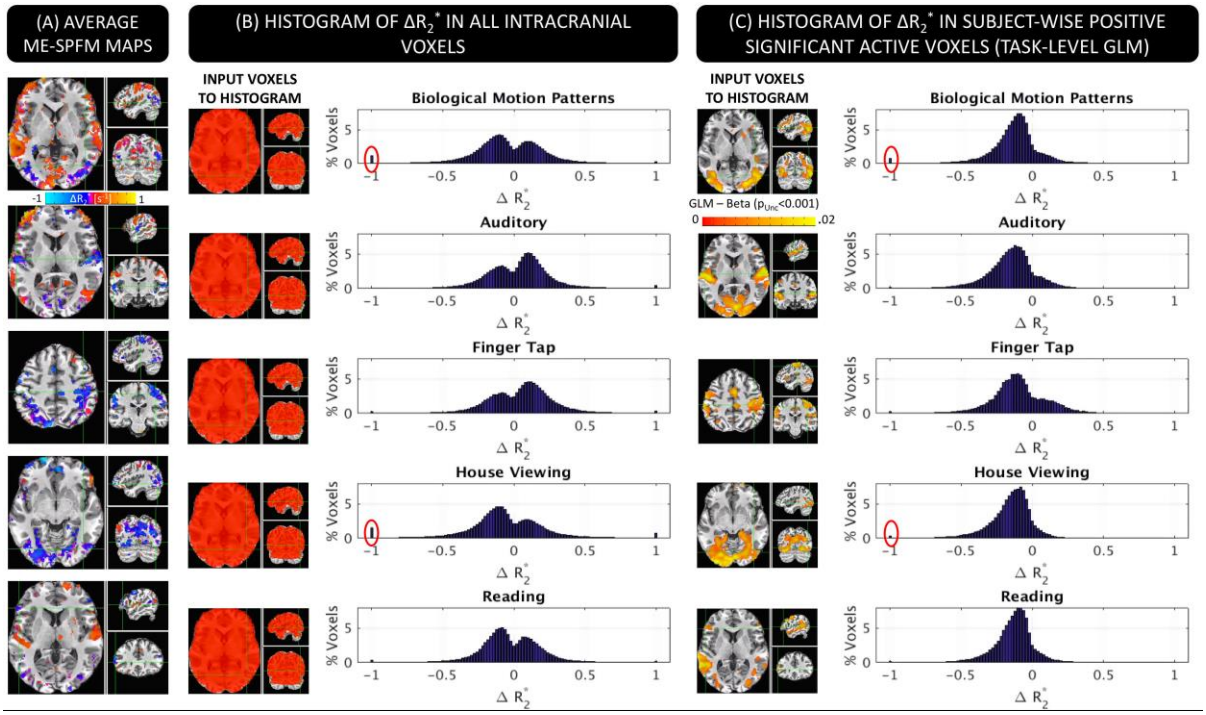
Support: NIH Grant ZIA MH002783
Juan de la Cierva Fellowship IJCI-2014-20821
Severlo Ochoa Programme for Centres/Units of Excellence in R& D (SEV-2015-490)

Title: Pseudo-quantitative deconvolution of neuronal-related BOLD events with unknown timing

Authors: *J. GONZALEZ CASTILLO[1], C. CABALLERO-GAUDES[2], P. BANDETTINI[3]
[1]SFIM/LBC/NIMH/NIH, Bethesda, MD; [2]Basque Ctr. for Brain, Cognition and Language, San Sebastian, Spain; [3]Lab. of Brain & Cog/Sect Function Imag, NIMH-NIH, Bethesda, MD

Abstract: Multi-echo (ME) fMRI results in K time-series per voxel; each acquired at a different TE. Well-known differences in TE dependence profiles for BOLD (linear dependence) and non-BOLD (no dependence) fluctuations can be exploited to automate denoising of ME fMRI time-series. Here, we propose a novel ME formulation of the Sparse Free Paradigm Mapping[(SPFM) algorithm that by combining a hemodynamic response model, the above-mentioned TE-dependence model and L1-norm regularized estimators, produces voxel-wise quantitative estimates of time-varying changes in the transverse relaxation ($\Delta R2^*$) and the net magnetization ($\Delta S_0/ S_0$). All this, without prior information about the timing of experimental events. To evaluate this method, we computed histograms of $\Delta R2^*$ estimates accompanying five distinct tasks (auditory, finger tapping, reading, viewing of houses and viewing of biological motion patterns). In most instances, estimates fell within physiologically plausible limits of neuronally-driven $\Delta R2^*$ at 3T. Figure 1.A shows ME-SPFM $\Delta R2^*$ maps for one representative subject. There is good agreement between traditional GLM (1.A) and ME-SPFM $\Delta R2^*$ maps (1.C); with areas of positive activation in the GLM maps being dominated by negative changes in $\Delta R2^*$ in ME-SPFM maps. Figure 1.B shows the histograms of ME- SPFM $\Delta R2^*$ for all intracranial voxels, where most $\Delta R2^*$ estimates fall in the range [-0.74, 0.74] s^{-1} of physiologically plausible values for neuronal activation. Also, Figure 3.C shows the histograms for only voxels with significant positive response according to GLM (pFDR<0.05), where ME-SPFM $\Delta R2^*$ estimates are mostly negative (e.g., [-0.74,0] s^{-1}). This demonstrates how ME-SPFM yields physiologically plausible quantitative estimates of $\Delta R2^*$, and only few voxels (red circles in Figure 1.C) exhibited excessively large $\Delta R2^*$ to be mislabeled as neuronal-related events.
These results indicate ME-SPFM provide a viable method to estimate $\Delta R2^*$ time-series with

interpretable units, even when experimental event timing is missing (e.g., naturalistic, resting-state).



Disclosures: J. Gonzalez Castillo: None. **C. Caballero-Gaudes:** None. **P. Bandettini:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

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Topic: I.07. Data Analysis and Statistics

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Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and development
Scientific Research on Innovative Areas, “Glial assembly: a new regulatory machinery of brain function and disorders”

Title: Classification of schizophrenia patients and healthy controls based on gray matter volumes using support vector machines

Authors: *M. YAMAMOTO[1], E. BAGARINAO[2], I. KUSHIMA[1,3], R. SUZUKI[1], A. BRANKO[1], T. INADA[1], T. IIDAKA[2], N. OZAKI[1]
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Abstract: Objective
Gray matter (GM) volume changes in schizophrenia patients (SCZ) have been demonstrated by meta-analyses of structural magnetic resonance imaging (MRI) studies, which indicated the possibility of classification of SCZ and healthy controls (CON) using patterns of GM volume changes. Therefore, we aimed to explore the use of a support vector machine (SVM) to classify two groups using structural MRI data.
Method
Fifty SCZ (26 males, mean age 38.8 years) and 51 CON (29 males, mean age 36.5 years) were scanned using a 3.0 T MR scanner (Siemens Magnetom Verio). All subjects provided written informed consent to participate in the study. The Nagoya University Graduate School of Medicine and Nagoya University Hospital ethics review committee approved this study. The acquired T1 images were preprocessed using Statistical Parametric Mapping and the VBM8 and smoothed (full-width at half-maximum = 8 mm), and modulated GM images were generated. These images were used in the classification analysis using linear SVMs with regularization parameter set to 1. A whole-brain mask was applied to the images and only voxels within the mask were included in the analysis. To reduce the dimensionality of the data, a principal component analysis was performed. The classification performance of trained SVMs was evaluated using a 10-fold cross validation approach. In addition to the classification accuracy, we also evaluated several classification measures including sensitivity, specificity, positive predictive value, and negative predictive value. The significance of each voxel's contribution in the classification performance was evaluated using a permutation test with 5000 iterations. All analyses were performed using in-house Matlab scripts and the LIBSVM software package (http://www.csie.ntu.edu.tw/~cjlin/libsvm).
Results
The classification accuracy was 76.2% (specificity; 76.4%, sensitivity; 76.0%). Regions contributing to the classification accuracy included not only decreased GM volumes in SCZ, such as the bilateral rectal gyrus, anterior cingulate gyrus, temporal pole, insula, and left occipital gyrus, but also increased volumes in the bilateral putamen and globus pallidus.
Conclusion
These regions were largely consistent with the findings of a previous large-scale analysis of a linear SVM (Rozycki et al., 2017). The current results indicated that our SVM method could detect the volume changes that classify the two groups in relatively small sample sizes.

Disclosures: M. Yamamoto: None. **E. Bagarinao:** None. **I. Kushima:** None. **R. Suzuki:** None. **A. Branko:** None. **T. Inada:** None. **T. Iidaka:** None. **N. Ozaki:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.06/LLL56

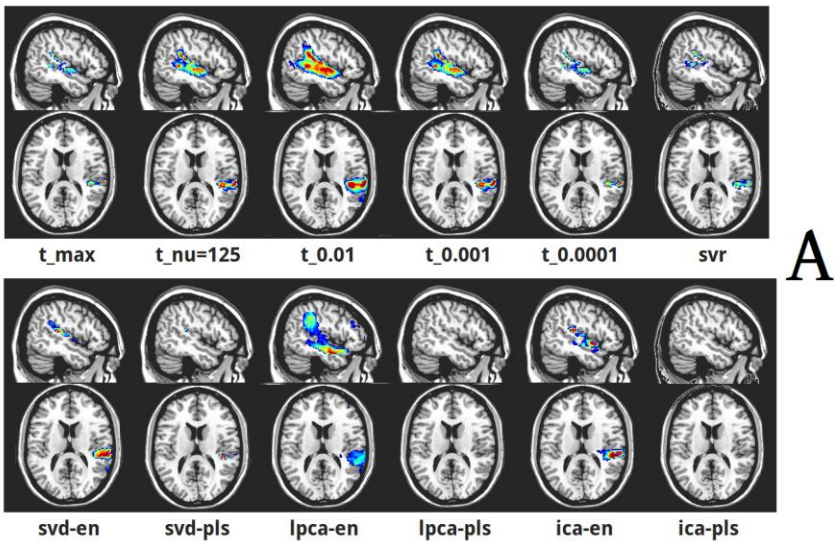
Topic: I.07. Data Analysis and Statistics

Support: VA RR&D 1|01RX001532-01
VA CSR&D 1I01CX000586-01A1

Title: Comparison of univariate and multivariate lesion symptom mapping methods for the analysis of brain-behavioral relationships

Authors: *T. J. HERRON[1], M. V. IVANOVA[2], N. F. DRONKERS[2], B. CURRAN[2], C. LUDY[2], A. ZHONG[2], A. U. TURKEN[2], J. V. BALDO[2]
[1]Neurology, Res., VA Northern California Hlth. Care Syst., Martinez, CA; [2]Res., US Dept. of Veterans Affairs, Martinez, CA

Abstract: Lesion symptom mapping (LSM) tools identify brain regions critically associated with neurologic and cognitive deficits in brain-injured patients. There have been many recent discussions comparing the advantages of multivariate (MV) versus univariate (V) LSM methods, with a notable direct comparison appearing recently [Pustina et al 2018]. Here we conducted a companion simulation study of the limits of detection reliability and spatial accuracy of artificial brain-behavior relationships (BBR) in gray matter (GM) using real lesion masks.
We first analyzed single parcel, proportional BBR conditions (% of target lesioned ~ % of behavioral deficit) in the left middle cerebral artery territory over a fully crossed design:
* 16 GM parcels as BBR targets
* Lesion masks from 2 different sites
* 12 lesion symptom mapping methods
* 4mm lesion mask smoothing vs. none
* patient sample sizes from 32 to 128
* multiple spatial accuracy measures.
We also tested "network" BBRs involving two cortical locations, both a redundant network and a dependent network, under the same crossed design. Lastly, we processed Western Aphasia Battery (WAB) data from 209 stroke patients to compare selected LSM contrasts.
Results from the single parcel BBRs showed good spatial accuracy for VLSM and most of the MVLSMs (see Table 1). Simulation results from the two-parcel "network" BBRs showed clear superiority of two data reduction MVLSM techniques and the cluster-size-threshold based maps (Table 2). The Figure shows two WAB analysis results.



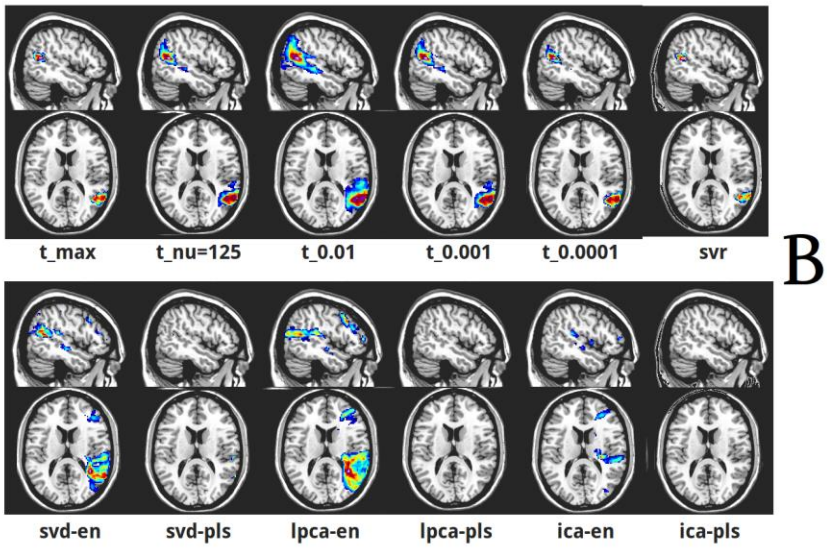


Figure: LSM results for the (A) repetition and (B) comprehension scores from the WAB where lesion size, age, education, months post event, and the other 3 WAB subscores were covaried out.

t_max: maximum regression value thresholded by permutation test
t_nu=125: same as t_max but using the 125th largest regression value [Mirman et al 2017]
t_0.01: cluster-size-based permutation test at fixed 0.01>p regression threshold (similarly t_0.001 t_0.0001)
svr: support vector regression [Zhang et al 2014] using svrlsm software functions [DeMarco et al 2018]
svd-: singular value decomposition data reduction over voxels [Siegel et al 2016]
lpca-: logistic principal component analysis data reduction over voxels [Schein et al 2003]
ica-: independent components analysis data reduction over voxels [FastICA 2.5]
-pls: partial least squares regression solution [Abdi 2010 ; pls toolbox]
-en: elastic net regression solution [Hastie et al 2103 ; glmnet toolbox]

ANOVA factor/interaction	F and partial ω^2	Details
LSM Type	$F_{11,165}=133$; $\omega^2=0.90$	DR+Elastic Net & SVR & VLSM good
Smoothing of Masks	$F_{1,15}=71$; $\omega^2=0.82$	4mm Gaussian FWHM smoothing +6.2 t
Number of Patients	$F_{6,90}=141$; $\omega^2=0.90$	Steep improvement: from 32 to 64 patients
LSM Type x Smoothing	$F_{11,165}=5.6$; $\omega^2=0.24$	SVR+VLSM most improved by smoothing
LSM Type x # Patients	$F_{66,990}=6.2$; $\omega^2=0.26$	SVR needs 64 subjects to do well, VLSM & some DR MVLSM only need 48 to do well.

Table 1: Single GM parcel proportional brain-behavior relationship (BBR) effects and interaction over the t-test difference between above-threshold LSM values inside vs. outside the target parcel. Only $p<0.0001$ effects and interactions shown. DR = data reduction.

ANOVA factor/interaction	F and partial ω^2	Details
LSM Type	$F_{11,165}=425$; $\omega^2=0.97$	DR+Elastic Net and small p cluster-size-based VLSM are good
Network Type	$F_{2,30}=96$; $\omega^2=0.86$	Redundant networks are the hardest to detect.
Number of Patients	$F_{3,45}=643$; $\omega^2=0.98$	Need 100+ patients in general to detect networks
Parcel	$F_{15,225}=12.1$; $\omega^2=0.43$	Main variability in detection is with lesion overlay edge parcels
LSM Type x # Patients	$F_{33,495}=35$; $\omega^2=0.70$	DR+Elastic Net might work with just 80 patients
LSM Type x Parcel	$F_{165,2475}=6.2$; $\omega^2=0.26$	No LSM works when one of parcel pairs is on the mask edge.
LSM Type x Network Type	$F_{22.330}=22$; $\omega^2=0.59$	SVD-EN best at identifying redundant networks.
# Patients x Network Type	$F_{6,90}=8.0$; $\omega^2=0.32$	Need 128+ patients for detecting redundant networks, usually
LSM x Network x # Pat.	$F_{66,990}=6.9$; $\omega^2=0.28$	$p<0.01$ cluster-size-based VLSM does OK in detecting most networks.

Table 2: Paired, networked GM parcels proportional brain-behavior relationship (BBR) effects and interactions over the t-test difference between LSM values inside vs. outside the target parcel pair. Only $p<0.0001$ effects and interactions shown. DR = data reduction.

Disclosures: T.J. Herron: None. **M.V. Ivanova:** None. **N.F. Dronkers:** None. **B. Curran:** None. **C. Ludy:** None. **A. Zhong:** None. **A.U. Turken:** None. **J.V. Baldo:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.07/LLL57

Topic: I.07. Data Analysis and Statistics

Support: This work was supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIP) (2016R1A2B3016609).

Title: Alternation in hemispheric asymmetry of morphological brain network for Alzheimer's disease

Authors: *Y.-H. CHOI, S. BANG, J.-M. LEE
Dept. of Biomed. Engineering, Hanyang Universit, Seoul, Korea, Republic of

Abstract: The asymmetry of the human brain has been widely studied in the neuroscience field. It is well known that the left hemisphere is specialized for language and handedness and the right hemisphere is dominant for some nonverbal functions such as spatial attention and the processing of faces. Asymmetry of volumetric measures such as cortical volume, surface area and cortical thickness using the structural magnetic resonance imaging (MRI) has been reported to have globally and regionally hemispheric difference with more pronounced leftward than right asymmetry. Importantly, neuropsychiatric and neurological diseases such as schizophrenia, Alzheimer's disease (AD) exhibit significant changes in hemispheric asymmetries. In recent years, graph-theoretical approach has been applied to allow capturing various topological properties of complex brain network such as functional segregation, integration. Many studies have utilized the theoretical framework of graph theory to investigate brain networks in AD through different neuroimaging techniques. These studies have reported altered local and global graph properties of morphological brain network in AD. However, the methodology of these previous studies limited the investigation of graph properties to group-level analyses. Despite the advances in morphological brain network research for AD, however, little is known about whether there are differences in the topological organization of brain depending on disease. In the this study, the intracortical similarities of cortical thickness between two regions were estimated by calculating the Jensen-Shannon divergence, across subjects. Hence, the morphological hemispheric brain network was obtained from a group of individuals. And then, we applied graph theoretical approaches to quantify the global and nodal properties for hemispheric morphological networks. Finally, we investigated whether hemispheric and disease related differences in the morphological hemispheric brain network exists or not.

Hemispheric and Group effects on global network metrics revealed by two-way repeated-measures ANOVA

		Clustering coefficient	Characteristic path length	Normalized clustering coefficient	Normalized characteristic path length	Global efficiency	Local efficiency
Hemispheric effect	F-value	**11.623**	0.003	0.079	1.399	0.934	**4.731**
	P-value	**0.001**	0.954	0.779	0.239	0.336	**0.031**

Group effect	F-value	0.943	0.951	1.291	0.812	1.480	0.979
	P-value	0.433	0.389	0.279	0.446	0.231	0.378
Interaction	F-value	0.936	0.288	**4.402**	0.058	0.096	1.277
	P-value	0.395	0.750	**0.014**	0.944	0.908	0.282
Significant results ($p<0.05$) are indicated by bold.							

Disclosures: Y. Choi: None. **S. Bang:** None. **J. Lee:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.08/LLL58

Topic: I.07. Data Analysis and Statistics

Support: Rutherford Discovery Fellowship (RDF-10-UOA-024)
Brain Research New Zealand PostDoctoral Fellowship

Title: Using simulations to investigate the prevalence of false positives in data-driven forms of partial least squares analysis

Authors: *R. P. ROBERTS, D. R. ADDIS
The Univ. of Auckland, Auckland, New Zealand

Abstract: Partial least squares (PLS) is a multivariate technique commonly used with neuroimaging data to detect similarities and differences in i) brain activity (task PLS) and/or ii) brain-behavior correlations (behavior PLS) across groups and conditions (pls.rotman-baycrest.on.ca). PLS can be run in a data-driven fashion, in which orthogonal latent variables (LVs) are produced identifying a combination of i) contrasts between condition, groups, and/or behaviors and ii) spatial patterns across the brain expressing this contrast. The number of LVs produced in data-driven analyses increases as the "dimensionality" (i.e. number of groups, conditions, and/or behaviors) of a design increases. An alternative user-driven approach involves imposing *apriori* contrasts on the data (one LV for each contrast). The significance of each LV is assessed by permutation testing, determining how likely the observed effect is to occur from random noise. In this study, we varied design dimensionality in fMRI simulations to assess the

likelihood of getting significant effects (α=.05) for data-driven and user-driven PLS methods using data that should produce null results. For task PLS, on each simulation, we used resting-state data from the Human Connectome Project (N=50), pseudo-randomly assigned conditions to blocks and calculated mean percent signal change for each condition. For behavior PLS, we used task data (N=46) with 2 conditions (task and rest), and random vectors were generated on each simulation to act as behaviors. In task PLS, dimensionality was manipulated by changing the number of conditions in the design (2-6); in behavior PLS, we changed the number of conditions (1-2) and behaviors (1-4). For each design, 1000 data-driven PLS simulations were run, and the *p*-value of the LV explaining the most variance (i.e., LV1) was recorded for each simulation. These results were compared to 1000 user-driven simulations. Results for data-driven PLS showed that while false positive rates were ~5% (i.e., α) for designs with low dimensionality (i.e., task PLS with 2 conditions; behavior PLS with 1 condition and 1 behavior), it monotonically increased as dimensionality increased. For task PLS with 6 conditions, 71% of simulations produced $p < .05$ effects. For behavior PLS with 2 conditions and 4 behaviors, 85% produced significant LVs. Importantly, this was not true for user-driven PLS (false positive rate of ~5% regardless of dimensionality). These results suggest user-driven forms of PLS more effectively minimize type-I error rates, and that, if data-driven forms of PLS are used, significance should be assessed with more stringent methods (e.g. split-half resampling).

Disclosures: R.P. Roberts: None. **D.R. Addis:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.09/LLL59

Topic: I.07. Data Analysis and Statistics

Support: Intramural Research Program of the National Institutes of Health
Fetzer Memorial Trust

Title: MEG estimates of connection stationarity differ between schizophrenic and normal control subjects

Authors: *S. E. ROBINSON[1], A. J. MANDELL[2]
[1]MEG Core Group, NIH/NIMH, Bethesda, MD; [2]Psychiatry, Univ. of California San Diego, La Jolla, CA

Abstract: Temporo-dynamic symbolic transfer entropy (tdSTE) was developed to study the time-course of event-related and spontaneous information transfer between pairs of brain regions. It employs symbolic states based upon rank order in the selected phase space and implemented using a leaky integrator that maintains a running estimate of the marginal and joint

probability density functions (PDFs) as a function of time. The *1/e* decay rate of the PDFs must be short enough to reveal the information transfer fluctuations while being long enough to obtain statistically stabile transfer entropy (TE) estimates. For a 3-dimensional phase space, information transfer increases with faster decay rates for both experimental data as well as for random surrogate data. We observe that the excess transfer entropy (eTE), i.e., the difference between TE of the data and that of the random surrogate) as a function of decay rate reflects the stationarity of communication between a given pair of brain regions. The maximum of this function represents the time-scale that information transfer is most stationary. The shape of this curve reflects the dispersion of stationarity for information exchanges between a given pair of brain regions. We computed excess kurtosis (g2) as a measure of dispersion of eTE versus decay rate. We evaluated this measure for 7 normal control (Nc) and 7 schizophrenic (Sz) resting MEG datasets. The source waveforms for each of 26 regions of interest (ROIs) were computed using an extended source LCMV beamformer in a 70-185 Hz bandpass, resulting in 1300 forward and reverse pairs. For each pair, we computed eTE for 40 decay rates, in log steps, ranging from 50 ms to 5 seconds. The false discovery rate (FDR) of the g2 differences (Sz minus Nc) were computed for all ROI combination. We find significant differences between Sz and Nc subjects for pairs connecting prefrontal, frontal, temporal, and parietal regions. The results for pairs of regions with p(FDR) < 0.05 are shown in the table. These results suggest that the the decay rate of information transfer can be used to study neurological and neuropsychiatric disorders.

g2 Difference Sz minus Nc

Source	Destination	g2 Difference	p(FDR)
L Cing-Ant G&S	L Cing-Ant G&S	4.819	0.049485
L Cing-Ant G&S	L Front Mid G	4.891	0.047804
R Temp Mid G	L Cing-Ant G&S	5.718	0.031438
R Front Inf-Tri G	L Front Inf-Orb G	5.756	0.022230
R Front Inf-Tri G	R Temp Inf G	5.309	0.023985
R Front Mid G	R Temp Inf G	7.152	0.001562
L Front Mid G	R Temp Mid G	9.181	0.000069
L Front Sup G	R Front Sup S	-6.398	0.017495
R Par Sup G	R Postcent G	5.717	0.023985
R Par Sup G	L Temp Inf G	-6.381	0.018069
L Par Sup G	L Postcent G	6.017	0.018768
R Postcent G	R Front Mid S	-7.159	0.004676
L Front Mid S	R Postcent G	6.741	0.006956
R Front Sup S	R Postcent G	-6.051	0.044001
R Postcent G	L Front Sup S	6.228	0.030126
L Postcent G	R Front Mid S	6.297	0.012486
R Temp Mid G	R Temp Mid G	5.883	0.049885

Disclosures: S.E. Robinson: None. **A.J. Mandell:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.10/LLL60

Topic: I.07. Data Analysis and Statistics

Title: Studying genetic influences on brain structure and functional connectivity using twin brains

Authors: *G. HWANG[1], A. KULKARNI[2], V. A. NAIR[3], B. B. BENDLIN[4], V. PRABHAKARAN[3], E. MEYERAND[1]
[1]Med. Physics, [2]Biomed. Engin., [3]Radiology, [4]Med., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Differentiating between genetic and environmental influences on the human brain using data from monozygotic (MZ) and dizygotic (DZ) twins allows for a better understanding of individual differences in brain and behavior. Here we use MRI data from the Human Connectome Project (HCP) with a unique approach to investigate this problem. 70 MZ (28.8±3.5 years, 39 Female), 67 DZ (29.1±3.5 years, 39 F), 67 sibling (28.4±3.3 years, 35 F, 1-3 years age difference), and 70 control (28.8±3.3 years, 39 F) pairs were analyzed. MRI images were acquired with 3T Siemens Skyra scanners using magnetization prepared gradient echo sequence (TR=2400ms, TE=2.14ms, 0.7 mm isotropic) for T1w, and simultaneous multislice imaging (8 bands, 72 slices, TR=720ms, TE=33.1ms, 2.0 mm isotropic, four 15-minute eyes fixated runs) for resting state functional scans. Data were processed with the HCP minimal processing pipelines. From the T1w images, 254 FreeSurfer features were extracted and normalized. Resting images, after standard processing steps, were further processed by independent-component-analysis X-noiseifier (FIX) correction. Bandpass filtering was applied (0.01-0.1Hz). Time series from 360 cortical regions from HCP's Glasser parcellation and 19 FreeSurfer-based subcortical regions were extracted. Pearson's correlations were computed to generate the connectivity matrices. For a given pair, the differences were calculated in the structural and functional features. To account for the arbitrariness in the order of subtraction, every difference was duplicated with its opposite sign value. The resulting difference features were compared between groups using the F-test, with Benjamini-Hochberg corrections. Only features that did not show significant differences between DZ and sibling groups, while showing significance in all other 5 comparisons (genetic comparisons) were considered to be influenced by the genetics. Many global volume measures and subcortical volumes, such as caudate, putamen, and cerebellum showed strong genetic influence ($p<0.01$ in genetic comparisons, while $p>0.2$ between DZ and sibling). Overall variances in the functional features were also the smallest in the MZ (0.039), then DZ (0.045), sibling (0.049), and control (0.058) groups. 15 resting connections, many of which from the visual or auditory cortices, showed significance. No structural or functional features that were consistently significant in all genetic comparisons showed significance

between DZ and sibling groups. High resolution HCP data with a careful method revealed the genetic influence in shaping the overall brain structures, subcortical volumes and functional connectivity.

Disclosures: G. Hwang: None. **A. Kulkarni:** None. **V.A. Nair:** None. **B.B. Bendlin:** None. **V. Prabhakaran:** None. **E. Meyerand:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.11/LLL61

Topic: I.07. Data Analysis and Statistics

Support: Department of the Navy Grant - 0047800-5
Marie Sklodowska-Curie Grant H2020-MSCA-GF-2017 GA-795807

Title: Interhemispheric similarities between diffusion measures of human brain white matter tracts

Authors: *G. LERMA-USABIAGA[1], T. GLOZMAN[2], B. A. WANDELL[1]
[1]Psychology Dept., [2]Electrical Engin. Dept., Stanford Univ., Stanford, CA

Abstract: Background. Vertical midline symmetries are characteristic of human body and brain structures. These symmetries extend beyond structure to tissue properties. In human white matter, for example, group level analyses show that MRI diffusion measures in homologous right and left hemisphere tracts are more similar (correlated) than measures between non-homologous tracts (Wahl et al., 2010, Li et al., 2012). These similarities have the potential to inform us about phylogenetic, ontogenetic, and functional properties; deviations from these similarities, particularly when observed in individuals, can detect, diagnose and predict pathologies. **Methods.** We analyzed diffusion weighted imaging data in seven datasets (N=1200). The measurements were made on a variety of scanners using different acquisition parameters. We developed quantitative measures of left-right similarities, at the individual subject level, of micro- and macro-structural properties of the white matter tracts. We compared the within subject left-right similarities to similarities between a participant and other individuals. **Results.** (A) There are significant differences in the diffusion data depending on MR scanner vendors, scanning sites and diffusion acquisition parameters. (B) A partial least square regression (PLSR) model that relates data from the two hemispheres eliminates site and sequence differences; the measurements in one hemisphere calibrate the model prediction for the other hemisphere. (C) The PLSR model explains about 90% (± 8%) of the variance between left and right hemisphere measured within participants and about 64% (± 12%) of the variance between a participant and the group mean; this value differs somewhat between tracts. (D) Most importantly, left-right

similarity indices can be calculated on individual participants, and these indices can diagnose an individual whose indices are inconsistent with the population distribution. **Conclusion.** We developed a fully automated site-independent tool to assess the similarity between diffusion measured in the major left-right tracts. These single-subject level MRI indices can be used to screen for anomalies in clinical and research settings.

Disclosures: G. Lerma-Usabiaga: None. **T. Glozman:** None. **B.A. Wandell:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.12/MMM1

Topic: I.07. Data Analysis and Statistics

Support: The William K. Warren Foundation

Title: Consistency across brain normalization algorithms in DTI analyses

Authors: *H.-W. YEH[1], M. BERGAMINO[1], S. KHALSA[1,2], M. PAULUS[1]
[1]Laureate Inst. for Brain Res., Tulsa, OK; [2]Univ. of Tulsa, Tulsa, OK

Abstract: Reproducibility is an essential foundation of science. Various factors may contribute to inconsistent findings and we researchers should do our best to control them as much as possible. In research using diffusion tensor imaging (DTI), an important pre-processing step is normalizing individual brain maps to a consensus template for group analyses. Currently, multiple algorithms or software are available for normalization but little is known about the impacts of using different algorithms. In this work, we evaluated the consistency of five normalization algorithms (AFNI, ANTs, DARTEL, FSL, and SPM) in DTI skeletonized and voxel based analyses (VBA).
A sample of 154 subjects consisting of three groups, 50 healthy controls (HC) (26 F, age mean (SD): 33 (11) y, PHQ9: 0.68 (1.1)), 59 moderately severe and severe depression (HD) (36 F, age: 36 (11) y, PHQ9: 18.5 (3.1)), and 45 mild depression (LD) (26 F, age: 38 (11) y, PHQ9: 8.5 (1.6)), underwent DTI acquisition and their fractional anisotropy (FA) values were normalized by each of the five normalization algorithms. For skeleton analysis, a consensus mask was generated to cover skeleton areas shared by the five algorithms. Consistency was evaluated by ICC(3,1) statistic (ICC henceforth) from two-way mixed-effects (random subject + fixed algorithm) model.
For all algorithms and groups together, voxels in skeletonized analyses showed a median ICC (mICC) of 0.52 and inter-quartile range (IQR) (0.37, 0.66), and mICC 0.38 (0.29, 0.50) in VBA. Removing each algorithm at a time (i.e. using four algorithms) only slightly altered mICC, ranging from 0.51 (without SPM) to 0.56 (without DARTEL) in skeletonized and from 0.35

(without SPM) to 0.41 (without ANTs) in VBA. Similar consistency was observed across the five algorithms within each group, with mICC 0.54, 0.55, and 0.51 for HC, LD, and HD in skeletonized analyses and 0.39, 0.42, and 0.37 for HC, LD, and HD in VBA, respectively.
In summary, consistency was poor to fair across normalization algorithms, and no single algorithm was substantially less or more consistent than the others; consistency was slightly lower in HD group than the other groups. Note that (a) ICC only indicates to what extent the algorithms are consistent, but not which algorithm is most valid (close to ground truth); (b) our findings refer to consistency "across" algorithms, but not "within" algorithms, which require repeated DTI scans. Further investigations are needed to achieve more consistent results. In conclusion, we suggest practitioners and reviewers bearing this information in mind when they compare results obtained from different normalization procedures or analysis methods.

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Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.13/MMM2

Topic: I.07. Data Analysis and Statistics

Support: Intramural Research Program of the NINDS

Title: Robust fMRI hyperalignment based on repeated movie stimuli

Authors: *H. MANDELKOW, J. DE ZWART, J. DUYN
NIH / NINDS / LFMI / AMRI, Bethesda, MD

Abstract: The imprecision of anatomical alignment methods commonly limits the spatial resolution and sensitivity of conventional fMRI analysis based on the univariate general linear model. Recently proposed machine-learning methods circumvent the between-subject alignment problem using various forms of common factor analysis, which compute a linear projection of the fMRI signal from each subject's anatomical space to a common albeit abstract "functional" space [1]. Such "*hyperalignment*" methods achieve highly significant classification accuracies in all published experiments, although their sensitivity is often boosted by aggregating multiple consecutive fMRI volumes to create larger, more distinctive patterns at the expense of temporal (stimulus) specificity [2].
We recently demonstrated that PCA-LDA classifiers achieve high classification rates for individual fMRI volumes of the fMRI response to naturalistic movie stimuli presented repeatedly to the same subject [3]. Using *hyperalignment* based on a constrained PCA of the global BOLD signal patterns from multiple subjects, we now confirm that the same classifiers also achieve high classification accuracy in between-subject classification, distinguishing even single fMRI

volumes 2s apart. Both within- and between-subject classification seems to rely primarily on large-scale fMRI signal patterns that are robustly reproduced across experimental runs and subjects. Our data show that the optimal fMRI resolution for such experiments is relatively low (~3mm) and that within-subject averaging of the training data in conjunction with dimensionality reduction by PCA most effectively increases classification accuracy. We conclude that a judicious choice of fMRI resolution, repeated training stimuli and robust classification algorithms based on PCA and the Mahalanobis distance are key to making fMRI hyperalignment robust enough for practical applications in detecting cognitive or psychiatric conditions on a single-subject basis.

[1] J. V Haxby et al. 2014, *Annu. Rev. Neurosci.*
[2] K. Vodrahalli et al. 2017, Neuroimage.
[3] H. Mandelkow et al. 2017, Neuroimage.

Disclosures: H. Mandelkow: None. **J. de Zwart:** None. **J. Duyn:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.14/MMM3

Topic: I.07. Data Analysis and Statistics

Support: NSF Grant DGE1122492

Title: Cluster failure or power failure? Balancing the scale with sensitivity

Authors: *S. M. NOBLE[1], D. SCHEINOST[2], R. T. CONSTABLE[2]
[1]Interdepartmental Neurosci. Program, [2]Radiology and Biomed. Imaging, Yale Univ., New Haven, CT

Abstract: Summary: Pioneering work in human neuroscience has relied on the ability to map activations using task-based fMRI, but recent work posed a major challenge to the field. Conventional methods for performing multiple comparisons corrections (MCC) were shown to yield insufficient specificity. However, that study's emphasis on specificity, although important, is incomplete. The accuracy of a method depends not only on its specificity but also its sensitivity, yet little research has been done on the sensitivity of MCC methods. As a first step, the present study extended publicly available scripts to perform a simulation of simple synthetic activations in real, resting-state data. The sensitivity of several procedures were assessed, as well as the spatial distribution of detected effects. **Methods:** For each grey matter voxel, an activation was synthesized using each combination of effect size (Cohen's *d*=small, medium, large), radius (r=8mm, 12 mm), and diffuseness (+/- smoothing). A subset of previously tested MCC methods were used to assess for activations: AFNI OLS (based on simulation of smoothness) and FSL

Perm (nonparametric). A previously untested, threshold-free method was added: FSL TFCE+Perm. To perform multiple tests at each of 10,000 voxels, scripts were parallelized for the Amazon cloud. To confirm the real-world relevance of this work, analyses will be repeated in task data. **Results:** At typical thresholds (CDT p=0.01), sensitivity of conventional methods to large effects was less than 5%, while sensitivity of TFCE was more than three times greater. In comparison, without correction, sensitivity is expected to be 80%. However, using a more stringent CDT increased sensitivity to levels about four times greater than TFCE. Across all tests, sensitivity to small effects was less than 1%. Spatial distributions of true and false positives were nonuniform and moderately correlated with one another (except for TFCE), though weakly or not correlated with the underlying smoothness. **Conclusion:** While we aim to confirm these results in real data, this work suggests that the power to detect effects using conventional MCC methods may be unreasonably low for the purposes of most studies. In addition, power is systematically even lower in many areas, suggesting a literature biased against detecting effects in many areas and a need to adopt spatially non-uniform corrections. Recently proposed strategies to improve sensitivity are crucial because optimizing for specificity, without considering sensitivity, undermines the accuracy and reproducibility of neuroimaging research. The present work adds to mounting evidence that it is time to balance the scale.

Disclosures: S.M. Noble: None. **D. Scheinost:** None. **R.T. Constable:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.15/MMM4

Topic: I.07. Data Analysis and Statistics

Support: UNAM-DGAPA IB201712
CONACYT 181508
CONACYT 329866

Title: Links between brain connectivity and cognitive performance in temporal lobe epilepsy

Authors: *R. RODRÍGUEZ CRUCES
Inst. of Neurobio., Natl. Autonomous Univ. of Mexico, Queretaro, Mexico

Abstract: Temporal lobe epilepsy (TLE) is the most common focal drug-resistant epilepsy and has been associated with white matter (WM) damage that extends beyond the epileptic focus (Otte el al; Epilepsia 2012). Neuropsychological evidence of structure-related cognitive impairments in TLE suggests that widespread structural anomalies relate with inter-individual cognitive performance differences in TLE (Rodriguez-Cruces et al; Epilepsy&Behavior 2017). Identification of specific patterns of network changes related to a particular cognitive profile is

highly relevant for the prognosis and adequate diagnosis in a progressive chronic disease such as TLE. We sought to relate cognitive performance to structural connectome in an integrative analysis. Our overall goal is to establish a particular pattern of white matter connectivity associated with a specific ensemble of clinical and neuropsychometrical features in TLE patients. We acquired structural magnetic resonance imaging (MRI) from 33 drug-resistance temporal lobe epilepsy patients and 25 -age and -sex matched healthy controls using a 3 T scanner. All subjects completed a full battery of cognitive tests (WAIS-IV & WSM-IV). A subject-level brain parcellation was estimated using a cortical (freesurfer) and subcortical segmentation tools (Manjón and Coupé 2016); which constituted the network nodes. Edge connection strength was calculated with streamline counts derived from anatomically constrained tractography and spherical deconvolution informed filtering of tractograms between two nodes (Smith, 2016). We obtained a 162x162 structural connectome matrix for each subject. Cognitive data were normalized to control using a z-score transformation and sorted into ipsilateral/contralateral to the seizure focus. Relationships between cognitive and connectome was established using canonical correlation analysis with strict control to avoid false positives.The current study explore cutting-edge methodology on a clinical population like TLE were we seek specific patterns of structural brain connectivity that relates to a particular cognitive profile in a multivariable manner.

Disclosures:

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.16/MMM5

Topic: I.07. Data Analysis and Statistics

Support: Tiny Blue Dot Foundation
Brain Injury Research Center at UCLA

Title: Network analysis in disorders of consciousness: Four problems and one proposed solution (exponential randomgraph models)

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Abstract: In recent years, the study of the neural basis of consciousness, particularly in the context of patients recovering from severe brain injury, has greatly benefited from the application of sophisticated network analysis techniques to functional brain data. Yet, current graph theoretic approaches, as employed in the neuroimaging literature, suffer from four important shortcomings. First, they require arbitrary fixing of the number of connections (i.e.,

density) across networks which are likely to have different “natural” (i.e., stable) density (e.g., patients vs controls, vegetative state vs minimally conscious state patients). Second, when describing networks, they do not control for the fact that many characteristics are interrelated, particularly some of the most popular metrics employed (e.g., nodal degree, clustering coefficient) - which can lead to spurious results. Third, in the clinical domain of disorders of consciousness, there currently are no methods for incorporating structural connectivity in the characterization of functional networks which clouds the interpretation of functional differences across groups with different underlying pathology as well as in longitudinal approaches where structural reorganization processes might be operating. Finally, current methods do not allow assessing the dynamics of network change over time. We present a different framework for network analysis, based on Exponential Random Graph Models (ERGM), which overcomes the above limitations and is thus particularly well suited for clinical populations with disorders of consciousness. We demonstrate this approach in the context of the longitudinal study of recovery from coma. First, our data show that throughout recovery from coma, brain graphs vary in their natural level of connectivity (from 10.4% to 14.5%), which conflicts with the standard approach of imposing arbitrary and equal density thresholds across networks (e.g., time-points, subjects, groups). Second, we show that failure to consider the interrelation between network measures does lead to spurious characterization of both inter- and intra-regional brain connectivity. Finally, we show that Seperable Temporal ERGM (STERGM) can be employed to describe network dynamics over time revealing the specific pattern of formation and dissolution of connectivity that accompany recovery from coma.

Disclosures: M. Johnson: None. **M.M. Monti:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.17/MMM6

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant ZIAMH002798

Title: A method for conducting fMRI-guided, electric field optimized transcranial magnetic stimulation at any cortical site

Authors: *N. L. BALDERSTON, C. ROBERTS, E. MASI, Z.-D. DENG, T. RADMAN, B. LUBER, S. H. LISANBY, M. ERNST, C. GRILLON
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Abstract: Transcranial magnetic stimulation (TMS) is a noninvasive method to stimulate the cortex using time-varying magnetic pulses. With the advent of neuronavigation and figure-8

coils, researchers can target specific cortical regions with sub-centimeter accuracy. Capitalizing on this spatial specificity, it is possible to target specific ongoing cognitive processes with a high-degree of functional specificity. Although there are many existing TMS targeting methods, many of these do not account for individual differences in head size/shape or neural anatomy or are not generalizable to regions of the brain without obvious behavioral outputs (e.g. prefrontal cortex). Functional magnetic resonance imaging (fMRI), a widely used method to study brain activity, can deliver subject-specific, high-resolution maps of the entire brain that reflect changes in metabolic activity due to task demands. Recent advances in electric-field (E-field) modeling have made it possible to estimate the current induced in the brain, given a coil location, geometry, and orientation, and this process can be iterated across possible orientations to identify the optimal configuration. In this work, we combined these tools to create a generalizable workflow for subject-specific TMS targeting, capable of optimizing both the site of stimulation, and the coil orientation. We tested the algorithm using data from an ongoing repetitive TMS study using working memory related BOLD activity to target the right dorsolateral prefrontal cortex. We used 3 different a priori target definitions (anatomical, functional, and meta-analytical) compared to no a priori target definition. We found that constraining the fMRI targeting using any of the a priori regions of interest: 1) reduced variability in the location of the fMRI target across subjects, 2) reduced the overall scalp-to-cortex distance of the TMS target and hence the stimulation intensity, 3) reduced the variability in optimal coil orientation across subjects based on iterative E-field modeling. Together these results suggest that fMRI data can reliably identify functional neural targets for TMS, given a priori target definitions. Additionally, by combining this approach with iterative E-field modeling, our pipeline can determine both the optimal site and coil orientation for stimulation. Finally, because this approach relies only on an a priori target region and a task to activate the target region, it is generalizable to other cognitive neuroscience paradigms and regions of interest.

Disclosures: N.L. Balderston: None. **C. Roberts:** None. **E. Masi:** None. **Z. Deng:** None. **T. Radman:** None. **B. Luber:** None. **S.H. Lisanby:** None. **M. Ernst:** None. **C. Grillon:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.18/MMM7

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant P20GM109097

Title: Testing emotional attachment and mutuality (team) fmri task for studying dyadic interactions

Authors: *K. BURROWS[1], K. L. KERR[2,1], D. C. DEVILLE[3,1], E. L. RATLIFF[2,1], K. T. COSGROVE[3,1], J. BODURKA[1,4], M. P. PAULUS[1], A. S. MORRIS[1,2], W. K. SIMMONS[1,5]
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Abstract: The Testing Emotional Attachment and Mutuality (TEAM) task is a cooperative game designed to assess brain hemodynamic responses in each member of a dyad when the other member makes a costly error. The TEAM aims to probe and measure how brain circuitry underlying attachment and mutuality responds when the 'other' has let that individual down. During task trials, a sequence of 4 colored arrows is displayed two times for 6 seconds, after which the subject has 4 seconds to reconstruct the sequence by pressing colored buttons on a response box. This is followed by a 6-second 'reveal'/feedback period, in which the subject sees his/her own response and a pre-generated response for the other member of dyad. On true feedback trials, the subject is shown his/her response and feedback that the other person's response was correct. On enforced error trials, the feedback is pre-generated to reveal that the other person's response was incorrect, resulting in a loss of money for both subjects. A 6-second 's' detection trial was used as an active baseline condition, in which subjects were instructed to look for letter "s" from a random 20-letter string. No money was at stake during the 's' detection trials. Three runs of the TEAM task were created based on optseq2, with each run containing 14 true feedback, 3 enforced error, and 14 's' detection trials.
Prior to scanning, subjects were instructed on how to perform the TEAM task together and told that they would start out with $50 as a team, and that $5 would be deducted from their earnings for each error made while performing the TEAM task, regardless of which subject made the error. However, subjects are not aware that they are not completing TEAM task together and that the feedback regarding the other member's performance has been pre-programmed.
22 healthy adults (2 male, age: 30 - 53 years) and 25 adolescents (9 boys, age: 14 - 16 years) completed the TEAM task while being scanned concurrently on two 3T GE MR750 MR scanners as part of a parent-child interaction study. Using AFNI, the beta values derived from the contrast of enforced error versus true feedback were extracted for each subject, then included in a one sample t-test for adults or adolescents. All statistical maps were corrected for multiple comparisons at $p < 0.05$ with a voxel-wise $p < 0.005$.
Anterior insula, caudate, thalamus, hypothalamus, ventral tegmental area, ventral pallidum and striatum, inferior frontal and precentral gyrus, medial and superior frontal gyrus were activated in response to enforced error compared to true feedback in both adult and adolescent subjects. Results show the TEAM task successfully recruitment of brain emotional processing and regulation circuitry.

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Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.19/MMM8

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant P20GM109097

Title: Transcription and coding of dyadic interactions for fmri hyperscanning

Authors: *A. MOORE[1], K. L. KERR[2], M. J. JOHNSON[4], E. L. RATLIFF[3,1], D. C. DEVILLE[4], K. T. COSGROVE[1], K. BURROWS[1], J. BODURKA[1], W. K. SIMMONS[5], A. S. MORRIS[1]
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Abstract: Maintaining ecological validity within fMRI neuroimaging paradigms continues to be a significant challenge in conducting research with human participants. Social constructs, such as how parent-child interactions may affect child development, can be particularly difficult to study and quantify. The Dyadic Inter-Brain Signaling (DIBS) Project aims to understand how parents' emotion regulation affects adolescents' emotion regulation as well as to identify the neural basis (e.g., brain neurocicuitry) underlying these dyadic influences. In order to examine these fundamental constructs in an ecologically valid manner, parents and their adolescent children completed a conflict resolution task while undergoing fMRI hyperscanning. The task is divided into two parts. First, the parent-child dyad is prompted to describe a specific conflict that they have reported occurs often between them (e.g., "chores at home") for 2 minutes. This is followed by a prompt to resolve the conflict through collaborative problem solving for another 2 minutes. Using fMRI, each dyad was scanned simultaneously to measure the neural responses underlying these interactions. Dyads communicated via headphones and microphones. Participants completed three scanning runs, with a different conflict presented in each run. The audio files from each run were then transcribed and coded for emotionally valenced statements. Statements made by participants were coded based on 11 different categories; 5 positive categories (e.g., validation) and 6 negative categories (e.g., derisive humor). In previous studies done outside the scanner, the transcriptions have been broken up into 10-second "talk-turns" which are then coded into a specific category. To accommodate fMRI, coding has been adapted to record the onset and duration of each individual coded statement in order to use these variables as regressors in fMRI data analysis. To date, transcriptions from 17 dyads have been coded. To insure internal validity, 71% of the transcriptions have been coded twice or cross-checked with 81% reliability. The acceptable level of reliability for traditional behavioral tasks is 85% with 25% of the total transcriptions cross-checked. The introduced method of behavioral coding holds great potential

for a wide range of neuroimaging studies, and demonstrates advancement in ecological validity for fMRI.

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Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.20/MMM9

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant P20GM109097

Title: A free-speech paradigm for studying dyadic interactions with fMRI hyperscanning

Authors: *K. L. KERR[1], A. J. MOORE[2,1], M. MISAKI[2], E. L. RATLIFF[1,2], K. T. COSGROVE[3,2], D. C. DEVILLE[3,2], K. BURROWS[2], S. F. TAPERT[4], W. K. SIMMONS[5], J. BODURKA[2,6], A. S. MORRIS[1,2]
[1]Human Develop. and Family Sci., Oklahoma State Univ., Tulsa, OK; [2]Laureate Inst. for Brain Res., Tulsa, OK; [3]Dept. of Psychology, The Univ. of Tulsa, Tulsa, OK; [4]Dept. of Psychiatry, UCSD, La Jolla, CA; [5]Mood Disorders Biomarkers Program, Janssen Res. & Develop., La Jolla, CA; [6]Stephenson Sch. of Biomed. Engin., The Univ. of Oklahoma, Norman, OK

Abstract: Human cognition, behavior, and development are all significantly influenced by relationships and social interactions. The vast majority of neuroimaging studies to date, however, involve the presentation of stimuli to individual participants while their brain responses are measured in isolation, with limited ecological validity. The study of social interactions is critical for understanding adolescence, as relationships with parents and peers significantly shape development at this stage. We therefore developed a paradigm in which parents and their adolescent children can interact while both are undergoing concurrent fMRI scanning (e.g., hyperscanning) at 3 Tesla with a 32-channel head coil (image resolution of $2.5x2.5x2.9mm^3$). Parents and their adolescent children were scanned simultaneously and asked to discuss specific conflicts that they have with each other. Participants communicated via active noise cancellation headphones and a microphone while in the MRI scanners. To address and suppress the speech-related motion artifacts in acquired fMRI data, we employed a continuous-speech 'de-noising' procedure developed by Xu et al. (2014). This procedure uses a dual-mask spatial independent component analysis method to pinpoint imaging artifacts based on their extracerebral spatial origins. An automated independent component classifier is then used to identify noise components, and the dataset is reconstructed by subtracting the noise components from the time

series. The de-noising procedure significantly reduced speech-related artifacts (reduction in average motion from 0.34 to 0.03, based on AFNI's 'enorm' value). For task-based fMRI analyses, participant speech was transcribed and coded for specific types of emotionally valenced statements in order for coded statements to be used for regressors of interest in task-based analyses. The quality of parent-adolescent interactions while in the MRI scanner is similar to what has been observed in prior studies that have used this task outside of the scanner, with an average number of 28 codable statements made by each member of the dyad over 3 scanning runs (total discussion time of 12 minutes). Results demonstrate that it is possible to successfully study real-life social situations, such as conflict discussions between parents and their children, while participants undergo fMRI scanning. Importantly, this methodology has wide applicability to study the neural bases of many social constructs with advanced, non-invasive neuroimaging.

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Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.21/MMM10

Topic: I.07. Data Analysis and Statistics

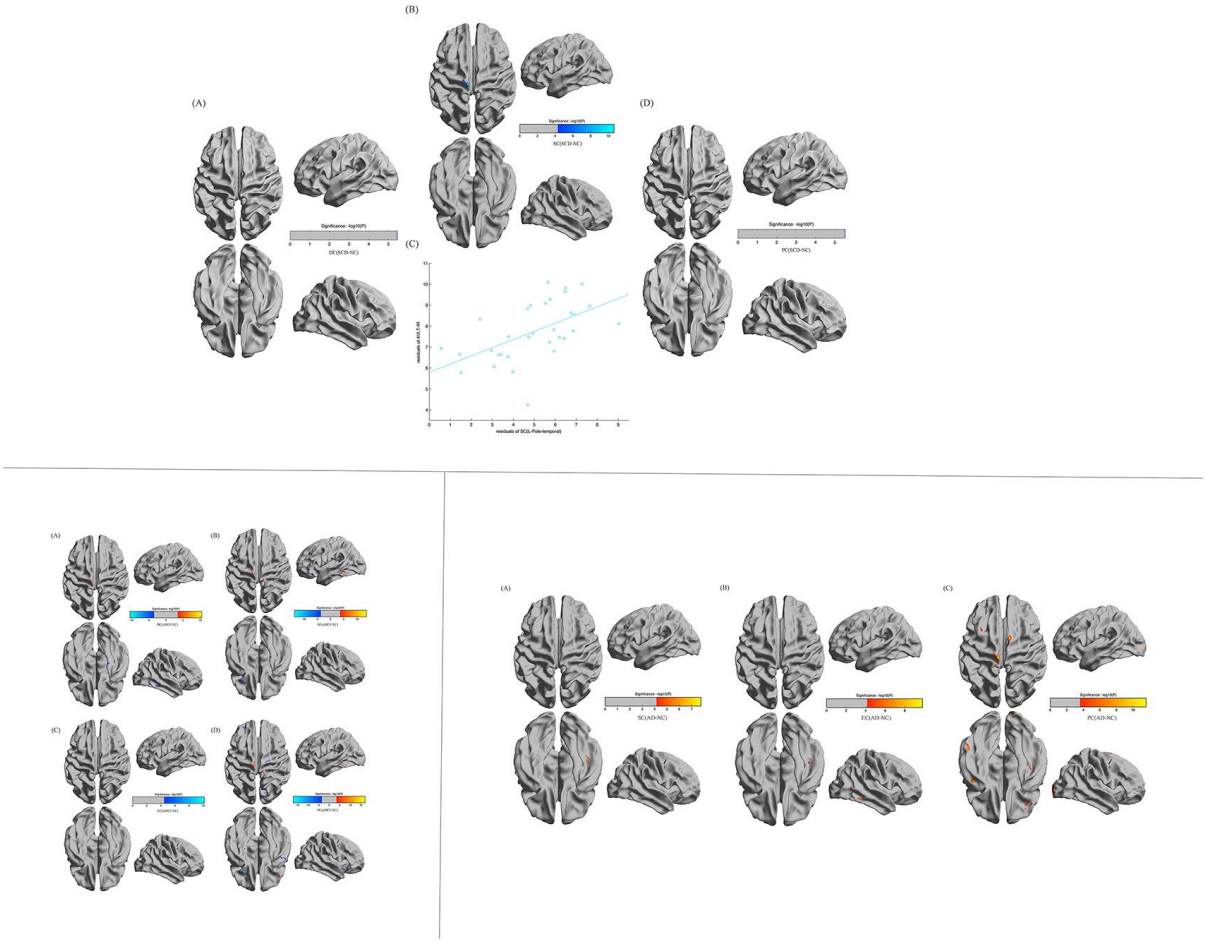
Support: NSFC Grant 11674388
NSFC Grant 11204369
IPCAS Startup Foundation Y1CX222005
973 Program 2015CB351702

Title: Multi-scale topological impairments of brain networks characterized by centralities in SCD, aMCI and AD

Authors: *L. JIANG[1], K. QIAO[2], Y. HAN[3], X.-N. ZUO, SR[2]
[1]Cognitive and Developmental Psychology, Inst. of Psychology Chinese Acad. of Sci., Beijing City, China; [2]Inst. of Psychology Chinese Acad. of Sci., Beijing, China; [3]XuanWu Hosp. of Capital Med. Univ., Beijing, China

Abstract: Evidence suggests that there were topological impairments in brain networks of Alzheimer's disease (AD) patients. However, few studies were performed in the perspective of multi-scale topology and across the entire AD progression. In the present study, four network centrality analyses at different scales of topology were performed with resting state functional Magnetic Resonance Imaging (rs-fMRI) on 32 subjective cognitive decline (SCD), 37 amnestic mild cognitive impairment (aMCI), 30 AD and 40 normal controls (NC): Degree Centrality (DC)

at local scale, Subgraph Centrality (SC) at meso-scale, Eigenvalue Centrality (EC) and Page-rank Centrality (PC) at global scale. All scans were acquired on a 3.0 T Siemens scanner (Erlangen, Germany) at Xuanwu Hospital, Capital Medical University. And all the images were preprocessed using Connectome Computation System (CCS) in our laboratory. Our results revealed that SCD, aMCI and AD all displayed multi-scale topological impairments in multiple brain regions, and SC in the left limbic network in SCD correlated with episodic memory positively. Decreased meso-scale centrality in SCD, bidirectional alterations in multiple scale centralities in aMCI and increased meso-global scale centralities in AD indicated that the deterioration process of AD might be associated with the increase of network topology scale. Such systematical clinical dimension across the entire AD progression as well as multiple scale topological characterization within intrinsic functional connectome of human brain, would supply new insights into the elucidation of neuroimaging pathology of AD.



Disclosures: L. Jiang: None. **K. Qiao:** None. **Y. Han:** None. **X. Zuo:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.22/DP15/MMM11

Topic: I.07. Data Analysis and Statistics

Support: European Union's Horizon 2020 Framework Program for Research and Innovation under Grant Agreement No. 720270 (Human Brain Project SGA1)

Title: Individual brain charting, a high-resolution fMRI dataset for cognitive mapping of the human brain

Authors: *A. L. PINHO, B. THIRION
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Abstract: Mapping functional neuroanatomy of the human brain has become a central challenge in cognitive neuroscience and it constitutes an essential step toward linking brain systems and behavior. While there is a rich literature on the neural correlates underlying task performence, little is still known about the overall functional organization of the brain and how it can be translated into cognition. Neuroimaging techniques, such as Functional Magnetic Resonance Imaging (fMRI) have contributed to the investigation of brain regions involved in a variety of cognitive processes. However, to date, no data collection has systematically addressed the functional mapping of cognitive mechanisms at a fine spatial scale. The Individual Brain Charting (IBC) project stands for a high-resolution (1.5mm) multi-task fMRI dataset that intends to provide the objective basis toward a comprehensive functional atlas of the human brain. The data refer to a cohort of 12 participants performing many different tasks. The large amount of task-fMRI data on the same subjects yields a precise mapping of the underlying functions, free from both inter-subject and inter-site variability. Here, we present the first release of the IBC dataset, which comprises a dozen of tasks, addressing both low- and high- level cognitive functions. The corresponding data-descriptor article is currently in press (Pinho et al., 2018) and the source data plus derivatives are publicly available in the OpenfMRI repository (ds000244) and NeuroVault (id2138), respectively. Future outcomes concern to the development of a neurocognitive atlas derived from the dataset, which will rely on the functional signatures of the tasks and their mutual cognitive components. They can be inferred from maps of brain activation, using mega-analytic approaches. Particularly, data-driven methods will be herein employed for the extraction of the fundamental networks that represent the neural basis of such cognitive components. The atlas will account for a full revision of the neural correlates associated with behavior. It can thus provide a better understanding of cognition in the human brain and its regulation by brain functioning across individuals.
Bibliography:

Pinho et al., "Individual Brain Charting, a high-resolution fMRI dataset for cognitive mapping", *Sci. Data* (2018) [in press]

Disclosures: B. Thirion: None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

Time: Monday, November 5, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 341.23/MMM12

Topic: I.07. Data Analysis and Statistics

Support: Institute of Cognitive Science, University of Colorado Boulder

Title: Topological brain network changes in psychiatric disorders

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Abstract: Brain network analysis has shown promise for characterizing psychiatric disorders but commonly employed graph measures confound network shape and efficiency. Previously described network efficiency changes could occur in all or only part of the brain network. To improve characterization of brain networks in psychiatric disorders we utilize hitting time to resolve existing confounds in functional brain network measures and identify theoretically important information processing structures. We show that skewness of the hitting-time distribution correlates with the presence of path-like features similar to sensory processing subnetworks common in the brain. Using a publicly available dataset, we find evidence that skewness in the distribution of hitting times of functional connectivity decreases as the sensory network is engaged in a task. Skewness is also greater in resting-state networks of individuals with schizophrenia and bipolar disorder providing potential public health relevance.

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Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 341.24/MMM13

Topic: I.07. Data Analysis and Statistics

Support: NIH K08 DA035972-01
2017 Trailblazer Award, Dpt. Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital

Title: Deep gray matter volume and intrinsic functional connectivity following complex perioperative critical care for noncardiac congenital anomalies: Pilot study

Authors: C. R. L. MONGERSON[1], D. J. HODKINSON[1,3], D. ZURAKOWSKI[1,3], R. W. JENNINGS[2,3], *D. BAJIC[1,3]
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Abstract: Objective. There is a fundamental gap in our understanding of how complex perioperative critical care in *full-term* infants affects brain development. *We hypothesized that critically ill premature patients <1 year old, compared to full-term patients and healthy infants, would exhibit (1) smaller deep gray matter (DGM) volumes and (2) altered intrinsic functional connectivity following complex noncardiac perioperative critical care, as determined by MRI.* Methods. Full-term (n=13) and preterm (n=12) patients, and healthy controls (n=10), <1 year corrected age underwent non-sedated MRI scans following completion of surgery and critical care management for noncardiac gastrointestinal congenital anomalies (e.g. long-gap esophageal atresia), as per IRB approval at Boston Children's Hospital. 3T MRI scanner with a 32-channel receive-only head coil (Siemens, USA) acquired high-resolution structural images using FSE sequence [TR/TE= 12430/110 ms; FA 120°; 2 mm slices; 0.35 mm^2 voxels]. Resting-state functional MRI (rs-fMRI) data were acquired using BOLD sequence [GE-EPI, TR/TE = 1830/36 ms; 2 mm^3 voxels; FA 65°; 280 volumes]. Morphologically Adaptive Neonatal Tissue Segmentation tool was used to segment T2-weighted structural images to obtain DGM volumes, presented as absolute (cm^3) and normalized (% total brain volume) measures. Rs-fMRI data was preprocessed using customized scripts written in MATLAB, including a participant-level motion scrubbing strategy excluding volumes with framewise displacement > 0.25 mm. Intrinsic networks were evaluated using independent component analysis. Components reflecting *basal ganglia, thalamic-cerebellar,* and *salience networks* were further analyzed. Statistics was performed using a general linear models regression approach to compare groups with corrected age at scan as a covariate. Results. Absolute DGM volumes were decreased in patients (irrespective of the gestational age) compared to controls (i.e. main effect of group; $F(32,2)=6.9$, $p=0.003$), but not when normalized to total brain volume ($F(32,2)=1.9$, $p=0.169$). Preliminary rs-fMRI analysis showed significantly higher functional connectivity within the *basal ganglia network* of patients, but no group differences for thalamic-cerebellar and salience networks. Conclusions. Our preliminary data suggest complex perioperative critical care in infancy is associated with structural and functional changes in DGM development regardless of gestational age at birth. Future studies should evaluate basal ganglia volumes, as well as possible long-term neurobehavioral sequelae including pain sensitivity, motor function and emotional processing.

Disclosures: C.R.L. Mongerson: None. **D.J. Hodkinson:** None. **D. Zurakowski:** None. **R.W. Jennings:** None. **D. Bajic:** None.

Poster

341. Data Analysis and Statistics: Human Data: Neuroimaging

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Program #/Poster #: 341.25/MMM14

Topic: I.07. Data Analysis and Statistics

Support: MOST-107-2634-F-075 -002

Title: Explainable deep learning of neuroimaging reveals key structural deficits in schizophrenia

Authors: *A.-C. YANG[1], C.-K. PENG[2], C.-P. LIN[3], S.-J. TSAI[4]
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Abstract: Background: Deep neural network (DNN) has facilitated the record-breaking of classification accuracy in fields such as speech or visual object recognition. However, limited studies have investigated the applicability of DNN to three-dimensional neuroimage data, and the interpretation of deep learning model remains like a black box. Here, we present an explainable DNN framework to identify key structural deficits in schizophrenia. **Methods:** Structural brain magnetic resonance images (MRI) were obtained from 200 schizophrenic patients and 200 age- and sex-matched healthy control subjects. The brain MRI images were normalized and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) space. We introduced an original KL-L1 regularization method as a feature selection layer in the DNN to reduce dimensionality of neuroimage data and automatically identify key brain voxels without prior knowledge of brain pathology. **Results:** The DNN classifier with KL-L1 regularization achieved an average test accuracy of 91.7% in WM, an average of 87.5% in GM, and 75.5% in CSF. The key GM voxels identified by the DNN were within brain regions including insula, precuneus, and superior temporal pole; WM voxels were associated with neural tracts, such as cingulum/hippocampus, splenium of corpus callosum, and posterior corona radiata. **Conclusions:** The present study shows that the DNN with KL-L1 regularization can identify key structural deficits that are effectively related to the known structural pathology of schizophrenia. We anticipate that this explainable deep learning approach may provide a useful framework for the search of objective biomarkers of mental illness in future studies.

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