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[Authors]. [Abstract Title]. Program No. XXX.XX. 2018 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2018. Online.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: FP7 People MC-CIG MomeCode 618444
H2020 ERC CoG LinPro 725780

Title: A whole genome library for genetic mosaic analysis

Authors: *X. CONTRERAS[1], J. SONNTAG[1], L. ANDERSEN[2], A. HEGER[1], R. L. JOHNSON[3], L. SCHWARZ[4], L. LUO[4], T. RUELICKE[2], S. HIPPENMEYER[1]
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Abstract: Mosaic Analysis with Double Markers (MADM) technology offers a unique approach to visualize and concomitantly manipulate sparse clones and small subsets of genetically defined cells in mice. For MADM, two reciprocally chimeric split-marker genes are targeted separately to identical loci on homologous chromosomes. The split-marker genes consist of partial coding sequences for green (eGFP) and red (tdTomato) fluorescent proteins separated by an intron containing the loxP site. Following Cre recombinase-mediated interchromosomal recombination during mitosis, functional green and red marker genes are reconstituted resulting in two daughter cells each expressing one of the two markers upon G2-X segregation. Introduction of a mutation distal to one MADM cassette allows the generation of genetic mosaics with wild-type daughter cells labeled with one color and homozygous mutant siblings with the other. Key MADM applications include lineage analysis of stem and progenitor cells; single cell labeling for morphological analysis and dynamic 4D live-imaging; and dissection of cell-autonomous gene function and non-cell-autonomous effects *in vivo*. Originally, MADM cassettes were inserted on Chr. 6 and MADM analysis of gene function was restricted to genes located distal to the *Rosa26* locus. To overcome this limitation, expand MADM-based gene analyses and establish MADM with optimized recombination fidelity, we have now generated ES cells and transgenic mice with novel MADM cassettes knocked in close to the centromeres of all 19 autosomes. Here we present our progress in the validation of new MADM strains, and the analysis of mitotic recombination efficiency in different MADM strains and in distinct brain regions. The dissection of any cell-autonomous gene function in virtually any cell-type will be enabled with the completion of the genome-wide MADM library.

Disclosures: X. Contreras: None. **J. Sonntag:** None. **L. Andersen:** None. **A. Heger:** None. **R.L. Johnson:** None. **L. Schwarz:** None. **L. Luo:** None. **T. Ruelicke:** None. **S. Hippenmeyer:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: Howard Hughes Medical Institute/Helen Hay Whitney Foundation
Becas Chile, Ministerio de Educación
Deutsche Forschungsgemeinschaft
NIH NINDS F32NS103221
MINECO BFU2016–80360-R
Heather and Melanie Muss Endowed Chair
NIH R37 HD32116

Title: Development of ependymal and postnatal neural stem cells; their origin from a common embryonic progenitor

Authors: *S. REDMOND[1], J. I. PARRAGUEZ[1], K. OBERNIER[1], M. FIGUERES-OÑATE[2], L. LÓPEZ-MASCARAQUE[2], L. C. FUENTEALBA[1], A. ALVAREZ-BUYLLA[1]
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Abstract: Two distinct epithelial cells in the walls of the adult mouse lateral ventricles have unique functions: multiciliated ependymal cells (E1) generate cerebrospinal fluid (CSF) flow, and neural stem cells (B1) continuously produce new neurons and glia. Both E1 and B1 cells are derived from radial glia (RG) but how the embryonic ventricular zone (VZ) transforms into the adult V-SVZ, and whether these two cell types originate from a common progenitor, remains unknown. In the adult mouse V-SVZ, E1 cells' large apical domain and B1 cells' small apical endings are organized into rosette-like structures (pinwheels). We show here the time-course of differentiation of RG into E1 and B1 cells and that during the first three weeks after birth, differentiating E1 cells expand their apical domain nearly 27-fold. In contrast, B1 cells retain small apical domains which coalesce into the centers of pinwheels. We next investigated whether E1 and B1 cells are clonally related. Using a retroviral barcode library and high-complexity transposable fluorescent reporters, we show that individual RG can give rise to clones containing E1 and B1 cells (or their progeny). Inducible Cre-mediated lineage tracing combined with BrdU labeling demonstrates that RG during late fetal development generate clones that contain only E1 cells or E1 and B1 cells. We used mice of both sexes and worked to ensure scientific rigor and

reproducibility by taking multiple experimental approaches to confirm each overall finding presented. This study reveals key developmental steps in the formation of the postnatal V-SVZ niche and shows that E1 and B1 cells can have a common origin.

Disclosures: S. Redmond: None. **J.I. Parraguez:** None. **K. Obernier:** None. **M. Figueres-Oñate:** None. **L. López-Mascaraque:** None. **L.C. Fuentealba:** None. **A. Alvarez-Buylla:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NIBIB
HHMI
NIH/NINDS
Allen Frontiers Group

Title: Multicolor cell lineage tracing in the developing ferret cerebral cortex

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Abstract: Over the course of development, the mammalian brain grows from a single layer of cells into a complex, multilayered structure. Stem cells in the ventricular zone proliferate and differentiate, giving rise to neuronal progenitors that migrate relatively short distances in the dorsal telencephalon, or long distances in the ventral telencephalon. In the smooth or lissencephalic brain, such as those of rodents, this migratory trajectory in the dorsal telencephalon has been shown to be relatively simple, with clones of up to 100 neurons forming cylindrical or conical shapes in the overlying cortical plate. However, in gyrencephalic species such as humans, it remains unclear if the convolutions of the brain correlate with a different migratory strategy for excitatory progenitors in the dorsal telencephalon. The goal of this work is to study the migratory paths of excitatory neuronal progenitors in an animal model of gyrencephalic brain development. Here we demonstrate that genetic labeling of dorsal telencephalic neurons using the PiggyBac transposase system in the developing ferret *(Mustela putorius furo*) brain can be used to quantify the degree of dispersion of related cells. Using the PiggyBac transposase system, we can stably label lineages of cells by delivering the transposase along with plasmids expressing three fluorescent proteins: red (monomeric red fluorescent protein, mRFP), green (enhanced green fluorescent protein), and blue (cyan fluorescent protein,

CFP). These colored protein-encoding genes are then combinatorially integrated into the genomes of dividing neural progenitor cells by the transposase. Different combinations of each of the three fluorescent proteins in individual cells therefore allow us to differentiate lineages based on their color expression. Image analysis of labeled cells from ferrets electroporated at embryonic day 37 and harvested at post-natal day 1 (P1), P7, and P14 reveals at least 10 distinguishable colors in any given experiment. Preliminary results thus far indicate that there is a high degree of intermingling between cells of any one color and cells of other colors, suggesting that clones from a single progenitor intermix widely with cells derived from other progenitors. This suggests that cells from a common progenitor do not form simple cylindrical shapes as seen in rodents. Continuing work aims to quantitatively analyze the precise patterns of clonal dispersion in the developing ferret cortex.

Disclosures: E.M. Degennaro: None. **R.S. Smith:** None. **D.M. Gonzalez:** None. **C.A. Walsh:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NINDS grant #R37 NS-071785-07 (to S.C.B.)

Title: Developmental characterization of the pig ganglionic eminence

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Abstract: Inhibitory neurons (interneurons) regulate information processing and interaction between cortical networks. While comprising only 20-30% of the total neuronal population of the cortex, interneurons are highly diverse with many subtypes identified by their molecular, morphological, and functional differences. The great complexity of the human cerebral cortex suggests an even higher degree of interneuron diversity. Interneurons are born in the ganglionic eminence (GE) and migrate tangentially to reach their final destinations and integrate into the local circuit. The GE has four recognized subdivisions: the medial (MGE), lateral (LGE), caudal (CGE) and preoptic area (POA). Much of what we currently know about interneuron origins, migration and integration derives from rodent studies. Here we use pigs (*Sus scrofa domesticus*) to study the GE composition and development in a large animal model with central nervous

system more closely resembling human. Tissue at embryonic day 30 (E30), E35 and E60 was used to analyze GE expansion and identify proliferative zones in the pig brain. Using a multi-disciplinary approach, we characterized the cytoarchitecture and interneuron progenitor composition, diversity and distribution throughout the developing pig telencephalon. At all ages analyzed, the ventricular zone of the lateral ventricle was observed along with increase/decrease volume of the subventricular zones matching the development stage of the GE. At E30 the dorsal ventricular ridge was prominent, and the underlying striatal primordium developed. By E35 a salient groove beginning in the intersection of the most anterior part of the MGE and LGE was observed, by E60 the sulcus separating the MGE from LGE was absent and both structures formed one undistinguishable entity. These anatomical observations were further confirmed with detailed histological analysis of regional and cellular identity, making it possible to discriminate between GE compartments at E35 according to their cellular components. Using the overlapping expression of Ki67, OLIG2, and DLX2 we were able to observe the transition from undifferentiated neural stem cell to intermediate progenitor and proliferative populations in the different GE domains. Whole hemisphere slice culture along with adeno-GFP labeling was used to study migration and cell division dynamics using time-lapse imaging. Finally, Brdu tracing of newborn and late born cells allowed us to confirm migratory routes and the destinations of different GE progenitor populations. Understanding interneuron development and diversity in the pig will help to better approach human development and related pathologies.

Disclosures: M.L. Casalia: None. **P.J. Ross:** None. **K. Sandoval:** None. **M. Paredes:** None. **S.C. Baraban:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIMH R01 MH081880
NIMH R37 MH049428
UCSF CTSI, 1111111
Predoctoral Training in Neurobiology, T32 GM07449-40

Title: Mafb and c-Maf control the fate, migration and maturation of MGE-derived PV^+ and SST^+ CINs

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Abstract: GABAergic cortical interneurons (CINs) are primarily generated by medial and caudal ganglionic eminences (MGE & CGE). CIN dysfunction is implicated in neuropsychiatric diseases such as epilepsy. Therefore, understanding CIN generation, maturation and function have important clinical implications.
MGE-derived CINs are composed of two major subgroups: somatostatin$^+$ (SST; early-born) and parvalbumin$^+$ (PV; late-born). MGE-derived CIN fate is initially determined in progenitors by transcription factors (TFs) such as *Nkx2-1, Lhx6* and *Dlx1&2*. Additional TFs that control CIN early development are still being uncovered. Here, we report that the *Mafb* and *c-Maf* TFs, which are genetically downstream of *Nkx2-1, Lhx6* and *Dlx1&2*, are critical for generating the correct amount, migration and function of PV$^+$ and SST$^+$CINs.
Combined deletion of Mafb and c-Maf (cDKO) from MGE progenitors resulted in an ~70% reduction of MGE-derived CINs at P35, with preferential decrease in the PV$^+$ CINs. Surviving CINs resided in deeper cortical layers and were more likely to be early-born SST interneurons. EdU incorporation experiments in cDKOs showed no change in MGE CIN progenitor numbers, but demonstrated a precocious neurogenesis and an increase in SST CINs. In addition, CINs in the cDKO have disrupted migration patterns and firing properties. Together, these results provide evidence that *Mafb* and *c-Maf* are required to produce the proper balance, and normal function of, PV$^+$ and SST$^+$ CINs.

Disclosures: L. Pai: None. **D. Vogt:** None. **A.C. Perez:** None. **G. McKinsey:** None. **J.S. Hu:** None. **R. Pla:** None. **F. Cho:** None. **L.V. Goodrich:** None. **J.T. Paz:** None. **J.L. Rubenstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIGMS R35 GM119831
NIMH R37 MH049428

Title: Gene regulatory networks in embryonic basal ganglia at single cell resolution

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Abstract: The embryonic basal ganglia contains progenitor zones known as the medial, caudal, and lateral ganglionic eminences (GEs). These eminences give rise to inhibitory interneurons that populate the adult brain. Interneurons are vital components of brain circuitry; perturbations to interneuron specification have been linked to neurological disorders such as schizophrenia and autism spectrum disorders. Interneuron specification is in part controlled by complex, region-specific transcription factor networks active in the GEs. However, the transcriptional networks regulating key early cell fate decisions are not entirely known. Progenitor populations from embryonic day (E) 11.5 mice with region-specific enhancer activity in the GEs fate-map to distinct adult interneuron populations, suggesting the existence of fate-determining transcriptional pathways active during early progenitor differentiation. We aim to understand how transcriptional networks within the GEs selectively regulate gene expression and genomic programming to control early interneuron lineage specification. We performed single-cell RNA-sequencing on cells from E11.5 caudal, lateral, and medial GEs in order to characterize transcriptional networks that control and potentiate immediate and long-term cell fate decisions of populations arising within the basal ganglia. Using both guided and unguided approaches to identify key transcriptional markers of transient cell states, we identified major progenitor populations and cell types within the GEs. By identifying transcriptional networks regulating early lineage specification of inhibitory interneurons, we hope to construct a map of the key regulatory factors enabling early interneuron diversity in the brain.

Disclosures: L. Su-Feher: None. **A.N. Rubin:** None. **S.N. Silberberg:** None. **K.J. Lim:** None. **J.L.R. Rubenstein:** None. **A.S. Nord:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: HHMI

Title: Towards developmental correlates of connectivity

Authors: *B. MARK, C. Q. DOE
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Abstract: A fundamental question in neurobiology is how the staggeringly diverse population of neurons present in the brain self-assembles into functional circuits. While a great deal of

progress has been made towards elucidating the developmental programs that drive the generation of neural diversity, much less is known about how these programs contribute to circuit formation. The role of lineage relationship, or neurons born from a common progenitor, and temporal relationship, neurons born at the same time, have recently been suggested to contribute to the establishment of connectivity. Perhaps one of the best studied systems for investigating the roles of neural progenitor lineage and birth timing in the generation of neural diversity is the Drosophila ventral nerve cord. More recently, the completion of an ssEM volume of the entire larval brain provides a nearly complete connectome permitting the investigation of how lineage relationship and birth order influence circuit formation. To address these questions, we have reconstructed the connectome of an entire neural progenitor lineage in the larval ventral nerve cord, and mapped the birth order and temporal gene expression profiles of every neuron in the lineage. We find that clonally related neurons have stereotyped morphologies and target regions, and that birth order further refines target region. Additionally, we find that clonally related neurons do not share connectivity despite targeting common regions of the neuropil, suggesting that target region is not totally predictive of partner choice, and that clonally related neurons may be more functionally heterogeneous than previously imagined. We propose that using connectomics to study development permits the study of developmental correlates of connectivity with a previously unachievable level of resolution.

Disclosures: B. Mark: None. **C.Q. Doe:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Science Foundation DBI-1612261
National Science Foundation IOS-1254060
National Science Foundation IIP-1538813
University of California President's and Chancellor's Postdoctoral Fellowship
California Institute for Regenerative Medicine RT1-01074
California Institute for Regenerative Medicine RB5-07254

Title: Enrichment of astrocyte-biased cells with a hydrodynamic oblique angle parallel electrode sorter (HOAPES)

Authors: *T. ADAMS[1], A. Y. L. JIANG[2], A. P. LEE[2], L. A. FLANAGAN[3]
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Abstract: Human neural stem and progenitor cells (hNSPCs) have therapeutic potential to treat neurodegenerative diseases since they provide neuroprotection and differentiate into the three cell types of the central nervous system - astrocytes, neurons, and oligodendrocytes. However, cultures of these cells are heterogeneous, containing progenitor cells with distinct differentiation properties and little is known regarding which types of progenitors are best for neural repair. Dielectrophoresis (DEP) is a technique that uses alternating current electric fields to separate cells based on the dielectric properties of their membrane and cytoplasm. With DEP, our group has demonstrated that astrocyte-biased and neuron-biased subpopulations can be isolated from mouse NSPCs at select frequencies and this behavior is linked to the cells' membrane capacitance and fate potential. Using this information, we've implemented a two-step sorting scheme to reduce heterogeneity in hNSPC populations. Step one defines a cell sample-specific sorting frequency, and step two separates cells at the sorting frequency in a hydrodynamic oblique angle parallel electrode sorter (HOAPES). The HOAPES device contains three main components: a filter (blocks large particles), passive-hydrodynamic cell aligner (controls cells' flow path), and oblique electrodes (separates cells). With the electric field applied, cells entering the oblique electrode region will either flow along the microchannel walls (unfocused) or focus along the centerline of the electrodes. In this work astrocyte-biased cells were detected and separated from heterogeneous hNSPCs using the HOAPES device. The sorting frequency for enrichment ranged from 150-300 kHz. A second higher frequency was tested such that cells were exposed to DEP but remained unsorted (control). Also, cells incubated in cell culture media and DEP buffer solution were tested as unsorted controls. Successful separation of astrocyte-biased cells was confirmed with differentiation and GFAP immunostaining. Cell enrichment was found to be ~1.75-fold, showing the first label-free enrichment of astrocyte-biased cells from hNSPCs. Effectively sorting hNSPCs is essential to further study these cells as treatment options for neurological diseases.

Disclosures: T. Adams: None. **A.Y.L. Jiang:** None. **A.P. Lee:** None. **L.A. Flanagan:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant T32GM007753
NINDS Grant NS032457
NINDS Grant NS35129
Manton Center for Orphan Disease Research
Howard Hughes Medical Institute

Title: ZNF335 regulates progenitor and neuronal cell identity in mammalian brain development

Authors: *Y. YANG[1], E. A. MURPHY[2], D. M. GONZALEZ[3], C. A. WALSH[4]
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Abstract: Proper mammalian brain development requires a tightly regulated and ever changing interplay of gene and protein expression. Spatial-temporal maintenance of subsets of progenitor cells as they go through differentiation and acquire neuronal cell-type specific markers is a hallmark of proper brain development. Many of the factors responsible for regulating essential switches in cellular identity remain unknown. Zinc finger protein 335 (ZNF335) has been shown to play an essential role in neuronal progenitor cell proliferation and differentiation, and disruption of ZNF335 expression levels, leads to microcephaly, or reduced cerebral cortical size in both human patients and knockout mouse models. Knockout mouse studies and high throughout sequencing demonstrated that loss of Znf335 leads to abnormal mixed-identity phenotypes. Taken together, Znf335 is essential for maintaining and dictating progenitor and neuronal cell identities.

Disclosures: Y. Yang: None. **E.A. Murphy:** None. **D.M. Gonzalez:** None. **C.A. Walsh:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: BIOGEN Idec
FRM SPF20151234950
Vaincre Alzheimer
France Parkinson

Title: Epigenetic modalities of allelic gene dosage: Implications in disease

Authors: *L. MARION-POLL, B. FORET, A.-V. GENDREL, D. ZIELINSKI, M. ATTIA, A. LE SAUX, L. SYX, E. HEARD
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Abstract: Genes are generally considered to be either silent or expressed from both alleles, except in some particular cases (e.g. X-chromosome inactivation, imprinted genes). Several allele-specific genome-wide studies on clonal cell lines have shown that 2-10% of the genes can be stably expressed in a monoallelic manner, from either one of the parental alleles (Gendrel et al, 2016). Interestingly, these genes were found to be particularly associated with autosomal

dominant disorders (e.g. epilepsy, neurodegenerative disorders, myofibrillar myopathy). However, previous studies were conducted on a limited number of clonal neural progenitor cell (NPC) lines, and little is known about the allelic behaviour of these different genes.
In this study, we dissected the allelic patterns of a selection of a dozen genes (specifically those associated with autosomal dominant disorders), using a large number of NPC clones. Strikingly, we find that individual genes have specific modalities of allelic expression. We show that these patterns arise during differentiation, giving rise to cell diversity and individuality, contributing to gene dosage. We also show that monoallelic expression can be cell-type specific *in vivo*. Most importantly we also demonstrate that the allelic imbalance is an epigenetic mechanism, that can be reversed using specific "epidrugs". Finally a mouse model for one of our candidate genes has been generated and we are currently investigating the pathological implications of random monoallelic expression *in vivo*, as a proof-of-concept.

Disclosures: L. Marion-Poll: None. **B. Foret:** None. **A. Gendrel:** None. **D. Zielinski:** None. **M. Attia:** None. **A. Le Saux:** None. **L. Syx:** None. **E. Heard:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: Jerome Lejeune Foundation

Title: Transcriptional targets of NeuroD1 during embryonic cortical development

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Abstract: Glutamatergic neurons populating the mature cerebral cortex are for the most part generated during prenatal life from a pool of progenitors located in the ventricular and subventricular zones, the proliferative niches of the mouse embryonic cortex. According to the classic cascade of transcriptional events governing cortical neurogenic mechanisms, Tbr2, expressed in intermediate progenitors populating the subventricular zone, replaces the expression of Pax6 which is expressed by radial glial cells located in the ventricular zone. Subsequently, the expression of Tbr1 marks the switch from the stage of proliferation to that of postmitotic differentiation. While in this transition, cells typically express NeuroD1. It is established that NeuroD1 has a crucial role in driving neuronal differentiation; however, the cascade of transcriptional effects driven by NeuroD1 are yet to be defined in details. To this purpose we

FACS sorted cells after 24 hours from the in utero electroporation of a construct containing a NeuroD1 promoter to highlight cells actively expressing NeuroD1 at E14.5. Next, transcription was screened through RNAseq. Our data show that NeuroD1 is co-expressed with a number of transcripts typical of both mitotic and postmitotic cells, in line with its differentiative role. Accordingly, its overexpression (through, again, electroporation) drives the ectopic expression of markers of differentiated, postmitotic neurons without strongly affecting the expression of other markers of proliferation. This suggests that NeuroD1 overexpression drives differentiation but has a minor impact on turning off proliferative transcriptional programs.

Disclosures: F. Bedogni: None. **L. Scaramuzza:** None. **C. Cobolli Gigli:** None. **N. Landsberger:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NINDS F31 NS103398
NIH NIMH R01 MH071679
NIH NINDS R01 NS081297

Title: Dissecting the developmental origins of forebrain cholinergic neuron diversity

Authors: *K. C. ALLAWAY[1,2,3], R. MACHOLD[3], G. FISHELL[1,2]
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Abstract: Acetylcholine plays an essential role in modulating the activity of cortical, hippocampal, and basal ganglia circuits to influence attention, learning and memory, motor output, and reward pathways. The primary source of acetylcholine within the forebrain are striatal cholinergic interneurons (SCIs) and basal forebrain cholinergic projection neurons (BFCNs). Despite the importance of cholinergic signaling, the specification and diversity of these neurons are poorly understood. The precursors for all forebrain cholinergic neurons are born in the same region of the embryonic brain, and it is not known how these cholinergic precursors ultimately develop into diverse populations of interneurons and projection neurons. Although there is phenotypic diversity within SCIs and BFCNs, the developmental origins of this diversity has not been characterized, nor are there molecular markers to define the subclasses of cholinergic neurons that embody this diversity. Here, we investigate these questions using genetic fate mapping and single-cell transcriptomics in mouse. Our spatial and temporal fate mapping suggests that while spatial origin does not have a strong impact on mature cholinergic

anatomical identity, the birthdate of cholinergic neurons predicts their projection topography. We also begin to characterize the transcriptional heterogeneity of cholinergic neurons across development.

Disclosures: K.C. Allaway: None. **R. Machold:** None. **G. Fishell:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.13/A13

Topic: A.01. Neurogenesis and Gliogenesis

Support: Vision Science Research Program
Foundation Fighting Blindness

Title: Functional and molecular characterization of cone photoreceptor lineage restricted progenitors

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Abstract: All seven major cell types of the mammalian retina are produced during embryonic development in a temporally stereotyped manner from a pool of progenitor cells present in the neuroblast layer. Despite this highly conserved order of retinogenesis, it is not clear whether all retinal progenitor cells (RPCs) are inherently multipotent, or if there are distinct, molecularly identifiable subclasses of RPCs with more restricted lineage potential. Furthermore, little is currently known to what extent environmental factors present in the developing retina are able to specify RPC fate outcomes. Here we show, using both adult retinal stem cells (RSCs) in mouse and human, and RPCs isolated from the embryonic retina, that all RPCs assume a cone lineage restricted potential through a default mechanism when removed from TFGβ, WNT, and BMP morphogen signalling pathways. When isolated *in vitro*, a single RSC will readily proliferate to form a free-floating sphere colony containing both non-pigmented RPCs and retinal pigmented epithelial progenitors (RPEPs). When whole adult murine or human RSC-derived sphere colonies were exposed to COCO (a TFGβ, WNT, and BMP signalling inhibitor) for 4 weeks, ~60% of the resulting cells were expressing s-opsin and cone arrestin, indicating that these cells are mature short-wave cone photoreceptors. To further probe what specific progenitors in the RSC-derived colonies COCO is acting on, single pigmented or non-pigmented progenitors were exposed to COCO for 4 weeks and assessed for clonal composition. These results indicate that all non-pigmented RPCs produced clones containing nearly pure populations of cone photoreceptors, while pigmented RPEPs were unable to produce any cone photoreceptors. When

RPCs were isolated from murine E14 retina and exposed to COCO for 4 weeks, nearly all resulting cells were cone photoreceptors, and preliminary experiments indicate that this cone lineage restriction may be possible from RPCs isolated at earlier (E12) and later (E19) stages. This evidence points towards a distinct cone lineage restricted progenitor that may be present during development in both mouse and human systems. Accordingly, we have completed an RNA-sequencing experiment profiling the transcriptomes of embryonic RPCs exposed to COCO at different time points along their differentiation trajectory. Preliminary data suggests that SOX15 may be a unique marker of a cone restricted progenitor cell, and further analyses will be completed to determine whether SOX15 is expressed in a subset of progenitors in the developing retina at embryonic timepoints when cone photoreceptors are being produced.

Disclosures: J.J. Belair-Hickey: None. **S. Khalili:** None. **B.G. Ballios:** None. **K.N. Grise:** None. **B.L.K. Coles:** None. **D. van der Kooy:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.14/A14

Topic: A.01. Neurogenesis and Gliogenesis

Title: Defining the role of L-type calcium channels and calcineurin/NFAT signaling in neuronal specification

Authors: *R. I. PETROVA[1,2], T. TORRES[2], A. ARJUN[1,2,3], C. KI[2,5], G. PANAGIOTAKOS[1,2,3,4]
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Abstract: The connectivity of the cerebral cortex is set forth during development, arising from the convergence of coordinated extrinsic and intrinsic signals that guide neural progenitor cells (NPCs) to differentiate into diverse pools of neurons and glia. In addition to genetic programs that regulate the adoption of specific neuronal fates, electrical activity has been shown to regulate cellular processes involved in the generation and maturation of neurons. The mechanisms by which electrical signals are transduced into long-term biochemical changes in NPCs to precisely regulate the acquisition of neuronal identity, however, remain poorly understood.
Ca^{2+} is the primary intracellular mediator of the effects of electrical activity, coupling electrical signals at the membrane to the regulation of transcription. Mutations in the genes encoding various subunits of voltage-gated Ca^{2+} channels, as well as members of the Ca^{2+}-activated calcineurin (CaN)/NFAT signaling pathway, have been repeatedly associated with a variety of

psychiatric disorders of developmental origin. We have found that variations in Ca^{2+} influx through the voltage-gated L-type Ca^{2+} channel (LTC) $Ca_v1.2$ bidirectionally regulate the generation of specific cortical projection neuron populations. Changes in the abundance of these populations have been implicated in several genetically-defined psychiatric syndromes, suggesting that Ca^{2+}-regulated mechanisms modulating differentiation are a point of convergence for psychiatric disease. In response to depolarization, LTC-mediated Ca^{2+} elevations are particularly effective at activating the CaN phosphatase complex, which then triggers nuclear translocation of the NFATc1-4 transcription factors. To interrogate how Ca^{2+} influx through LTCs and downstream CaN/NFAT signaling mechanisms regulate cortical development, we employed a series of gain- and loss-of-function approaches targeting the CaN/NFAT pathway, using a combination of pharmacology, *in utero* electroporation and genetic models. We uncovered that persistent NFAT activation *in vivo* results in a change in cortical projection neuron specification, similar to what we observed when manipulating LTC-mediated Ca^{2+} influx, suggesting that the LTC-NFAT signaling axis plays key roles in cortical neuron development.

Disclosures: R.I. Petrova: None. **T. Torres:** None. **A. Arjun:** None. **C. Ki:** None. **G. Panagiotakos:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.15/A15

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH KO8
AO Spine North America
McCormick Faculty Award

Title: microRNA controls corticospinal motor neuron development by modulating LMO4 activity

Authors: *J. L. DIAZ[1], V. B. SITHTHANANDAN[2], V. LU[4], J. L. MACDONALD[5], N. GONZALEZ-NAVA[2], L. PASQUINA[6], P. SARNOW[3], T. PALMER[2], J. D. MACKLIS[7], S. A. THARIN[8]
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Abstract: Corticospinal motor neurons (CSMN) are a phenotypically defined sub-population of cortical neurons that project through the spinal cord and direct voluntary movement. Paralysis in spinal cord injury is largely due to loss of functional CSMN, which do not spontaneously regenerate. While a number of transcription factors have been associated with CSMN development, their controls are poorly understood. Our aim is to address whether specific microRNAs (miRNAs), which are small, non-coding RNAs that can control multiple post-transcriptional gene pathways, are necessary and sufficient to convert immature cortical neurons into mature CSMN. We previously showed miR-CSMN-1, a miRNA enriched during CSMN development, promotes CSMN fate vs. the highly related callosal projection neurons (CPN) in embryonic cortical cultures. Here we demonstrate that in embryonic stem cell (ES-cell) derived neurons, miR-CSMN-1 gain-of-function (GOF) leads to an increase in the number of CTIP2+ neurons compared to control, while miR-CSMN-1 loss-of-function (LOF) resulted in a decrease, which is in agreement with the effect seen in embryonic cortical cultures. Based on bioinformatics studies we hypothesized miR-CSMN-1 acted via LMO4, a transcription factor important for CPN development, and we demonstrated via rescue experiments that over-expression of LMO4 reduced the effect of miR-CSMN-1 in embryonic cortical cultures. Here we show LMO4 overexpression is able to partially rescue the miR-CSMN-1 GOF phenotype based on cell specific markers of upper layer II/III neurons (CPN). miR-CSMN-1 GOF caused a decrease in CPN verses control, shown by a reduction in CUX1+ cells. When the LMO4 protein was overexpressed along with miR-CSMN-1 GOF, the %CUX1+ cells increased back towards control levels. In ES-cells we have preliminary evidence that miR-CSMN-1 GOF also decreases LMO4 expression in differentiating ES-cells. We conclude that miR-CSMN-1 is controlling CSMN verses CPN fate direction early in development, and is doing so by regulating key transcription factors, specifically LMO4.

Disclosures: J.L. Diaz: None. **V.B. Siththanandan:** None. **V. Lu:** None. **J.L. MacDonald:** None. **N. Gonzalez-Nava:** None. **L. Pasquina:** None. **P. Sarnow:** None. **T. Palmer:** None. **J.D. Macklis:** None. **S.A. Tharin:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.16/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH T32 NS082174
2018 UC Irvine-Brython Davis Fellowship
NSF CAREER IOS-1254060
Neilsen Foundation SCIRTS-296387

Title: Highly-branched N-glycans generated by MGAT5 control neural stem cell differentiation and cell surface protein expression

Authors: *A. R. YALE[1], E. KIM[2], L. CHO[1], C. REEVES[5], L. VERMA[1], E. S. MONUKI[3], P. D. GERSHON[4], M. DEMETRIOU[2], L. A. FLANAGAN[2]
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Abstract: Neural stem and progenitor cells (NSPCs) have the potential to treat many diseases and injuries due to their ability to secrete beneficial factors and form the major cell types of the central nervous system. Understanding the mechanisms regulating NSPC differentiation will improve their use as therapeutics. Glycosylation can modulate the expression and function of almost all proteins on the cell surface and is capable of impacting a variety of cellular processes. Despite its importance, glycosylation's role in NSPC fate remains unclear. Our lab found that N-glycosylation patterns correlate with NSPC fate potential; specifically, NSPCs expressing more highly-branched N-glycans generate more astrocytes and fewer neurons. Increasing expression of highly-branched N-glycans on NSPCs by N-acetylglucosamine (GlcNAc) treatment enhances astrocyte formation at the expense of neurogenesis. This effect was specific to incorporation of GlcNAc in the N-glycan branching pathway since blocking an early enzyme in the pathway with kifunensine abrogated the GlcNAc effect on NSPC differentiation. Mass spectrometry analysis of plasma membrane proteins from control and GlcNAc-treated NSPCs identified changes in the levels of several cell-cell and cell-ECM adhesion proteins, suggesting that glycosylation impacts fate by regulating cell surface proteins that respond to extracellular cues. We hypothesized that NSPC fate might be regulated by downstream enzymes in the branching pathway rather than the presence or absence of all N-glycan branching. We therefore measured levels of N-glycan branching enzymes in astrocyte-biased NSPCs and found higher expression of MGAT5, a late-stage branching enzyme necessary for the formation of highly-branched N-glycans. Differentiating cortical NSPCs derived from MGAT5-deficient mice resulted in more neurons and fewer astrocytes compared to littermate control NSPCs. We also analyzed neurogenesis *in vivo* and found elevated expression of neuronal markers NeuN and TuJ1 in the cerebral cortices of MGAT5-deficient mice. Thus, the loss of MGAT5 and highly-branched N-glycans favored neurogenesis and impaired astrocyte generation. MGAT5-mediated N-glycan branching significantly impacts NSPC differentiation, potentially by modifying cell surface proteins.

Disclosures: A.R. Yale: None. **E. Kim:** None. **L. Cho:** None. **C. Reeves:** None. **L. Verma:** None. **E.S. Monuki:** None. **P.D. Gershon:** None. **M. Demetriou:** None. **L.A. Flanagan:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.17/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: California Institute for Regenerative Medicine (CIRM) RB5-07254
Nielsen Foundation Grant -SCIRTS-296387

Title: Cell surface complexity modulates membrane capacitance and fate choice of human neural stem cells

Authors: *S. TIWARI[1], E. KIM[1], C. REEVES[2], J. L. NOURSE[1], C. SOEMARDY[1], L. A. FLANAGAN[1]
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Abstract: Human neural stem and progenitor cells (hNSPCs) have potential as therapeutic candidates for the treatment of neurodegenerative diseases or neurotraumas. Important issues that need to be addressed to improve utility of these cells in clinical trials include characterization of the heterogeneity in stem cell populations and ways to modulate their fate. Our previous studies have shown differential membrane capacitance values for cell populations with astrogenic and neurogenic fate. In the present study we have investigated the modulatory effect of cell surface complexity on membrane capacitance and cell fate of hNSPCs.Whole cell membrane capacitance was measured using the 3DEP analyzer, a micro-well device that uses alternating current electric fields to quickly quantitate capacitance. The cell surface of hNSPCs was altered by treating cells with N-acetylglucosamine (GlcNAc), which feeds into N-glycosylation pathways leading to the formation of complex, highly-branched sugars. Treatment of hNSPCs with GlcNAc significantly increases N-glycan branching on the cell surface (lectin LPHA, mean fluorescence intensity (MFI) untreated 18485±2069 SEM, GlcNAc treated MFI 40863±4428 SEM; $p<0.001$). Increasing N-glycan branching on hNSPCs also significantly increases membrane capacitance (untreated 7.5 mF/m2, GlcNAc treated 9.3 mF/m2; $p<0.001$), showing that cell surface glycosylation patterns impact whole cell membrane capacitance values. Modulation of cell surface N-glycan branching impacts cell differentiation potential too. Increase in these highly branched N-glycans increases the percentage of SOX2+ precursors (17.13±4.33 untreated, 44.74±10.63 GlcNAc treated; Mean ±SEM; $p <0.02$) while decreasing the total number of MAP2+ neurons formed (16.91±1.35 untreated, 10.99±1.57 GlcNAc treated; Mean ± SEM; $p< 0.0001$). The increase in cell surface highly branched N-glycans reduces the expression of integrins such as alpha V,2, 5, 6, 7, 9 and β1,5 and 8. The effects of GlcNAc treatment on differentiation are potentiated in the presence of insulin and transferrin, potentially through changes in the level of receptor glycosylation and subsequent downstream signaling. Taken together these results indicate a direct association between membrane capacitance, cell surface complexity and fate choice of hNSPCs.

Disclosures: S. Tiwari: None. **E. Kim:** None. **C. Reeves:** None. **J.L. Nourse:** None. **C. Soemardy:** None. **L.A. Flanagan:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.18/A18

Topic: A.01. Neurogenesis and Gliogenesis

Support: iGE3

Title: Plasticity in neurogenic competence of cortical progenitors in the developing mouse neocortex

Authors: *P. OBERST[1], C. CONCETTI[1], D. JABAUDON[1,2]
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Abstract: During neocortical development, progenitors located in the ventricular zone sequentially give rise to distinct subtypes of excitatory neurons which assemble to form the circuits for high-order sensory-motor and cognitive functions. Deep layer neurons are born first, in the early stages of corticogenesis, while superficial layer neurons are born later on, toward the end of corticogenesis. The successive production of deep and superficial layer neurons results from an aggregate progression in the neurogenic competence of progenitor cells, but little is known on the mechanisms driving competence progression as well as on the contribution of intrinsic and environmental factors to this process. To address these questions, we used FlashTag (Telley et al., Science 2016) to isolate isochronic cohorts of progenitor cells and investigate their neurogenic commitment using heterochronic transplantation. Our results provide a cell-type specific account of the plasticity of neocortical progenitors at sequential stages of neurogenesis.

Disclosures: P. Oberst: None. **C. Concetti:** None. **D. Jabaudon:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.19/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: 17H05775
17K07102
Cell Science Research

Mochida Memorial Foundation for Medical and Pharmaceutical Research
Takeda Science

Title: ASD-linked gene FoxG1 controls inhibitory circuit development in a dose-dependent manner

Authors: *G. MIYOSHI[1,2], Y. UETA[1], H. OSAKI[1], Y. YAGASAKI[1], R. MACHOLD[2], G. J. FISHELL[3,2], M. MIYATA[1]
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Abstract: The recent discovery of cases involving up-regulation (gene duplication) or down-regulation (heterozygous haploinsufficiency) of the transcription factor FoxG1 in autism spectrum disorder (ASD) patients has implicated altered FoxG1 gene dosage in ASD etiology. Here we report that FoxG1 expression levels undergo dynamic changes during the course of forebrain development in a manner that is tightly correlated with the differentiation and maturation stage of GABAergic neurons. Precisely regulated dynamic expression of FoxG1 during specification and migration is essential for the proper distribution of forebrain GABAergic neurons, and that even relatively subtle changes in its expression during development can impair the formation of inhibitory circuits. These findings provide clarity as to the dose-dependent requirement for FoxG1 and why even relatively minor changes in its expression during development result in severe neurological impairment.

Disclosures: G. Miyoshi: None. **Y. Ueta:** None. **H. Osaki:** None. **Y. Yagasaki:** None. **R. Machold:** None. **G.J. Fishell:** None. **M. Miyata:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.20/DP01/A20

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH NCI R33 CA202900
ACS-RSG-16-217-01-TBG

Title: Generating *in vivo* somatic mouse mosaics with locus-specific, stably-integrated transgenic elements for studies of gene function in neural development

Authors: G. KIM[1], D. RINCON FERNANDEZ PACHECO[1], D. SAXON[2], A. YANG[3], S. SABET[1], M. DUTRA-CLARKE[1], R. LEVY[1], A. WATKINS[1], H. PARK[4], A. A. AKHTAR[5], P. W. LINESCH[6], N. KOBRITZ[1], S. CHANDRA[1], J. MOLINA[1], K. HOANG[7], J. A. TSYPORIN[8], K. SEDIVAKOVA[1], S. BANNYKH[1], B. CHEN[9], M. DANIELPOUR[1], *J. J. BREUNIG[10]

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Abstract: Viral vectors and *in vivo* electroporation (EP)-mediated gene transfers are widely used to deliver exogeneous DNA and create somatic mosaicism in mice and other model animals. They are quick to employ by avoiding mouse engineering, but in either stable or transient transfection, they both lack the exquisite control over transgene copy number, gene zygosity, and genomic-locus specificity in the case of integrated elements, all of which genetically engineered mouse models (GEMMs) can provide. Here, we develop and demonstrate a simple and generalizable *in vivo* method, mosaic analysis by dual recombinase-mediated cassette exchange (MADR). MADR allows for stable labeling of mutant cells that express transgenic elements from a precisely-defined chromosomal locus. We detail a toolkit of MADR elements for combinatorial labeling, inducible/reversible transgene manipulation, tertiary recombinase expression, and genetic manipulation of human cells. Further, we demonstrate the power and versatility of MADR by tracing neural precursor cell lineages in vivo using mixed, reporter-identified zygosity or with gain- and loss-of-function mutations. We demonstrate several transgenic manipulations which alter the profile of resulting cell fates, allowing for single-cell resolution insights into the phenotypic analysis in vivo. Thus, MADR provides a high-throughput genetic platform for the dissection of development and disease, and this rapid method can be adapted to thousands of already existing gene-trap mice

Disclosures: G. Kim: None. **D. Rincon Fernandez Pacheco:** None. **D. Saxon:** None. **A. Yang:** None. **S. Sabet:** None. **M. Dutra-Clarke:** None. **R. Levy:** None. **A. Watkins:** None. **H. Park:** None. **A.A. Akhtar:** None. **P.W. Linesch:** None. **N. Kobritz:** None. **S. Chandra:** None. **J. Molina:** None. **K. Hoang:** None. **J.A. Tsyporin:** None. **K. Sedivakova:** None. **S. Bannykh:** None. **B. Chen:** None. **M. Danielpour:** None. **J.J. Breunig:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.21/A21

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH - NS088529

Title: Characterization of the MAPK pathway in the embryonic mouse ventral telencephalon

Authors: *M. TALLEY[1,2], L. A. EHRMAN[2], D. NARDINI[2], S. QIN[2], R. R. WACLAW[2]
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Abstract: The lateral and medial ganglionic eminences (LGE and MGE) in the ventral telencephalon contain distinct regional progenitor domains that give rise to specific subtypes of GABAergic neurons. The MAPK pathway is a major growth signal during development and has been implicated in neurogenesis and gliogenesis, but it remains unknown if it is involved in progenitor subdomains of the ventral telencephalon. To characterize the MAPK pathway in the LGE and MGE, we analyzed the expression of phospho-ERK1/2 (p-ERK1/2) and the MAPK pathway target gene *Etv5* at different stages of ventral telencephalon development. We found that Etv5 is largely expressed in ventricular zone (VZ) progenitor cells with a regional enrichment in the dorsal region of the LGE (dLGE) and ventral most region of the MGE at E13.5 and E15.5. Etv5+ cells were detected in the dorsal region of the Gsx2 expression domain of the dLGE and also in the ventral most region of the Nkx2.1 expression domain in the MGE. P-ERK1/2 showed a similar expression pattern to that of Etv5 at E13.5 and E15.5. Interestingly, by E18.5 p-ERK1/2 does not show a regional bias in expression and is robustly expressed in the majority of VZ progenitors in the telencephalon. Our results suggest the regional enrichment of Etv5 and p-ERK1/2 in distinct progenitor regions of the MGE and LGE. To address a role for MAPK pathway activation in the ventral telencephalon, we utilized *Rosa-MEK1DD* mice to express a cre inducible constitutively active MEK allele throughout [C1] the LGE using *Gsx2e-cre* mice. Our preliminary results suggest that activation of the MAPK pathway in the LGE increases the number of Gsx2+ progenitor cells in the LGE. Moreover, we found an increase in the dLGE subventricular zone (SVZ) and interneuron marker Sp8. Interestingly, the ventral LGE and striatal projection neuron marker Isl1 are reduced. We also detected ectopic expression of the oligodendrocyte progenitor cell (OPC) marker Pdgfra, which is distinct from the increased Gsx2/Sp8+ cells. Our results suggest that expansion of the MAPK activity during LGE development promotes specific regional progenitor domains and neuronal/glial subtypes.

Disclosures: M. Talley: None. **L.A. Ehrman:** None. **D. Nardini:** None. **S. Qin:** None. **R.R. Waclaw:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.22/A22

Topic: A.01. Neurogenesis and Gliogenesis

Support: NC/N003128/1

Title: Using cerebral organoids to investigate the role of Foxg1 in forebrain development

Authors: *J. J. MARSHALL[1], A. GONZALEZ RAMOS[2], P. KAKNI[2], S. LOWELL[3], J. O. MASON[2]
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Abstract: The transcription factor Foxg1 is a high-level regulator of embryonic forebrain development. *Foxg1*$^{-/-}$ mutant mice show multiple defects including dramatically decreased proliferation of dorsal telencephalic progenitors, a complete failure to form ventral telencephalic tissue and a significant expansion of the Wnt-expressing cortical hem. In humans, *FOXG1* heterozygosity leads to the recently described neurodevelopmental disorder FOXG1 Syndrome. Our current understanding of Foxg1's functions is mostly based on studies with genetically modified mice. However, these have some limitations, in particular tracking cell behaviours in real time is not currently practical in mouse embryos *in vivo.* Cerebral organoids offer an attractive model system to study the mechanisms of Foxg1 action, given their relative accessibility. We have set out to compare the phenotypes of *Foxg1*$^{-/-}$ organoids with the well-characterised phenotypes of *Foxg1*$^{-/-}$ mutant mice, to give us confidence that the same developmental mechanisms operate in both systems and that therefore organoids are valid tools to study these mechanisms. We used CRISPR/Cas9 technology to generate multiple lines of *Foxg1*$^{-/-}$ and *Foxg1*$^{+/-}$ mouse ES cell lines, together with isogenic controls. Organoids derived from *Foxg1*$^{-/-}$mouse ES cells showed clear cortical neuroepithelium, with distinguishable progenitor and neuronal layers. Our analysis of the *Foxg1*$^{-/-}$ organoid phenotype focusses on three key aspects. (1) We will determine whether the dramatic expansion of the cortical hem seen in mouse mutants is also found in the organoids. Control organoids contained clear groups of cells that expressed high levels of Wnt ligands and activated a Wnt reporter transgene, indicating the presence of canonical Wnt signalling as found in the cortical hem *in vivo*. Similar experiments with *Foxg1*$^{-/-}$organoids are currently underway. (2) We will use EdU labelling to determine whether *Foxg1*$^{-/-}$cortical progenitors in the organoids show the premature lengthening of the cell cycle and premature neuronal differentiation seen in mutant mice. (3) We will establish a robust protocol to produce ventral telencephalic organoids and use this to determine whether *Foxg1*$^{-/-}$ cells in organoids can adopt ventral telencephalic fates.

Disclosures: J.J. Marshall: None. **A. Gonzalez Ramos:** None. **P. Kakni:** None. **S. Lowell:** None. **J.O. Mason:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.23/A23

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 1R01NS095734

Title: *In vivo* dynamics of the notch ligand in dividing radial glia

Authors: *X. ZHAO, S. GUO
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Abstract: Asymmetric division, which produces two daughter cells of different fates, is fundamental for generating cellular diversity. In the developing organs of both invertebrates and vertebrates, asymmetrically dividing progenitors generate a Notch^{hi} self-renewing and a Notch^{lo} differentiating daughter. Cortical polarity plays a role in regulating this asymmetry. However, the mechanism by which such asymmetry is established is not understood. Here we employ in vivo time-lapse imaging in the developing zebrafish brain to delineate the dynamics of Notch ligand DeltaD (Dld) during the entire mitotic cell cycle of radial glia (RG), the principal vertebrate neural stem cells. We have found that the Notch/Delta asymmetry in the RG cells is dynamic during the division. We have identified that Dld endocytic trafficking is directional in the dividing RG cells. The directional Notch/Delta trafficking becomes apparent when the cell division is close to be completed. Furthermore, we have found that the daughter cell receiving Dld toward the end of cell cycle would continue to be proliferative. Molecular mechanisms that regulate such directional trafficking is currently under active investigation.

Disclosures: X. Zhao: None. **S. Guo:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.24/A24

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01 NS074972
R01 NS081297
MH071679-12
NIH DP2-HG-009623
ALTF 1295-2012
NIH F30MH114462
T32GM007308

Title: Developmental diversification of forebrain inhibitory neurons

Authors: *R. C. BANDLER[1], C. MAYER[2], C. HAFEMEISTER[3], R. MACHOLD[4], R. SATIJA[3], G. FISHELL[5]
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Abstract: Diverse subsets of cortical interneurons have vital roles in higher-order brain functions. To investigate how this diversity is generated, here we used single-cell RNA sequencing to profile the transcriptomes of mouse cells collected along a developmental time course. Heterogeneity within mitotic progenitors in the ganglionic eminences is driven by a highly conserved maturation trajectory, alongside eminence-specific transcription factor expression that seeds the emergence of later diversity. Upon becoming postmitotic, progenitors diverge and differentiate into transcriptionally distinct states, including an interneuron precursor state. By integrating datasets across developmental time points, we identified shared sources of transcriptomic heterogeneity between adult interneurons and their precursors, and uncovered the embryonic emergence of cardinal interneuron subtypes. Our analysis revealed that the transcription factor Mef2c, which is linked to various neuropsychiatric and neurodevelopmental disorders, delineates early precursors of parvalbumin-expressing neurons, and is essential for their development. These findings shed new light on the molecular diversification of early inhibitory precursors, and identify gene modules that may influence the specification of human interneuron subtypes.

Disclosures: R.C. Bandler: None. **C. Mayer:** None. **C. Hafemeister:** None. **R. Machold:** None. **R. Satija:** None. **G. Fishell:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.25/A25

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC Grant 31200798
NSFC Grant 20131351353
Tsinghua CLS

Title: Loss of VCAM1 expression in embryonic hippocampal NSCs impairs adult neurogenesis and hippocampus dependent memory

Authors: *G. CHEN[1,2], Q. SHEN[2]
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Abstract: The subgranular zone (SGZ) of the hippocampus is one of the two brain regions that harbors neural stem cells (NSCs) which are capable of giving rise to new neurons throughout life in rodents. The SGZ is derived from the hippocampal primordium region in the embryo.

However, the intrinsic and extrinsic factors that governing the development of NSCs in the SGZ is largely unknown. We have recently reported that persistent expression of vascular cell adhesion molecule 1 (VCAM1) in embryonic NSCs is required for adult neurogenesis and regeneration in the subventricular zone (SVZ) of the lateral ventricular wall, the other major neurogenic region in the brain. Here we report that VCAM1 protein is abundantly expressed in NSCs of the hippocampal primordium beginning from the embryonic day 12.5 (E12.5) and in early postnatal hippocampal neural progenitor cells (NPCs), but little in the adult hippocampal NPCs as revealed by confocal immunofluorescence microscopy. By crossing *VCAM1*$^{flox/flox}$ mice with cortex-specific EMX1-Cre or NPC-specific Nestin-Cre mouse line, we conditionally knocked out VCAM1 (cKO) in the developing hippocampal NSCs from early embryonic period. Interestingly, we found premature differentiation of NSCs at postnatal stage and impaired adult hippocampal neurogenesis. In agreement with these results, we also found reduced numbers of neurospheres generated from adult hippocampal NPCs in the knockout mice group compared to control group (wild type and heterogeneous mice). Using standard contextual fear conditioning test, we examined the behavior of VCAM1 cKO mice and observed a significant memory defect. Ongoing work will further investigate the impacts and molecular mechanisms of VCAM1 on the development of hippocampal NSCs and hippocampus-dependent behaviors. Here, we will present our work to better understand the development and function of hippocampus, especially the role of the sub-population NSCs that express VCAM1 for the hippocampal dependent learning and memory.

Disclosures: G. Chen: None. **Q. Shen:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.26/A26

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSFC Grant 31671068

Title: HMGN2 deficiency develops microcephaly through impaired chromatin accessibility

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Abstract: Human patients of microcephaly have reduced cortical surface area without apparent changes in cortical thickness, suggesting that “cortical units” could be lost. However, transgenic mouse models carrying genetic mutation or KO of microcephaly-associated genes do not always

recapitulate this phenotype. Here we report that knock-out of HMGN2, a nucleosome binding protein, leads to microcephalic phenotypes in mice similar to that in human. We found that HMGN2 was highly expressed in RGs and newborn neurons in the developing forebrain. By inbreeding HMGN2$^{+/-}$mice generated from KOMP(Hmgn2$^{tm1a(KOMP)Wtsi}$), we observed gradually increasing loss of HMGN2$^{-/-}$mice from E18.5 to weaning. A subset of surviving HMGN2 null mice developed microcephaly as early as E18.5. By P14, we found decreased brain weight and length of anterior-posterior axis in those KO brain. These brains had smaller cortical surface area but the cortical thickness was not severely affected. We did not detect significant difference in Caspase3 staining between KO and wild type brains, and cell number including Cux1^{+} neurons per cortical column in neocortex did not significantly decrease. BrdU administration at E15.5 or in utero electroporation using a binary piggyBac transposase plasmid system revealed that neither neuron migration nor neuron branching was affected at P14. However, the neuron/glia ratio was significantly reduced. Interestingly, all HMGN2 KO cortex at P1 exhibited an increased displacement of ventricular NSCs at intermediate zone, which may lead to loss of NSCs and cortical radial units. RNA-seq of WT or KO cortex at P14 showed that microcephalic HMGN2$^{-/-}$ mice exhibited an altered transcriptome signature. Furthermore, ATAC-seq at P14 cortex revealed a remarkable decrease in both overall peak number and signal intensity, accompanied by changes in chromatin state at the epigenetically regulated regions. Taken together, loss of HMGN2 results in a significant loss of global chromatin accessibility, leading to decreased division of RGs and premature brain development. Our findings suggest HMGN2 null mice could serve as a mouse model of microcephaly that resembles human patients and ferret model with ASPM deletion.

Disclosures: X. Gao: None. **W. Tian:** None. **Q. Shen:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.27/A27

Topic: A.01. Neurogenesis and Gliogenesis

Title: Dynamic RNA localization and local translation in the radial glial cells of the mammalian brain

Authors: *L.-J. PILAZ[1], D. L. SILVER[2]
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Abstract: Radial glial cells are the neural stem cells of the developing embryonic brain. Radial glial cells have a unique morphology that enables them to accomplish multiple functions. Indeed, these cells possess a long basal process that spans the whole cortex radially, and ends with basal endfeet tightly connected to a basement membrane. This process serves as a guidepost for

neuronal migration and may serve as an antenna to receive extracellular signals from the niche. Despite the importance of these basal structures, little is known about the molecular mechanisms controlling their functions. Here, we uncover fascinating mechanisms taking place in the basal process. We image messenger RNAs being transported at high speed from the cell body to the basal endfeet within living mouse brain tissue. We then show that these basal endfeet RNAs can locally produce proteins. Next, we discover 115 additional RNAs that accumulate in the basal endfeet. Importantly about 30% of those RNAs have been implicated in neurological diseases and might play a significant role during brain development. Additionally, we show that RNA transport is influenced by FMRP, an RNA-binding protein linked to Fragile X Syndrome. Using mutant forms of FMRP, we dissect FMRP function for RNA localization and local translation in the basal process and endfeet. We also further investigate the role of candidate localized mRNAs. In particular, we focus on how these mechanisms affect radial glial cell morphology through cytoskeletal remodeling. This study opens up a whole new avenue to study brain development and exposes new mechanistic layers within stem cells of the developing brain.

Disclosures: L. Pilaz: None. **D.L. Silver:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.28/A28

Topic: A.01. Neurogenesis and Gliogenesis

Support: Medicine by Design
CIHR
NSERC CREATE in M3

Title: Clonal lineage tracing and single cell analyses of neural stem and progenitor cells in the embryonic mouse ventral forebrain germinal zone

Authors: *S. YAMMINE[1], I. BURNS[2], J. GOSIO[2], D. J. VAN DER KOOY[3]
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Abstract: We define two distinct types of neural stem cells (NSCs) from the embryonic ventral germinal zone (GZ) using clonal lineage tracing and single cell transcriptomics. Primitive (p)NSCs express Oct4 (but do not express *GFAP*), and mouse embryo-derived pNSCs proliferate rapidly to form clonogenic neurospheres when grown in LIF. PNSCs arise earlier in development than *GFAP*-expressing definitive (d)NSCs that form clonogenic neurospheres in FGF2/EGF. To assess the differences in functional outputs of both NSC types, we performed clonal lineage tracing within neurospheres grown in either LIF or EGF/FGF2, to enrich for neural progenitor

cells (NPCs) directly downstream pNSCs or dNSCs, respectively. PNSCs from the E17.5 ventral forebrain GZ gave rise to more unipotent neuronal progenitor cells than dNSCs, whereas dNSCs gave rise to more unipotent astrocyte progenitor cells. Both NSCs gave rise to bipotent NPCs that produce neurons and astrocytes, which consistently proliferated more than unipotent NPCs. Surprisingly, pNSCs give rise to many unipotent neuronal progenitor cells that were GFAP+ before they became post-mitotic neurons. These clonal progenitor lineage tracing data allowed us to construct a hierarchy of progenitor subtypes downstream of pNSCs and dNSCs. To validate this hierarchy, identify markers for distinctly specified NPCs, and assess gene expression differences between these NPCs, we performed Drop-seq on E17.5 neural stem and progenitors cells from neurospheres grown in either LIF or FGF2/EGF. We used the unsupervised algorithm p-Creode as an additional means to map out the lineage transition states of NPCs, which corroborated our findings of several different types of bipotent NPCs. Combined, these data provide single cell resolution of NPCs present in the pre-natal brain, including NPCs downstream of rare pNSCs that would likely be missed from population level analyses in vivo.

Disclosures: S. Yammine: None. **I. Burns:** None. **J. Gosio:** None. **D.J. Van Der Kooy:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.29/A29

Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS
NIMH
HHMI

Title: Studying cell lineage and clonal distribution in adult human brain using somatic mutations

Authors: *S. N. KIM[1,2,3], R. N. DOAN[1,3], A. R. BARTON[4], J. W. TSAI[1,3], M. A. LODATO[1,3], S. LEE[4], P. J. PARK[4], C. A. WALSH[1,2,3,5]
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Abstract: Recent studies on somatic mutations in the human brain show that they occur commonly enough that they may represent a durable, forensic record of the patterns of cell division during normal human brain development. Limited preliminary data suggest that clones labeled by functionally silent somatic mutations can also be found localized or surprisingly widely distributed across the cortical hemisphere. However, the extent to which clonal

restrictions may influence cortical topography in the human brain has never been studied. In this study, we performed extensive somatic mutation discovery to explore neuronal lineages and clonal distributions across the human cerebral cortex by using single nucleotide variants (SNVs) as genetic markers in the human brain.
Whole genome sequencing (WGS, 30-40X) of DNA amplified from single neuronal nuclei from the prefrontal cortex (PFC) of two post-mortem neurotypical individuals allowed detection of potential clonal somatic SNVs, while 200X WGS of DNA from Brodmann areas (BAs) 17 and 18 of occipital cortex in the same individuals detected hundreds of additional potential clonal somatic SNV candidates. These variant candidates were subsequently validated using Sanger and other sequencing platforms. Validated clonal variants were further genotyped in additional single-neuron genomes from the PFC, as well as in DNA samples from several sites across the entire cerebral hemisphere. Genotyping of single cells from PFC allowed construction of a single-cell lineage map, with placement of single cells into several distinct clades. Genotyping DNA samples from across the cortex assessed topographic patterns of clonal structure.
SNVs were discovered at a wide range of mosaic fractions, suggesting that high-mosaic SNVs occurred during early cell divisions, whereas low-mosaic SNVs likely occurred at later stages. Some SNVs occurring at low mosaic fractions (≤1%) show restricted distribution to PFC or to BA17, suggesting some clonal restriction. All SNVs discovered so far with mosaic fraction >2% were detected widely across the cortex. Our data suggest that small clones contributing ≤1% of the cells of a cortical region show modest restriction to cortical areas, but that clones labelled at earlier stages show widespread dispersion across the cortex. Overall, our findings using clonal variants as lineage markers will expand our understanding of the normal pattern of development in the human cerebral cortex.

Disclosures: S.N. Kim: None. **R.N. Doan:** None. **A.R. Barton:** None. **J.W. Tsai:** None. **M.A. Lodato:** None. **S. Lee:** None. **P.J. Park:** None. **C.A. Walsh:** None.

Poster

195. Neural Cell Lineage Specification

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 195.30/A30

Topic: A.01. Neurogenesis and Gliogenesis

Support: 103714MA

Title: Heterogeneous progenitor behaviour orchestrates mammalian cortical development

Authors: A. LLORCA[1], G. CICERI[1], R. BEATTIE[2], C. STREICHER[2], S. HIPPENMEYER[2], *M. MARAVALL[3], O. MARÍN[1]
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Abstract: During the development of the mammalian cerebral cortex radial glia cells (RGCs) produce different subtypes of excitatory pyramidal cells (PCs). At the population level, these cells are generated in an inside-out pattern that is highly correlated with their birthdate (Molyneaux BJ. et al, 2007). Although being subject of intense study over the past decades, the developmental mechanisms underlying the generation of PC diversity remain unclear. Classical models of cortical neurogenesis suggest that PC diversity arises from progressive restriction of cortical RGCs that generate PCs for progressively more superficial layers during corticogenesis (Quin S. et al, 2006; Guo C. et al, 2013). In contrast, recent studies propose the existence of separate pools of progenitor cells with restricted potential to generate specific classes of PCs (Franco SJ. et al, 2012). In this study, we combine retroviral lineage tracing and Mosaic Analysis with Double Markers (MADM) techniques with Cre/LoxP mouse genetics to trace the progenies of individual RGCs in the mouse cerebral cortex. By unbiasedly analysing the outcome of hundreds of progenitors, we have obtained information about the contribution of different RGCs to the establishment of PC diversity. Our results indicate that the most abundant progenitor cells in the rodent cortex have the potential to generate PCs for several cortical layers. However, we also observe that the diversity of RGCs or their behaviour is larger than previously recognized. In addition, only a small fraction of cortical lineages contains of all the different subtypes of PCs, while most progenitors only generate a few of them. This diversity of cortical progenitor behaviours may play a prominent role in the orchestration of the complex and diverse laminar organisation of different areas across the mammalian cerebral cortex.

Disclosures: A. Llorca: None. **G. Ciceri:** None. **R. Beattie:** None. **C. Streicher:** None. **S. Hippenmeyer:** None. **M. Maravall:** None. **O. Marín:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.01/A31

Topic: A.03. Stem Cells and Reprogramming

Support: Japan AMED Grant 15652077

Title: Transplantatin of hypothalamic neuron from mouse embryonic stem cell

Authors: *H. NAGASAKI[1], Y. KODANI[1], H. SUGA[2], Y. S. KANEKO[1], A. NAKASHIMA[3]
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Abstract: BACKGROUND Recently, various hypothalamic neurons have been successfully engineered from pluripotent stem cell lines. The *in vitro* production of most types of the rostral-hypothalamic neuron from pluripotent stem cell would have various advantages on the studies on specification, migration, drug development, and regenerative medicine. So far, we have established the method to purify hypothalamic precursors from embryoid culture of mouse embryonic stem cell (mESC) to remove undifferentiated cells that would inhibit neural growth. Also, we have defined the conditions to selectively induce hypothalamic neuron by modulating sonic-hedgehog pathway that is essential for dorso- ventral axis of neural organogenesis. The vasopressin neuron from mESC is functionally equivalent to the intrinsic one in various aspects of morphology, endocrinology, and electrophysiology. With an aim to assess the possibility to regenerative therapy for hypothalamic diseases, we have grafted mESC derived hypothalamus to mouse or rat brain. METHODS and RESULTS EB5, a mESC cell line, was transfected with Rosa26 targeting vector Ai9, and then treated with Cre recombinase to stably express tdTomato (EB-Tomato). EB-Tomato was induced to hypothalamus by floating culture method and purified using cell-surface antigens to remove undifferentiated, or mesodermal, or endodermal cells. For differentiation, these cells were enzymatically dissociated and cultured on RepCell^{TM} dish. After 28days when cells are fully developed hypothalamic nature, cells were dissociated again and transplanted to hypothalamic region using the stereotaxic apparatus on either of SCID/NOD mice or Splague Dawley rat brain at two days post-delivery. Either in allograft and heterograft, Td-Tomato positive neuron survived around the supraoptic region of hypothalamus for 30 days. Some grafted neuron migrated up to 750 um and directly contacted with intrinsic vasopressin neurons. Immunoreactivities of vasopressin, NPY, or POMC were found in some of the grafted cells. CONCLUSION We have illustrated that the allo- and hetero-graft of hypothalamic neuron from *in vitro* organogenesis of mESC is possible. These results will proceed the regenerative therapy for various hypothalamic disorders.

Disclosures: H. Nagasaki: None. **Y. Kodani:** None. **H. Suga:** None. **Y.S. Kaneko:** None. **A. Nakashima:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.02/A32

Topic: A.03. Stem Cells and Reprogramming

Title: Survival, differentiation and migration of the EGFP-expressing neural stem cells transplanted into a mouse model of spinal cord injury

Authors: *C. WANG, X. LI, F. TIAN, P. LI
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Abstract: Although neural stem cell (NSC) injection therapy has been shown to promote functional recovery after spinal cord injury (SCI), the exact mechanism is not clear. In the current study, we injected primary NSCs isolated from EGFP expressing ($EGFP^+$) transgenic mice into the area of direct injury to examine the survival, differentiation and migration of the transplanted NSCs. Mice were randomly divided into control (30), injury (30) and NSC-treatment groups (30). SCI was introduced using Allen's contusion model for the injury and NSC-treatment groups. For the treatment group, 1×10^6 $EGFP^+$-NSCs were injected into the area of direct injury. The Basso Mouse Scale (BMS) and inclined plane test were used to evaluate the behavioral recovery at 1week (w), 2w, 4w, 6w and 8w after the SCI. At each time point, 6 mice in each group were sacrificed to detect changes in Nissl bodies, and the expression of Nestin, ChAT and GFAP using Nissl staining, immunohistochemistry (IHC) and qPCR. The BMSs of mice were 0 after SCI. They were significantly higher in the NSCtreatment group than injury group at 2w ($p<0.05$). The inclination angle of the swash plate was also significantly higher in the NSC-treatment group than the injury group after 4w ($p <0.05$). The IHC staining showed that transplanted $EGFP^+$-NSCs can survive, differentiate and migrate to other areas of the body. We observed that some NSCs differentiated into glia, a smaller number into neurons, while some remained undifferentiated. The qPCR results were consistent with the IHC data. At 1w after injection, Nestin expression was detected in both the injury and treatment groups with the latter group significantly higher than the former. The difference diminished at 2w after injection and the level of Nestin expression was similar to the control group at 6w after injection. The ChAT expression in NSC-treatment and injury groups decreased initially at 1w and then began to increase at 2w after SCI, with the former significantly higher than the latter. Similarly, the GFAP expression was also increased in both NSC-treatment and injury groups after SCI, with the NSC-treatment group lower than the injury group. A reduced number of Nissl bodies in NSC-treatment and injury groups were observed at 1-2w after SCI. However, after the emergence of new Nissl bodies at 4w, the number of Nissl bodies in the NSC-treatment group was higher than that in the injury group. In conclusion, we observed that the transplanted NSCs can survive, differentiate and migrate in host mouse after SCI. The behavioral tests also showed that the NSCs can promote functional recovery, likely by forming a conducive micro-environment to resume and facilitate the recovery of SCI.

Disclosures: C. Wang: None. **X. Li:** None. **F. Tian:** None. **P. Li:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.03/A33

Topic: A.03. Stem Cells and Reprogramming

Support: WUHS (GK)

Illumina, Inc (MT, LC)

Title: The neurodevelopmental toxin methylazoxymethanol (MAM) induces DNA methylation changes in differentiated human iPSC-derived neuroprogenitor cells (hNPCs)

Authors: *G. E. KISBY[1], A. C. CHLEBOWSKI[1], D. GRYGORYEV[2], L. CARBONE[3], B. DAVIS[3], K. A. NEVONEN[3], S. A. RODDY[1], A. MITINA[1], K. M. NAGAI[1], M. TURKER[2]
[1]Basic Med. Sci., Western Univ. of Hlth. Sci., Lebanon, OR; [2]Oregon Inst. of Occup. Hlth. Sci., [3]Biostatistics and Bioinformatics Core, Oregon Hlth. Sci. Univ., Portland, OR

Abstract: iPSC-derived cortical human neuroprogenitor cells (hNPCs) are a powerful tool to explore the role of environmental chemicals in neurodevelopmental disorders (NDDs). To determine if toxins can induce epigenetic changes in developing human neurons we used methylazoxymethanol (MAM), a chemical that produces NDDs (e.g., schizophrenia, epilepsy) in rodent models. First, hNPCs were treated with 100 ∝M MAM for 24h and then induced to differentiate into cortical glutamatergic neurons. DNA from hNPCs was isolated before and immediately after MAM treatment and after the toxin treated hNPCs had been differentiated for 5 days. DNA methylation was examined using the Illumina TruSeq Methyl Capture method. Differentially methylated regions (DMRs) were identified using Methylkit and the closest transcription start site (TSS) for each DMR was annotated. We compared MAM-treated hNPCs with control hNPCs at 24h (1,378 DMRs) and after differentiation for 5 days (1,553 DMRs) to identify targeted pathways. GO (gene ontology) analysis of MAM treated (24h) vs. control hNPCs only identified a single pathway (developmental process) that was enriched in DMRs. In contrast, multiple GO pathways (e.g., synaptic transmission, nervous system development, signal transduction) were identified in differentiated hNPCs derived from the MAM treated hNPCs. A KEGG Pathway analysis confirmed that the DMR-enriched genes of hNPCs at the 24h time-point of MAM treatment were limited (10 pathways) and non-neuronal specific. In contrast, KEGG Pathway analysis of the DMR-enriched genes of 5-day differentiated neurons identified 37 pathways after MAM treatment, many involved in neuronal differentiation and function (e.g., glutamatergic function, axon guidance, signal transduction). Thus, the MAM-induced epigenetic changes specifically targeted neuronal pathways during the differentiation of human neurons. These studies indicate that MAM induced changes in the DNA methylation of genes involved in the differentiation of human neurons and are consistent with the ability of this developmental toxin to disrupt glutamatergic function in rodent models of schizophrenia and epilepsy by epigenetic changes. Thus, MAM treated hNPCs are a good model for identifying epigenetic mechanisms that underlie NDD.

Disclosures: G.E. Kisby: None. **A.C. Chlebowski:** None. **D. Grygoryev:** None. **L. Carbone:** None. **B. Davis:** None. **K.A. Nevonen:** None. **S.A. Roddy:** None. **A. Mitina:** None. **K.M. Nagai:** None. **M. Turker:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.04/A34

Topic: A.03. Stem Cells and Reprogramming

Support: NIA 1RF1AG057148-01

Title: A new approach to model human brain-like tissue in a dish using silk as a scaffold

Authors: *R. WILLEN[1], S. LOMOIO[1], W. CANTLEY[2], D. H. COX[1], D. L. KAPLAN[2], G. TESCO[1]
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Abstract: Induced pluripotent stem cells (iPSCs) are an important and dynamic model for the study of human diseases. It has been demonstrated that iPSCs can be differentiated into neurons, astrocytes, and microglia, and cultured in 2D and 3D systems. Current 3D models are primarily in the form of organoids, which are a good structural model for iPSCs due to their self-organizing nature. While the 2D and organoid models are dynamic, there are significant limitations. 2D cultures cannot accurately mimic diverse cell types and interactions. Organoids have weak flow of nutrients and oxygen to the system, resulting in hypoxia in the innermost cellular layers, caspase activation, and necrosis after longer periods of time. This results in the inability of the organoid to develop past fetal stages, making it difficult to study an aging system. Lack of compartmental control resembling the structure of a brain makes it difficult to culture diverse cell types that would create a representative human brain environment. To address these limitations, we have developed a novel 3D model for culturing iPSC-derived cells. We have integrated neural precursor cells (NPCs) derived from an EB protocol into a donut-shaped porous silk sponge with an optically clear collagen-filled central window. The NPCs then differentiate in culture into hNeurons, growing processes and maturing in their synaptic activity. Immunostaining and gene expression analysis for specific cell type markers identify diverse cell populations including neurons and astroglial cells in brain-like tissue. Furthermore, neurons are spontaneously active as shown by electrophysiological recordings and calcium imaging over at least 9 months in culture. The spacious silk pores allow for free diffusion of nutrients and oxygen, preventing necrosis and allowing us to perform long term in vitro studies (over a year). Whereas before, to study the cellular interactions occurring inside an organoid, invasive procedures would have to be performed. With our model, you have a clear look into the network through this central window that doesn't disrupt the system. The window provides easy access for live imaging and electrophysiological studies, differing it from a classic organoid. Our model also allows for the possibility of a co-culture of neurons and microglia, mimicking realistic

human brain environments. Due to these advancements, this model could have a big impact on the study of neurodegenerative diseases, and beyond.

Disclosures: R. Willen: None. **S. Lomoio:** None. **W. Cantley:** None. **D.H. Cox:** None. **D.L. Kaplan:** None. **G. Tesco:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.05/B1

Topic: A.03. Stem Cells and Reprogramming

Support: R01MH108528
R01MH094753
R01MH109885
R01MH100175
U19MH1073671
R01MH111359
R01NS057198

Title: Spontaneous functional network activity in organoids resembles programmed early human brain development

Authors: *C. A. TRUJILLO[1], R. GAO[2], P. NEGRAES[1], I. A. CHAIM[3], A. DOMISSY[3], M. VANDENBERGHE[4], A. DEVOR[4], G. W. YEO[3], B. VOYTEK[2], A. R. MUOTRI[1]
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Abstract: Structural and transcriptional changes during early brain maturation follow fixed developmental programs defined by genetics. However, the physiological mechanisms leading to the emergence of an active neural network are not well understood, primarily due to experimental inaccessibility of the initial stages of the living human brain. Here, we developed cortical organoids that spontaneously exhibit periodic and highly regular oscillatory network events, followed by a transition to irregular and spatiotemporally complex patterns. Oscillatory network events mediated delta-high gamma phase-amplitude coupling, while GABAergic blockade increased network-synchronous events and abolished oscillatory dynamics. Additionally, we found that the Methyl-CpG-binding protein 2 (MECP2) is important for the timely emergence of synchronous oscillatory activity, corroborating that functional maturation might be compromised in MECP2-related genetic disorders. Finally, a machine learning approach was used to demonstrate that network activity between 28- to 38-week-old organoids closely mimics features of late-stage preterm infant electroencephalography. These results argue

that experience-independent cortical activity may also follow stable genetic programming, as a convergent feature of the early developing human brain. By closing the gap between *in vitro* neurodevelopmental models and the brain, this study provides heretofore unique opportunities for investigating and manipulating the role of synchronous network activity in the developing human nervous system.

Disclosures: C.A. Trujillo: None. **R. Gao:** None. **P. Negraes:** None. **I.A. Chaim:** None. **A. Domissy:** None. **M. Vandenberghe:** None. **A. Devor:** None. **G.W. Yeo:** None. **B. Voytek:** None. **A.R. Muotri:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.06/B2

Topic: A.03. Stem Cells and Reprogramming

Support: R01 EY024984
Indiana Brain and Spinal Cord Injury Fund
IU Collaborative Reserach Grant
IU Signature Center for Brain and Spinal Cord Injury
CTSI PreDoctoral Fellowship
IUPUI Gradudate Office First Year University Fellowship
Purdue Research Foundation Fellowship

Title: Astrocytes regulate the developmental timeline of retinal ganglion cells differentiated from human pluripotent stem cells

Authors: *K. LANGER[1], R. VIJ[1], S. OHLEMACHER[1], A. SRIDHAR[1], E. FEDER[1], M. C. EDLER, JR[1], A. J. BAUCUM II[1,2], T. R. CUMMINS[1,2], J. S. MEYER[1,2,3]
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Abstract: Human pluripotent stem cells (hPSCs) can serve as effective in vitro models of both neural development as well as neurodegeneration, as they can give rise to all cell types of the body and be expanded indefinitely. Additionally, when derived from specific patient populations, they can serve as powerful tools for disease modeling as well as pharmacological screening. However, in order for hPSCs to optimally serve in these capacities, they must fully recapitulate the features of the affected in vivo cell type, including the ability to exhibit mature neuronal characteristics. Retinal ganglion cells (RGCs) serve as the essential connection between the eye and the brain, with this connection disrupted in blinding disorders such as glaucoma, causing severe degeneration and eventual death of RGCs. Previously, we have demonstrated the ability

to derive RGCs from hPSCs, including those derived from specific glaucoma patient populations. However, these cells demonstrated a limited ability to exhibit a number of features of mature RGCs. Thus, efforts of the current study were focused to characterize the functional maturation of hPSC-derived RGCs in vitro based upon morphological complexity and electrophysiological properties. hPSC-derived RGCs demonstrated increased neurite complexity over time, increased ionic currents and excitability, and displayed increased expression of synaptic proteins. Furthermore, the interplay of RGCs and astrocytes have been largely overlooked to date, with these cells being known to tightly associate within the in vivo retina. As such, additional efforts focused on co-culturing RGCs with astrocytes to determine their effects on synaptic complexity and functional maturation. RGCs co-cultured with astrocytes demonstrated enhanced and expedited morphological and functional characteristics compared to RGCs cultured alone. The results of this study are the first of its kind to extensively study the functional and morphological maturation of RGCs in vitro as well as study how astrocytes modulate and expedite this maturation when grown in association with RGCs.

Disclosures: K. Langer: None. **R. Vij:** None. **S. Ohlemacher:** None. **A. Sridhar:** None. **E. Feder:** None. **M.C. Edler:** None. **A.J. Baucum II:** None. **T.R. Cummins:** None. **J.S. Meyer:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.07/B3

Topic: A.03. Stem Cells and Reprogramming

Support: BMBF e:Med
IMPRS-TP

Title: A standardized *in vitro* neural differentiation platform of induced pluripotent stem cells to model complex psychiatric diseases

Authors: *C. RUMMEL, M. J. ZILLER
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Abstract: At present, available differentiation protocols from embryonic and induced pluripotent stem cells (iPSCs) to neurons show a high heterogeneity in the produced cell fates and cellular states. Therefore, the alterations in molecular and cellular endophenotypes are frequently dominated by the effect of technical and biological noise rather than the individual genotype. Thus, highly reproducible in vitro differentiation approaches are essential for robust quantification of endophenotypes to study highly polygenic diseases driven by genetic variants with individual small effect sizes. Here we present a standardized pipeline for the in vitro

differentiation and characterization of cortical excitatory neurons from schizophrenic patients and controls offering a unique workflow for larger cohorts.
Making use of the recently reported Neurogenin-2 driven transdifferentiation which further patterns the emerging neurons by inhibition of the SMAD- and WNT pathway (Zhang et al.; Nehme et al.), the homogeneity of the generated neuronal population was verified by the cellular endophenotype. To that end, we took advantage of a High-Content Screening imaging system to quantify excitatory cortical identities (Tbr1, Cutl1, Satb2) and neuronal properties such as neurite and synaptic morphology (Synpasin, PSD95). In addition, we analyzed the network formation of functional neurons by electrophysiological measurements.
In order to facility an in-depth analysis of the link between the genome, the epigenome (Assay for Transposase-Accessible Chromatin using sequencing) and, the transcriptome (mRNA sequencing) we mapped regions of open chromatin and correlated changes in enhancer activity with RNA-Sequencing data for individual genetic backgrounds. To account for the fact that the epigenetic landscape changes upon neuronal activity, we additionally included in our paradigm the stimulation of neurons by potassium chloride (KCl).
Our standardized workflow offers the promising strategy to capture the impact of the polygenic disease burden of individual patients suffering from complex diseases such as schizophrenia, in a homogeneous disease relevant cell population.

Disclosures: C. Rummel: None. **M.J. Ziller:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.08/B4

Topic: A.03. Stem Cells and Reprogramming

Support: Division of Intramural Research, National Institute of Mental Health, National Institutes of Health

Title: Modeling aspects of the chromosome 16p11.2 duplication in neural progenitor cell, neurons from patient-specific induced pluripotent stem cells

Authors: X. JIANG, L. WILLE, E. BESANCON, L. KASSEM, W. CORONA, *S. D. DETERA-WADLEIGH, F. J. MCMAHON
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Abstract: A rare 650 kb duplication on chromosome 16p11.2 (dup16p11.2) is associated with neurodevelopmental disorders, schizophrenia, and bipolar disorder. This project aims to explore the use of induced pluripotent stem cell (iPSC) technology to study the biological impact of dup16p11.2 in neural cells and screen for therapeutic agents. Fibroblast samples were obtained

from 3 carriers and 3 sex-matched non-carriers belonging to an extended family ascertained through a proband with bipolar disorder. We also obtained additional unrelated carriers from the Rutgers Univ. Repository. All iPSC were reprogrammed using lentiviral methods, then differentiated into neural progenitor cells, neurons, or astrocytes using published protocols. Some cells were treated with valproic acid (VPA) at 1 mM dosages often used to treat bipolar disorder. Neurons were characterized with immunostaining and confocal microscopy. Genome-wide gene expression was measured by microarray or RNA sequencing. Several genes within the duplicated region showed increased expression in carriers compared to non-carriers. In neurons, ALDOA, KCDT13, KIF22, PPP4C, QPRT, and TMEM219 showed the greatest increase (1.5- to 2-fold). Carriers showed more neurite formation during the first two weeks of neural progenitor cell differentiation, but developed fewer MAP2-positive neurons after 4 weeks (ratio of carriers:non-carriers = 72%). MAP2-positive neuron counts remained lower in carriers even after more than 8 weeks of culture (ratio< 50%). Consistent with these observations, gene set enrichment analysis of the many genes differentially expressed in carriers revealed significant decreases in GO terms related to neuronal differentiation (P<2.29E-14, activation z-score, -2.2), brain development (P<2.69E-19, activation z-score -1.82), synaptic transmission(P<1.26E-08, activation z -score -2.0), and enrichment for the glutamate receptor signaling pathway (P<5.17E-06). VPA treatment for 5 wks during neuronal differentiation led to increased counts of mature neurons in carriers. These early data show that dup16p11.2 leads to increased expression of genes within the duplicated region and a marked reduction in the differentiation and survival of neurons that is partly rescued by VPA. The dup16p11.2 also perturbed expression of large sets of genes involved in important neurodevelopmental pathways. Patient-specific iPSC are a promising approach to the neurobiology of rare copy number variants associated with neuropsychiatric disorders and may provide an efficient platform for screening novel therapeutics.

Disclosures: X. Jiang: None. **L. Wille:** None. **E. Besancon:** None. **L. Kassem:** None. **W. Corona:** None. **S.D. Detera-Wadleigh:** None. **F.J. McMahon:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.09/B5

Topic: A.03. Stem Cells and Reprogramming

Support: NIDA Grant 1DP1DA044359-01

Title: Bottom-up engineering and characterization of human neural culture systems

Authors: *R. TAM, T. RUDIBAUGH
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Abstract: Neuroscience harnesses experimental systems that span a wide range of spatial and temporal scales from fMRI in humans, (opto)genetics in living animals, to single cell electrophysiology and molecular biology in slice and cell cultures. The overlaps and connections between these systems have greatly advanced our understanding of brain and behavior. Here we describe a preliminary approach to address a current gap in this network of experimental models: the ability to manipulate and track dynamic molecular- and cellular-scale responses in human systems, especially in high throughput. We will describe preliminary work generating 2D and 3D ex vivo neural cultures derived from human pluripotent stem cells. Interfacing molecular biology manipulations with these systems, we are engineering robust assays to quantify a broad range of input-output characteristics of different human neural cell types including changes in synaptic activity and gene expression in response to neurotransmitters and other external stimuli. In addition, as a first step in trying to bridge the gap between neuronal cell culture and in vivo complexity, we are synthetically networking distinct cell types known to naturally synapse to each other in the brain. This work engineers complementary tools for the neuroscience community that are easily manipulated and tracked at the molecular and cellular scales, and whose complexity can be gradually built up and tested in stages.

Disclosures: R. Tam: None. **T. Rudibaugh:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.10/B6

Topic: A.03. Stem Cells and Reprogramming

Support: AMED 17bm0804003h0001
AMED 18bm0804014h0102
JSPS 17k10083

Title: Widespread transcripts analysis in purified human neuronal nuclei using cage-seq

Authors: *M. ISHIKAWA[1], H. OKANO[2]
[1]Dept. Physiol., Keio Univ. Sch. Med., Tokyo, Japan; [2]Keio Univ. Sch. of Med., Tokyo, Japan

Abstract: Although it is generally accepted that a cellular differentiation, stress responses, and a neuronal activity require changes to transcriptional networks, more dynamic regulation of promoters and enhancers at specific sets of genes has not been widely analyzed. Especially, little is known about how neuronal activity regulates gene promoter and enhancer activation in human brain; partially known in a rodent brain. In this study, we aimed at the technologies using human pluripotent stem cell. A newly efficient neuronal induction method leads to generate ~95 % neurons (regionally identified to forebrain) from human pluripotent stem cells. These neurons

exhibit the adequate expression levels of glutamate receptors, synaptic morphologies, and electrophysiological responses. After treating with glutamates, we harvest total RNA, including mi/lncRNAs, with time. To comprehensively profile the activity of gene transcription at each promoter site, we performed a powerful high-throughput technology called cap-analysis gene expression (CAGE), which allows to map the transcription start sites (TSSs) and the core promoter dynamic usage. CAGE uses the cap-trapping as the first step to capture the 5' ends of the cDNAs, which are then transformed into short stretches corresponding to the mRNA TSSs and concatenated for Sanger sequencing, while the further studies enabled it to be adapted to the next-generation sequencing platforms. Interestingly, we found out much products of which TSSs are different in a single gene, according to glutamate processing time. Moreover, we identified human-specific potential TSSs of genes, including synapse plasticity, learning and memory, cell morphology-related genes. We are now studying about these TSSs in iPSCs derived from patients with neuropsychiatric disorders or developmental disorders.

Disclosures: M. Ishikawa: None. **H. Okano:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.11/DP02/B7

Topic: A.03. Stem Cells and Reprogramming

Support: JSPS KAKENHI 17H04302
JSPS KAKENHI 30779153
JSPS PD Research fellowship 17J10294

Title: Self-organized human neuronal network activity derived from cerebral organoids

Authors: *H. SAKAGUCHI, J. TAKAHASHI
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Abstract: The cerebrum is a major center for brain function, and its activity is derived from the assembly of activated cells in neural networks. It is currently not possible to study complex human cerebral neuronal network activity at single cell resolution. Here, using cerebral organoids, we report self-organized and complex human neural network activity that dynamically changes with drug treatment at single cell resolution. Self-organized neuronal network formation was observed following a dissociation culture of human embryonic stem cell-derived cerebral organoids. The spontaneous and synchronized activities of different networks was measured via calcium imaging, and subsequent novel analysis enabled examination of cell activity at single cell resolution, providing simultaneous raster plots, cluster analyses, and cell distribution data. Finally, we demonstrated the feasibility of our system to assess drug-inducible

dynamic changes of the network activity. This model could provide a comprehensive functional analysis of human neuronal networks for the study of human brain function.

Disclosures: H. Sakaguchi: None. **J. Takahashi:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.12/B8

Topic: A.03. Stem Cells and Reprogramming

Support: MHLW Sciences Research Grant H28-Kagaku-Ippan-003
AMED Grant JP17mk0104027

Title: Silver nanoparticles inhibit neural induction via mitochondrial dysfunction in human induced pluripotent stem cells

Authors: S. YAMADA[1], *D. YAMAZAKI[2], Y. KANDA[2]
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Abstract: Silver nanoparticles (AgNPs) are important nanomaterials that are involved in biomedical applications because of their anti-bacterial and anti-viral activities, and have been applied in broad consumer products, including cosmetics and textiles. Despite their extensive use, AgNPs have been reported to cause various types of cytotoxicity, including developmental toxicity and neurotoxicity. However, the potential action of AgNPs on early fetal development has not been elucidated. The present study determined the effects of AgNPs on neural induction in human induced pluripotent stem cells (iPSCs), used as a model of human fetal stage. We found that exposure to AgNPs reduced the expression of several marker genes, including *OTX2*, a marker of neurogenesis in the neural induction from iPSCs. Since neural differentiation requires ATP as a source of energy, the intracellular ATP content was also measured. We found that AgNPs decreased intracellular ATP levels in iPSCs. Since AgNPs suppressed energy production, a critical mitochondrial function, the effects of AgNPs on mitochondrial dynamics were further studied. The results revealed that AgNPs induced mitochondrial fragmentation and reduced the level of mitochondrial fusion protein mitofusin 1 (Mfn1). Moreover, we found that knockdown of *Mfn1* in iPSCs inhibited neural induction via *OTX2* downregulation. Taken together, these data suggested that AgNPs could induce cytotoxicity, including neurodevelopmental toxicity, via Mfn1-mediated mitochondrial dysfunction in iPSCs. Thus, mitochondrial function in iPSCs can be used for assessing the cytotoxic effects associated with nanomaterials, including AgNPs.

Disclosures: S. Yamada: None. **D. Yamazaki:** None. **Y. Kanda:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.13/B9

Topic: A.03. Stem Cells and Reprogramming

Support: KAKENHI JP25505008
AMED JP17bm0404018

Title: Purification of mouse ES cell-derived hypothalamic progenitors using cell surface markers

Authors: *Y. KODANI[1], H. SUGA[3], N. YAMAMOTO[4], Y. S. KANEKO[1], A. NAKASHIMA[2], H. NAGASAKI[1]
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Abstract: Recent advances in stem cell technology have enabled *in vitro* generation of hypothalamic neurons from mouse and human pluripotent stem cells. In the case of mouse embryonic stem cells (mESCs), hypothalamic differentiation is efficiently induced by three-dimensional culture in a growth factor-free medium (Wataya et al., 2008, *PNAS*). In this method, about 70% of total cells acquire hypothalamic progenitor identity within 1 week, but the remaining portion contains undifferentiated cells as well as mesendodermal lineages. Of note, the undifferentiated cell population exhibits a high level of proliferative activity and can negatively affect survival of developing neurons. To overcome this problem, we have previously purified GFP-labeled hypothalamic progenitors by fluorescence-activated cell sorting (FACS), which was often cytotoxic and low-yielding for the progenitors. In the present study, we developed a novel purification method for mESC-derived hypothalamic progenitors without genetic manipulation and significant cytotoxicity. We have identified cell surface markers specific to non-hypothalamic lineage cells by analyzing surface antigen profiles of differentiating mESCs. By use of the antibody cocktail against these markers, non-hypothalamic cells were labeled with fluorophores or magnetic beads and then depleted by FACS or magnetic-activated cell sorting (MACS). This process retrieved hypothalamic progenitors with purity > 90%, and MACS greatly surpassed FACS in the viability and yield of the purified cells. Subsequent differentiation steps generated a variety of hypothalamic neurons and glial cells without emergence of undifferentiated cells. The engineered hypothalamic tissues with this method would be useful on basic sciences, drug-development, and regenerative medicine.

Disclosures: Y. Kodani: None. **H. Suga:** None. **N. Yamamoto:** None. **Y.S. Kaneko:** None. **A. Nakashima:** None. **H. Nagasaki:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.14/B10

Topic: A.03. Stem Cells and Reprogramming

Support: Human Spare Parts program, The Finnish Funding Agency for Innovation, TEKES
Finnish Cultural Foundation

Title: Network activity development of cultured cortical neurons: Comparison between embryonic rat and human pluripotent stem cell -derived systems

Authors: *T. HYVÄRINEN[1], A. HYYSALO[1], E. KAPUCU[2,3], L. YLÄ-OUTINEN[1], S. NARKILAHTI[1]
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Abstract: Electrical activity development of embryonic rat cortical neurons has been typically measured using microelectrode array (MEA) technology, which enables efficient study of populations of neurons and allows repeated measurements of the same network. Although rodent MEA studies form the basis for the technology, human specific characteristics need to be better evaluated for applications such as *in vitro* models and drug discovery. In the present study, human pluripotent stem cells (hPSC) were differentiated to cortical neurons and their functional development was compared with primary rat cortical cultures (E17-E18). The hPSCs differentiated into mixed neural culture where development of neurons was followed by emergence of astrocytes after extended culture time. Neurons expressed markers for both upper and lower cortical layers and consisted mainly of glutamatergic and GABAergic subtypes. The MEA data demonstrates that with current differentiation method for hPSC-derived cortical neurons we can achieve spike rates close to that seen in rat cortical networks *in vitro*. Importantly, hPSC-derived neurons formed connective networks that reflect those described with rat cortical cultures. Network wide synchronous bursting behavior was evident in both rat and hPSC-derived cultures, and hPSC-neurons sustained their synchronicity through the measurement period up to 100 days. Achieving repeatedly synchronous network wide activity in hPSC-derived neuronal cultures demonstrates feasibility of these cells for applications such as *in vitro* modeling in order to discover human specific outcomes.

Disclosures: T. Hyvärinen: None. **A. Hyysalo:** None. **E. Kapucu:** None. **L. Ylä-Outinen:** None. **S. Narkilahti:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.15/B11

Topic: A.03. Stem Cells and Reprogramming

Support: R01 EY024984
Indiana Department of Health Brain and Spinal Cord Injury Fund
IU Collaborative Research Grant from the Office of the Vice President of Research
IU Signature Center for Brain and Spinal Cord Injury

Title: Human pluripotent stem cell-derived retinal ganglion cells display extensive neurite outgrowth in response to intrinsic and extrinsic signals

Authors: *C. FLIGOR[1], P. W. CAMPBELL[2], K. B. LANGER[1], C. ZHANG[4], D. M. SUTER[5], W. GUIDO[3], J. S. MEYER[1]
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Abstract: Retinal ganglion cells (RGCs) serve as a vital connection between the eye and the brain and as such, the loss of RGCs often leads to blindness. Human pluripotent stem cells (hPSCs) can be differentiated into RGCs, providing an unlimited source of cells for translational strategies such as disease modeling, cell replacement, and drug screening. The success of these strategies depends on the ability of RGCs to extend lengthy neurites which integrate with an appropriate target tissue. Additionally, once this axonal pathfinding is accomplished, these axons must also be able to form functional synaptic connections. During development, intrinsic and extrinsic cues such as neuronal activity, extracellular matrix composition and growth factor signaling are beneficial for survival, proper guidance and innervation of RGC axons. However, many previous studies of RGC outgrowth have been based on animal models with little emphasis on the response of human RGCs to these factors. Therefore, the development of an *in vitro* model utilizing hPSC-derived RGCs would allow for the precise study of factors that may enhance axonal outgrowth and encourage synaptogenesis of RGCs with their target tissue. As such, efforts have focused on the development of effective assays to test the ability of hPSC-derived RGCs to extend axons in response to a variety of cues as well as display target specificity. In order to better identify those guidance receptors expressed specifically within hPSC-derived RGCs, the transcriptional profiles of individual cells were analyzed. Results demonstrated that these cells possess receptors that are essential in influencing outgrowth as well

as target specificity. Subsequently, the ability of both extrinsic and intrinsic factors to enhance RGC neurite outgrowth was analyzed. Enriched populations of RGCs were isolated and plated to allow for neurite outgrowth, with significant outgrowth observed within the first 24 hours. Finally, to determine target specificity aggregates of hPSC-derived RGCs were co-cultured with explants of mouse lateral geniculate nucleus (LGN), the primary post-synaptic target of RGCs. RGCs displayed target specificity with the longest neurites projecting towards LGN explants. Overall, these results will facilitate the replacement of RGCs following their loss due to disease and degeneration, as extensive axonal outgrowth will be critical for the development of personalized transplant therapies for optic neuropathies.

Disclosures: C. Fligor: None. **P.W. Campbell:** None. **K.B. Langer:** None. **C. Zhang:** None. **D.M. Suter:** None. **W. Guido:** None. **J.S. Meyer:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.16/B12

Topic: A.03. Stem Cells and Reprogramming

Support: R01GM084979

Title: Dantrolene inhibits impairment of neurogenesis and synaptogenesis in the iPSC from Alzheimer's disease patients

Authors: *H. WEI[1], Y. WANG[2], G. LIANG[3], Y. SHI[4], J. KESSLER[5]
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Abstract: Neurogenesis and synaptogenesis are impaired in Alzheimer’s disease (AD). We have investigated the role of over activation of the ryanodine receptor (RYR) Ca2+channel on neurogenesis and synaptogenesis, and the potential beneficial effects of dantrolene on induced pluripotent stem cells (iPSCs) from AD patients. iPSCsfrom normal control, sporadic AD (SAD), and familiar AD(FAD) patients were cultured and developed into neuroprogenitor cells (NPCs). These cells were thencultured into cholinergic neurons in the presence or absence of dantrolene. Cell viability were measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction, and the proliferation was determined by cell number counts with trypan blue exclusion and bromodeoxyuridine (Brdu) incorporation.

Autophagy activity and flux were determined by measuring the LC3 II protein levels with or without the autophagy flux inhibitor (Bafilamycin). The cytosolic calcium concentrations ([Ca2+]c) were measured using dye Fura-2. Neurogenesis process (iSPC to NPC to cholinergic neurons), lysosome V-ATPase, and synaptogenesis were determined and compared using immunostaining. Neurogenesis from NPC to cholinergic cortical neurons, was significantly impaired in SAD, which was inhibited by dantrolene. Mean numbers of intersections between dendrites and concentric circles of these cortical neurons were shown as a function of the distance (μm) of the circles from the soma. The distances were significantly decreased in both SAD and FAD, which was inhibited by dantrolene in the SAD cells. Synaptic density, determined by presynaptic marker synapsin-1 and postsynaptic marker PSD95 double immunostaining, significantly decreased in both SAD and FAD cells, and was inhibited by dantrolene in FAD cells. The differentiation of NPC into cortical neurons wassignificantly decreased in both SAD and FAD cells, and was ameliorated by dantrolene treatment. Cell viability and proliferation in both SAD and FAD were impaired, andassociated with significantly low lysosome V-ATPase and low acidity, which were inhibited by dantrolene. Autophagy was impaired in SAD and FAD, and dantrolene promoted the autophagy induction and activity. Dantrolene significantly inhibited NMDA mediated elevation of [Ca2+]cby primary antagonism of RYR in both SAD and FAD cells.Our results suggest that dantrolene ameliorated theimpairment of neurogenesis and synaptogenesis, in association with its effects on intracellular Ca2+ and autophagy, in iPSC from either SAD or FAD patients.

Disclosures: H. Wei: Other; I have conflict of interest that I am member of advisory board of Eagle Pharmaceutical Company which produce and sell ryanodex, a new formula of dantrolene. **Y. Wang:** None. **G. Liang:** None. **Y. Shi:** None. **J. Kessler:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.17/B13

Topic: A.03. Stem Cells and Reprogramming

Title: Transient activation of Rb promotes human pluripotent stem cell differentiation

Authors: *J. LI, C. NARAYANAN, D. SAMBO, J. BIAN, T. BRICKLER, S. CHETTY
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Abstract: The propensity for differentiation varies substantially across human pluripotent stem cell (hPSC) lines. This greatly restricts the potential of using hPSCs for stem cell-based therapies. Thus, understanding the underlying mechanisms regulating multilineage differentiation of hPSCs is of great value for regenerative medicine. In a prior study, we reported that culturing hPSCs in dimethylsulfoxide (DMSO) prior to directed differentiation enhanced

differentiation across all three germ layers. Moreover, the DMSO treatment promoted activation of the retinoblastoma protein (Rb) and reduced hyperphosphorylation of Rb. The percentage of hPSCs in the early G1 phase of the cell cycle also greatly increased. In this study, we demonstrate that the DMSO treatment improves the efficiency of hPSC differentiation through the Rb-E2F pathway. We employ four different strategies to manipulate the activity of Rb in hPSCs: knockdown of Rb alone using short hairpin RNA against the Rb protein, inactivation of all Rb family members (Rb, p107, and p130) using an inducible lentiviral vector that expresses the dl1137 mutant of SV40 T antigen, overexpression of a constitutively active (non-phosphorylatable) form of Rb to activate Rb, and inhibition of downstream Rb targets (e.g. E2F pathway). While knockdown of Rb and its family members suppresses differentiation across all three germ layers following the DMSO treatment, transiently activating Rb mimics the DMSO effect and increases differentiation capacity. Inhibition of the E2F pathway also increases the differentiation capacity of hPSCs. Activation of Rb is also associated with increased chromatin accessibility of several early developmental genes in a cell cycle dependent manner in hPSCs. These results highlight an important role for transient activation of Rb in hPSC differentiation. Using these mechanistic insights, we identify new tools to improve the prospects of using human pluripotent stem cells for therapy, particularly for neurodegenerative and neuropsychiatric disorders.

Disclosures: J. Li: None. **C. Narayanan:** None. **D. Sambo:** None. **J. Bian:** None. **T. Brickler:** None. **S. Chetty:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.18/B14

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant AG047335
UTSA C.O.S Biology Start-Up

Title: Accelerating the fate specification of human pluripotent stem cell-derived forebrain progenitors into cortical neuronal subgroups

Authors: *C. HUTCHINSON[1], Z. S. JORDAN[2], M. C. VARELA[2], K. THANGAMANI[2], A. M. MAROOF[3]
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Abstract: The neocortex consists of both excitatory projection neurons and inhibitory interneurons, with each population undergoing fate specification through an intricate cascade of molecular events during development. Current protocols to pattern human pluripotent stem cells

(hPSC) to fate-specified cortical neurons take between one to three months, with limited efficacy and functionality. Using hPSCs that harbor transgenic green fluorescent protein (GFP) reporters for putative deep layer cortical neurons (FEZF2::GFP) or interneurons (NKX2.1::GFP), we have identified molecular pathways essential for neural progenitor cell proliferation. After screening for small molecule inhibitors of these signaling pathways, we identified a combination that enhanced the specification of forebrain-patterned neural progenitor cells into post-mitotic cortical neurons within three weeks. We characterized these neuronal subgroups by using immunocytochemistry, fluorescence activated cell sorting (FACS) analysis, and quantitative polymerase chain reaction (qPCR). Furthermore, after enriching for post-mitotic neurons using fluorescently-conjugated antibodies and GFP by FACS, these neurons will be grafted into neonatal immunocompromised mice to determine their integrative capacity and axonal trajectories from the cortex. Our results establish rapid and efficient methods to enhance the specification of cortical neuronal fates, and their potential for functional integration will be essential for future disease modeling or cell-based therapies.

Disclosures: C. Hutchinson: None. **Z.S. Jordan:** None. **M.C. Varela:** None. **K. Thangamani:** None. **A.M. Maroof:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.19/B15

Topic: A.03. Stem Cells and Reprogramming

Support: UL1 TR000043 NCATS/NIH Clinical and Translational Science Award (CTSA) program
NIH R21 NS093540-01
USAMRMC TS140033.02

Title: Comparison of human embryonic stem cell-derived Purkinje cells to mouse Purkinje cells over development

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Abstract: The cerebellum plays a critical role in motor control, including eye saccades, balance, and coordination. Recent studies have also highlighted a role for the cerebellum in non-motor functions, including feed-forward learning, visuo-spatial memory, attention, and emotion. Developmental defects in cerebellar control of these motor and cognitive functions likely contribute to diseases associated with cerebellar pathology and dysfunction, such as autism and

ADHD. While mouse models of such complex disorders have provided critical insights, mouse genetic models do not always recapitulate human disease phenotypes. Human embryonic stem cells (hESCs) provide an opportune system to model human neurodevelopmental disorders. Sundberg et al. used this approach to analyze TSC2 patient-derived Purkinje cells. Here we describe a novel method to generate Purkinje cells from hESCs and use transcriptional profiling to compare hESC-Purkinje cell development to mouse Purkinje cell development.
A method to differentiate hESCs into Purkinje cells was developed by recapitulating key developmental signaling events to guide the hESCs from neural induction through cerebellar specification, Purkinje cell generation, and finally maturation. Transcriptional profiling (RNAseq/microarray) was used to assess cell identity and maturation state of differentiating hESC-Purkinje cells in comparison to developing mouse Purkinje cells at various time points. To extract cell-type specific RNA from mixed cultures and from whole mouse cerebellum we used translating ribosome affinity purification (TRAP). In this method, a GFP-L10a ribosomal fusion protein is expressed in a Purkinje cell specific manner using Pcp2 genetic elements. TRAP allows extraction of cell type specific RNA directly from mixed cultures without the need for dissociation. Extracted RNA was subjected to RNAseq/microarray analysis and results were assessed using metagene projection. Results from these studies provide important insights into Purkinje cell development and will be useful in assessing changes in patient iPSC-derived Purkinje cells.

Disclosures: D.E. Buchholz: None. **T.S. Carroll:** None. **A. Kocabas:** None. **X. Zhu:** None. **H. Behesti:** None. **L. Stalbow:** None. **Y. Fang:** None. **M.E. Hatten:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.20/B16

Topic: A.03. Stem Cells and Reprogramming

Support: SANPORC, NIH R01OD018272

Title: Generation of expandable, transplantable, sendai virus-reprogrammed human iPSC-derived neural precursors (NPCs): An *in vitro* and *in vivo* NPCs grafting study

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Abstract: Background: Human induced pluripotent stem cells (hiPSCs)-derived NPCs represents potential cell source for cell-replacement therapies in treatment of a variety of neurodegenerative disorders. One of the critical denominator in developing clinical grade NPC cell lines is defined by cell line: i) expandability, ii) genetic stability, and, iii) predictable *in vivo* post-grafting differentiation and safety profile. In addition the *in vivo* cell delivery format (i.e. single cell suspension or neurospheres) is important in achieving a consistent cell densities to be delivered into intended *in vivo* target(s) such as brain or spinal cord. In our current study we tested our previously developed protocol to generate expandable, single cell monolayer-grown NPCs by using manual selection of morphologically-defined NPCs clones. Method: Established hiPSCs, generated by reprogramming of peripheral blood mononuclear cells with Sendai virus vectors encoding Yamanaka factors was used. First, to generate the hiPSC-derived NPCs, the iPSC colonies were induced to form embryoid bodies (EBs). EBs were then transferred to poly-L-Ornithine / Laminin (PLO/L) coated dishes in NPC media supplemented with 20 ng/ml of bFGF, until the formation of neural rosettes was observed. Then neural rosettes were differentiated to the NPCs. Morphologically-defined NPCs colonies (100-200 cells) were then manually isolated and further expended for more than 10 passages. Established NPCs were characterized by following methods: 1) karyotype stability, 2) immunofluoresecence staining with markers of: pluripotent cells, neural rosettes and neural stem / neural progenitor cells, 3) flow cytometry analysis: NPCs markers, 4) 3-4 weeks induction by withdrawal of bFGF, and, 5) the presence of spontaneous oscillation in cytosolic calcium in induced neurons, and 6) by grafting of NPCs into the striatum or spinal cord in the immunosuppressed rats. Results: Established iPSC-NPCs showed: i) normal karyotype at passage 12, ii) expression of markers typical for NPCs (but not pluripotent or neural rosettes markers), iii) differentiation into all three neural cell types (neurons, astrocytes, oligodendrocytes), and, iv) ability of terminally differentiated neurons to generate action potential (calcium oscillation) in vitro. Conclusion: These data demonstrate that human iPSC-derived NPCs can be effectively generated and expanded in vitro. Established cell line has a typical characteristics of committed NPCs line with no residual pluripotent contaminants. A long-term in vivo grafting studies will define the safety and tumorigenic potential of generated iPSC-NPCs.

Disclosures: M. Shigyo: None. **Y. Kobayashi:** None. **S. Marsala:** None. **T. Kato:** None. **N. Takamura:** None. **A. Kishino:** None. **T. Kimura:** None. **M. Marsala:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.21/B17

Topic: A.03. Stem Cells and Reprogramming

Support: FONDECYT 1150933 (LVN)

CONICYT 21151115 (SBA)

Title: Wnt5a induces differentiation and development of adult neural progenitor cells through activation of non-canonical Wnt signaling cascades

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Abstract: During embryonic development, Wnt signaling pathway regulates self-renewal, maintenance and differentiation of neural progenitor cells (NPCs). In the adult brain, Wnt signaling regulates dendrite development, synapse formation and synaptic plasticity. Specifically, Wnt5a ligand, which is expressed in adult brain and activates non-canonical Wnt signaling cascades, is essential for dendritic spine morphogenesis and for maintenance of dendritic arbor. Here, we evaluated the role of Wnt5a in differentiation of adult neural progenitor cells (aNPCs) isolated from the hippocampus of 6-week-old mice and in development of aNPCs-derived neurons. aNPCs were maintained in serum-free media supplemented with EGF and FGF-2. Differentiation was induced by growth factors withdrawal in the presence or absent of Wnt5a and specific inhibitors of Wnt signaling cascades. We evaluated neuronal and astrocytic differentiation using the immature neuronal marker DCX and the astrocytic marker GFAP, respectively. Morphological development was assessed in neurons positive for DCX using 2D reconstructions. We determined that recombinant Wnt5a induced differentiation of aNPCs into neurons without affecting astrocyte differentiation. In addition, Wnt5a induced an increase in total neurite legth and number of intersections, and increased morphological complexity assessed by Sholl analysis. CamKII inhibitor KN93 prevented the effect of Wnt5a on neural differentiation while treatment with the PKC inhibitor Go6976 or the JNK inhibitor TAT-TI-JIP had no effects. On the other hand, morphological effects of Wnt5a were prevented by KN93 and TAT-TI-JIP but not by Go6976. These results suggest that Wnt5a induces neuronal differentiation of aNPCs through activation of Wnt/Ca^{2+}pathway and induces morphological development aNPCs-derived neurons through both non-canonical Wnt signaling cascades, Wnt/Ca^{2+} and Wnt/PCP.

Disclosures: S.B. Arredondo: None. **A. Herrera-Soto:** None. **S.H. Santibanez:** None. **L. Varela-Nallar:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.22/B18

Topic: A.03. Stem Cells and Reprogramming

Support: NARSAD Independent Investigator Award

Title: Modeling human oligodendrocyte development and maturation in 3D neural spheroids

Authors: R. P. MARTON[1], Y. MIURA[1], Q. QI[1], S. A. SLOAN[2], R. LEVY[1], O. REVAH[1], *S. P. PASCA[3]
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Abstract: Investigating human oligodendrogenesis and the interaction of oligodendrocytes with neurons and astrocytes is necessary for understanding essential developmental pathways and the mechanisms underlying white matter disorders. However, this is challenging due to the inaccessibility of primary tissue and the limitations of current in vitro models. Here, we develop a novel differentiation method of human pluripotent stem cells (iPSCs) to generate neural organoids or spheroids that contain oligodendrocytes as well as neurons and astrocytes. We demonstrate that the oligodendrocytes derived by our method advance through developmental stages and are transcriptionally similar to oligodendrocytes derived in vivo. iPSC-derived oligodendrocyte progenitor cells migrate in 3D and the process can be visualized and analyzed by live imaging. Mature oligodendrocytes cease migrating and myelinate neurons produced in the same neural spheroid. This method can be used to study oligodendrocyte development, migration, and myelination, as well as alterations to these mechanisms as they occur in white matter disorders.

Disclosures: R.P. Marton: None. **Y. Miura:** None. **Q. Qi:** None. **S.A. Sloan:** None. **R. Levy:** None. **O. Revah:** None. **S.P. Pasca:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.23/B19

Topic: A.03. Stem Cells and Reprogramming

Support: Ministerio de Economía y Competitividad, Spain
ISCIII-Subdirección General de Evaluación and European Regional Development Fund (ERDF) [RETICS and CIBERNED]
Catalonia Trade and Investment, Generalitat de Catalunya and ERDF [ADVANCE(CAT)], Spain
CHDI Foundation Inc., USA

Title: Differentiation of human pluripotent stem cells to functional mature forebrain neurons *in vitro* and integration *in vivo* upon transplantation

Authors: A. COMELLA BOLLA[1,2,4,5], J. ORLANDI[6], M. STRACCIA[1,2,4], A. MIGUEZ[1,2,4,5], P. SANDERS[1,2,4,5], G. BOMBAU[1,2,4,5], M. GALOFRÉ[1,2,4,5], J. BLASI[7], N. ALLEN[8], J. ALBERCH[3,4,5,9,10], J. SORIANO[11], *J. M. CANALS[1,2,4,5,9]

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Abstract: Huntington's disease (HD) is a neurodegenerative disorder affecting forebrain neurons, with striatal medium spiny neurons (MSNs) being the main cell type affected. Cell-based therapies are good candidates to replace the degenerated neurons and treat the symptoms. Here we present a detailed characterisation of a feeder-free differentiation protocol that produces functional mature forebrain neurons from human pluripotent stem cells (hPSCs) in 37 days *in vitro* (DIV). Using our differentiation protocol we assessed the *in vitro* differentiation of hPSC lines to mature neurons by immunocytochemistry and gene expression analysis using high throughput qPCR. Neuronal activity and excitability were analyzed by single-cell calcium imaging and NETCAL, a customized-MATLAB software. We also studied the survival and differentiation of these cells in an *in vivo* environment by transplanting hPSC-derived neural progenitors (NPCs) into the striatum of neonatal mice. Telencephalic NPCs formed from 12 to 16 DIV demonstrated an increase in gene expression of telencephalic markers including the striatal genes ASCL1, GSX1/2, DLX1/2 and EBF1. At 16 DIV cultures were mostly composed of subpallial (DLX^+ and $EBF1^+$) and pallial ($PAX6^+$) progenitors. Subsequent terminal differentiation produced near 100% of $MAP2B^+$ neurons by 23 DIV. These neuronal cultures contained GABA+, CTIP2+ and TH+ neurons together with a sub-population of glutamatergic TBR1+ neurons and also MSNs (CTIP2+/DARPP-32+). These neurons showed a mature phenotype with the expression of synaptic markers, voltage-gated ion channels and neurotransmitter receptors. Functional analysis at 37 DIV revealed a high proportion (84%) of spontaneously active neurons that are divided into 3 main groups of high, intermediate or low activity. Furthermore, differentiation increased neuronal excitability with neurons at 30 DIV displaying higher and faster responses to depolarizing stimuli compared to those at DIV 18. In addition, neurons at 30 DIV expressed functional NMDA receptors.16 DIV NPCs that were transplanted into the striatum of neonatal mice survived, and integrated host environmental cues to differentiate to MSNs. These hPSC-derived MSNs also successfully integrated into the host circuitry as at 3 months post-transplantation they had innervated the globus pallidus.In conclusion, we present a protocol for the rapid differentiation of hPSCs to functional mature neurons in 37 DIV. This approach is suitable for studying HD in vitro, as a platform for

pharmacological tests, and as a viable cell-based therapy strategy to treat neurodegenerative diseases.

Disclosures: A. Comella Bolla: None. **J. Orlandi:** None. **M. Straccia:** None. **A. Miguez:** None. **P. Sanders:** None. **G. Bombau:** None. **M. Galofré:** None. **J. Blasi:** None. **N. Allen:** None. **J. Alberch:** None. **J. Soriano:** None. **J.M. Canals:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.24/B20

Topic: A.03. Stem Cells and Reprogramming

Support: U19 NIMH106434

Title: Exosomes from Bipolar patient iPSC-derived astrocytes

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Abstract: Bipolar Disorder (BP) is a recurrent mood disorder that is characterized by alternating episodes of mania and depression. Despite its high heritability, no single gene has been clearly associated with BP. To identify novel approaches and pathways in BP, we obtained skin samples from BP patient and undiagnosed control (C) individuals, de-differentiated them to induced pluripotent stem cells (iPSC) and then to astrocytes. RNA from BP and C astrocytes was extracted and RNAseq analysis carried out. Hierarchical cluster analysis identified “Exosome” as the first and most significant cluster, $p \leq 5 \times 10^{-3}$, Benjamini correction. Exosomes are released by cortical neurons and astrocytes in culture, and microRNAs are differentially expressed in exosomes derived from BP vs C postmortem brain tissue. Little is known about what transcripts and proteins are delivered to neurons, how they regulate biological functions of the target cell, or how that may be altered in mood disorders. To examine exosome cargo and interactions with neural precursor cells (NPC), astrocytes were differentiated from 3 bipolar and 3 control iPSC lines, and supernatants collected for 7 days. Exosomes were isolated using ultra-centrifugation and analyzed using NanoSight technology. Western blot analysis identified exosomal markers: CD63, HSP70, CD9, and CD81. RNASeq analysis identified 252 exosome transcripts, 58 were upregulated in BP astrocytes, and 54 were upregulated in control astrocytes. 32 microRNAs were present; 9 were uniquely expressed in exosomes from BP patient astrocytes and 9 different microRNAs were expressed only in control astrocytes, including mRNAs for cytoskeletal

elements, extracellular matrix, signaling pathways, neurodegeneration, and notably transcripts that identify exosomes. Research is in progress to characterize exosome number, size, lipid and protein content. Checkerboard analyses of their function in neuronal differentiation is being carried out by labeling exosomes derived from bipolar patient astrocytes with PKH67 and adding them to bipolar and control NPC. Given the current interest in clearing toxic proteins from Alzheimer, tauopathy and Parkinson's disease patient brains, exosomes may present a unique target in BP. Supported by U19 NIMH106434.

Disclosures: K. Walker: None. **A.M. Laszczyk:** None. **C. Delong:** None. **K. Lim:** None. **R. dhond:** None. **T. kulhanek:** None. **M. mcinnis:** None. **K. O'Shea:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.25/B21

Topic: A.03. Stem Cells and Reprogramming

Title: The differentiation of episomally reprogrammed icell hematopoietic progenitor cells into functional microglia

Authors: *N. MADFIS, D. RAJESH, M. HANCOCK, S. BURTON, C. MUNN, S. HILCOVE, K. KIM, T. BURKE
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Abstract: Microglia are immune-competent cells residing within the brain that play a critical role in maintaining immunological balance for normal brain function. As phagocytic cells, they are activated following clearance of pathogens and secreted proteins and respond by either exacerbating or dampening a pro-inflammatory environment. Primary human microglia are difficult to acquire and stably culture *in vitro*. We generated and characterized functional human induced pluripotent stem cell-derived microglia (iCell® Microglia) from episomally reprogrammed iCell Hematopoietic Progenitor Cells (proprietary technology) under defined conditions based on technology developed by the Blurton-Jones laboratory exclusively licensed to FCDI from the University of California-Irvine. iCell Microglia express CD45, CD11b and CD33, and consistent with a microglial phenotype, they also express PU.1, CX3CR1, IBA, TREM-2 and P2RY12. The purity for all these markers is greater than 80% and the retain the expression of all these markers post cryopreservation. iCell Microglia were able to phagocytose opsonized bacteria and fibrillar Aβ within a span of 2-60hrs and reveal a ramified morphology when treated with 5μM Thiazovivin. Additionally, iCell Microglia secrete cytokines and chemokines including TNFα, IL-8, IL-10, CCL2, CCL4, CCL3, CCL4, CXCL10, CXCL11, CXCl1, CXCl2 and CXCL10 when stimulated with LPS and interferon gamma. iCell Microglia will serve as a great tool for disease modeling and drug testing for neuroscience research.

Disclosures: **N. Madfis:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics. **D. Rajesh:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics. **M. Hancock:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics. **S. Burton:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics. **C. Munn:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics. **S. Hilcove:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics. **K. Kim:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics. **T. Burke:** A. Employment/Salary (full or part-time):; FujiFilm Cellular Dynamics.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.26/B22

Topic: A.03. Stem Cells and Reprogramming

Support: NICHD (R01HD079682)
Project ALS (A13-0416)
NYSTEM Predoctoral Grant (C026880)

Title: Proneural factors Ascl1 and Neurog2 contribute to neuronal subtype identities by establishing distinct chromatin landscapes

Authors: ***B. AYDIN**[1,2], A. KAKUMANU[4], M. G. ROSSILLO[3], N. RINGSTAD[3], S. MAHONY[4], E. MAZZONI[2]
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Abstract: Basic helix-loop-helix (bHLH) proneural transcription factors (TFs) are integral to the generation of diversity in the developing nervous system. Ascl1 and Neurog2 are the two main proneural TFs in the vertebrates which are expressed in a complementary manner and are not functionally interchangeable. Although both proneurals induce generic (pan-neuronal) neuronal fate, they also contribute to the specification of neuronal subtype identities. However, the molecular mechanisms by which Ascl1 and Neurog2 control and coordinate neurogenesis and neuronal subtype specification remain unclear. By using isogenic embryonic stem cell lines, we investigated the mechanism by which the two bHLH TFs Ascl1 and Neurog2 engage with chromatin to induce neuronal differentiation, and affect the activities of neurogenic TFs expressed downstream of both Ascl1 and Neurog2. We found that Ascl1 and Neurog2 generate neurons by binding to largely different sets of genomic sites when expressed in similar chromatin and cellular contexts. Their divergent binding is due to distinct DNA sequence specificity of the bHLH domain towards preferred E-boxes. The initial divergent binding of Ascl1 and Neurog2

results in distinct regulatory landscapes that influence the binding pattern and the regulatory activity of downstream neurogenic TFs in establishing shared (generic) and neuron-specific (subtype-specific) gene expression profiles. Thus, in addition to controlling differential gene expression, the divergent binding of proneural TFs has an additional consequence in neuronal differentiation by differentially altering the chromatin landscapes that shape the activities of downstream neurogenic TFs which are widely expressed in the nervous system. Hence, we speculate that the regulatory activity of the shared widely expressed TFs will not be identical when expressed downstream of Ascl1 or Neurog2 during neurogenesis. Finally, our findings suggest a mechanism by which neuronal diversity is generated through altering the activity of the widely expressed neuronal TFs by divergent functions of the upstream proneural TFs.

Disclosures: B. Aydin: None. **A. Kakumanu:** None. **M.G. Rossillo:** None. **N. Ringstad:** None. **S. Mahony:** None. **E. Mazzoni:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.27/B23

Topic: A.03. Stem Cells and Reprogramming

Title: A novel protocol to induce retinal ganglion cell differentiation from human pluripotent stem cells

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Abstract: Purpose:
To establish a novel protocol for a rapid retinal ganglion cell (RGC) differentiation from human induced pluripotent stem cells (hiPSC)/embryonic stem cells (hESC) suitable for cell transplantation.
Methods:
To shorten the time for stem cell differentiation to neural progenitor cells, we utilized a lentivirus system to introduce *neurogenin 2* (*Ngn2*), a transcription factor that induces neural fate via inhibiting glial gene expression, in hiPSCs/hESCs for facilitating RGC-like cell differentiation. We also co-transfected cells with *Sox4*, which strongly promotes RGC fate. RGC markers, Brn3a and RBPMS, were detected in RGC-like cells by immunofluorescence staining and qPCR. The RGC-like cells were co-cultured with retinal explants or intravitreally injected to rat eye, and co-stained with RBPMS and human nuclei markers. Data were analyzed by ANOVA with Tukey's test with P value of <0.05 considered statistically significant.
Results:
We found that overexpression of Ngn2 promotes neural cells differentiation to RGC-like cells

from both hiPSC and hESC. Starting from day 5, we were able to detect neural marker beta 3-tubulin and RGC marker Brn3a in RGC-like cells. We further observed that these RGC-like cells could survive on mouse explant retina and extend their axons up to 7 days after transplantation. Additionally, we observed the RGC-like cells survival in rat retina up to 7 days after injection and
their specific growth on ganglion cell layer. Furthermore, overexpression of *Sox4* in RGC-like cells elongates axon outgrowth *in vivo*.

Conclusion:

This novel protocol significantly shortens the time for RGC-like cell differentiation from stem cells by almost half. This could provide a source of RGC-like cells for transplantation in RGC-related disease such as glaucoma.

Disclosures: C. Sun: None. **K. Chang:** None. **S. Wu:** None. **X. Xia:** None. **J.L. Goldberg:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.28/B24

Topic: A.03. Stem Cells and Reprogramming

Support: NIH Grant 1R01GM112696-01

Title: A time course analysis of cell components and electrophysiological properties in cerebral organoids derived from human induced pluripotent stem cells

Authors: *S. LOGAN, Y. YAN, C. JIANG, X. LIU, L.-K. YU, T. ARZUA, Z. BOSNJAK, Q.-S. LIU, X. BAI
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Abstract: Neurodevelopmental disease modeling has long been a challenge for scientists, primarily due to limitations of animal models and the lack of an appropriate *in vitro* human model resembling the developing brain. The recently established three dimensional (3D) human cerebral organoids using induced pluripotent stem cells (iPSCs) by Dr. Jürgen Knoblich's lab has revolutionized the availability of human models for experimental studies *in vitro*. However, little is known about the evolution over time of cell components and important neuronal electrophysiological parameters in iPSC-derived neurons. Therefore, through a combination of qRT-PCR and immunostaining, we analyzed the expression of pluripotency, developmental, and ion channel markers over time as iPSCs differentiated to cerebral organoids, from day 0 to day 60 after the initiation of neuronal differentiation. Additionally, we investigated the formation of synapses through electron microscopy, and used whole-cell patch clamping to assess the

electrical and chemical channel activity within the neural network. The results showed that cerebral organoids developed progressively in culture dishes. Over time, the expression of pluripotent and neural stem cell markers was reduced, with an increase in neuron, astrocyte, oligodendrocyte, and ion channel markers as the cerebral organoids matured. The electrophysiological data revealed that neurons within cerebral organoids displayed action potentials, and contained functional glutamatergic (AMPA and NMDA) and gamma-Aminobutyric acid (GABA)-ergic currents within formed synapses. Collectively, in comparison with previous 2D neural *in vitro* models, cerebral organoids more accurately reproduce neurodevelopmental characteristics of the *in vivo* human brain. Our findings of the emergence of different neural lineages throughout cerebral organoid maturation, combined with network connectivity and electrophysiological profile, provide additional evidence of translational relevance. Thus, the cerebral organoid model is promising for use in studies on human neurodevelopment, modeling neurodevelopmental diseases (e.g., autism), and application in personalized medicine.

Disclosures: S. Logan: None. **Y. Yan:** None. **C. jiang:** None. **X. Liu:** None. **L. Yu:** None. **T. Arzua:** None. **Z. Bosnjak:** None. **Q. Liu:** None. **X. Bai:** None.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.29/B25

Topic: A.03. Stem Cells and Reprogramming

Title: 3D spheroid culture workflow using iPSC-derived human neurons

Authors: *K. XU[1], Z.-W. DU[1], A. DANG[2]
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Abstract: Human induced pluripotent stem cells (iPSC) derived neurons are now considered a more relevant in vitro model system for psychiatric and neurological diseases. They can be used for the development of physiological cell models, human disease models, and drug library screening. Three dimensional (3D) cultures are recognized as more physiologically relevant since they provide a more accurate reflection of the microenvironment, cell-to-cell interactions, and biological processes that occur in vivo. The implementation of 3D spheroid culture plays an important role as an alternative approach for drug development and therapeutic applications in central neural system (CNS) disorders. To develop a neuronal 3D spheroid culture system, we tested iPSC-derived human motor neurons and cortical glutamatergic neurons using the S-BIO PrimeSurface® Ultra Low Attachment Microplates. After 2 hours, plated neurons started to settle down at the bottom of the well and form large clusters. On day 3, 3D spheroids could be seen clearly under phase contrast. On day 7, the spheroids were more condensed, and Calcein

AM and EthD-1 were used to stain live and dead cells, respectively. The size of the 3D spheroids was proportional to the number of neurons seeded per well. In addition to the morphological measurements, the effect of a known cytotoxic compound was also evaluated on the spheroids. The results presented here demonstrate the feasibility of generating uniform and reproducible spheroids using the human neurons and the potential application for neurotoxicity studies.

Disclosures: K. Xu: A. Employment/Salary (full or part-time):; BrainXell Inc. **Z. Du:** A. Employment/Salary (full or part-time):; BrainXell Inc. **A. Dang:** A. Employment/Salary (full or part-time):; S-BIO, Sumitomo Bakelite Co., Ltd.

Poster

196. Stem Cells and Neural Differentiation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 196.30/B26

Topic: A.03. Stem Cells and Reprogramming

Support: GM109089

Title: Intrinsic determinants of human CGE-like GABAergic interneurons

Authors: *C. FLORUTA, P. CHANDER, J. P. WEICK
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Abstract: Cortical GABAergic interneurons (INs) derived from the caudal ganglionic eminence (CGE) comprise a diverse array of subtypes, and their dysfunction is associated with developmental, psychiatric, and neurodegenerative disorders. Interestingly, the CGE-derived Calretinin (Calr)-expressing population shows an expanded role in primates where their numbers are significantly greater than in rodents. We recently found that default differentiation of human pluripotent stem cells (hPSCs) produces a robust CGE-like $Calr^+$ IN population in addition to cortical pyramidal neurons. However, our understanding of their developmental regulation and maturational potential is incomplete. *In vivo* studies suggest critical roles for the GS homeobox 2 (GSX2) and the Nuclear Receptor Subfamily 2 Group F member 2 (NR2F2/COUPTFII) transcription factors in the specification of CGE derivatives. Interestingly, batch analysis of hPSC-derived neurons (hPSNs) shows low levels of GSX2 expression suggesting possible novel mechanisms for human CGE-like specification. However, lentiviral-mediated overexpression of either COUPTFII or GSX2 tagged to EGFP caused significantly greater specification of GABAergic phenotypes compared to controls expressing EGFP alone. For instance, 95% of hPSC-derived neurons (hPSNs) that overexpressed COUPTFII also expressed GABA ($n=2$, $p<0.001$) compared to only 40% of control populations. Furthermore, hPSNs in cultures that received CRISPR-Cas9 knockout constructs directed toward GSX2 showed a significant reduction in the percentage of GABAergic neurons (control gRNA 31.6 ± 6.2%; GSX2 gRNA

11.9 ± 3.9%; n=1, p<0.01). However, KO of COUPTFII produced variable results on GABAergic specification compared to GSX2 KO, similar to *in vivo* rodent studies. Overall, we uncovered multiple intrinsic factors that are critical for the specification of hPSNs to a CGE-like GABAergic fate. Overall, understanding the development of this population of interneurons may present unique insights into primate-specific cognition and assist with the development of therapeutic interventions and disease models for a number of neurological conditions including autism and epilepsy.

Disclosures: C. Floruta: None. **P. Chander:** None. **J.P. Weick:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.01/B27

Topic: A.05. Axon and Dendrite Development

Support: Ramalingswami Reentry Fellowship from Department of Biotechnology, India

Title: Investigating molecular mechanisms regulating polarity establishment in mouse hippocampal neurons

Authors: *M. J. DEEPAK[1], V. CHAUHAN[2], C. CHANNAKESHAVA[1], M. TANWAR[1], D. NAIR[1]
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Abstract: Establishment and maintenance of cell polarity involves a very fine coordination of various signalling pathways, intracellular trafficking, plasma membrane dynamics and cytoskeleton, the failure of which can result in developmental disorders. Neuronal differentiation is a very critical phase during neuronal development which has strong implication for the formation of neuronal connections and for neuronal network activity. Generation of neuronal polarity is characterized by specification of neuronal processes as a single axon and multiple dendrites during neuronal development. Interestingly, though the neurites grow symmetrically during early in development, the transition to an asymmetric growth pattern during neuronal differentiation occurs in a short time span of few hours. During this period, there is a fast extension of the axon in contrast to the neighbouring dendrites, which display a slower growth pattern. Only once the axon has reached a minimum length, the dendrites start to grow faster. This specification between the neuronal processes is characterized by rapid changes of specific molecular markers between the neuronal processes as well. Though some of these molecular players which are specific between the axon and dendrites have been identified, the actual mechanism underlying the process of neuronal differentiation still remains to be understood. The

focus of my lab is to unravel the molecular mechanisms underlying axonal specification during neuronal development. An inter disciplinary approach of manipulating the molecular players critical for neuronal development using molecular biology, genetics, pharmacology and optogenetics and following their spatial organization and dynamics by superresolution microscopy is adopted to address this.

Disclosures: M.J. Deepak: 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.; Indian Institute of Science, Bangalore, India. **V. Chauhan:** 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.; Indian Institute of Science, Bnagalore, India. **C. Channakeshava:** 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.; Indian Institute of Science, Bangalore, India. **M. Tanwar:** 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.; Indian Institute of Science, Bangalore, India. **D. Nair:** A. Employment/Salary (full or part-time):; Indian Institute of Science.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.02/B28

Topic: A.05. Axon and Dendrite Development

Support: NSF RUI 1748523

Title: Evaluating the effects of inducing autophagy inunc-33mutants

Authors: H. TROMBLEY, M. WILSON, *A. HOLGADO
Dept. of Biol. Sci., St. Edward's Univ., Austin, TX

Abstract: Autophagy, a mechanism used by cells to recycle and catabolize protein aggregates and cellular waste, is highly conserved for homeostasis and survival of an organism. Recent reports indicate CRMP-2/UNC-33/Dpysl2, a neuronal protein essential for axonal development, is regulated during induced autophagy. As a result, our research aims to study the interplay of UNC-33 and neuronal autophagy, through the construction of a double mutant strain containing

unc-33 and *daf-2* mutations in the nematode *Caenorhabditis elegans (C. elegans)*. *daf-2* encodes for an insulin-like growth factor receptor and, when mutated, results in conditional mutant phenotypes and induced autophagy. The construction of the *unc-33; daf-2* double mutant strain resulted in a synthetic lethality at the non-permissive temperature of 25°C. Preliminary analysis shows that 56% of double mutant nematodes die as embryos, with 100% penetrance at 72 hours. Further investigation of the synthetic lethality includes EMS mutagenesis, suppressor screens, and genomic sequencing. Extension of the study involves the characterizing of abnormal phenotypes created by the double mutant genotype by classifying dauers, and fluorescent tagging of autophagosomes. Preliminary data using *unc-33*(e204) nematodes suggests that *daf-2* mediated induction partially rescues *unc-33* neuronal and phenotypic defects.

Disclosures: H. Trombley: None. **M. Wilson:** None. **A. Holgado:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.03/B29

Topic: A.05. Axon and Dendrite Development

Support: NSF RUI 1748523

Title: Analyzing how environmental and developmental factors affect UNC-33 expression

Authors: *F. HERNANDEZ, B. ROSAS, H. TROMBLEY, A. HOLGADO
St. Edward's Univ., Austin, TX

Abstract: An emerging avenue of research aimed towards the development of therapies for Alzheimer's Disease (AD) includes the investigation of Microtubule Associated Proteins (MAPs), other than tau neurofibrillary tangles, such as CRMP2/UNC-33. CRMP2 is a protein expressed in rat hippocampal neurons that promotes axonal elongation and microtubule assembly and an orthologue of CRMP2, called UNC-33, is a set of protein isoforms present in *Caenorhabditis elegans* (*C. elegans*). Recent research suggests that CRMP2/UNC-33 functionality is regulated by autophagy, the engulfing of cytoplasmic elements into the autophagolysosome for degradation, and occurs either through basal autophagy or as a result of nutrient starvation. Previous findings have suggested that autophagy stimulated by starvation promotes axonal growth and that basal autophagy is necessary for protection against neurodegeneration. It is thus hypothesized that autophagy behaves as a protective mechanism in neuronal development in that it may have a role in regulating the levels of UNC-33 expression in neurons. In order to examine this, the aim of this study was to investigate the link between UNC-33 and autophagy with or without nutrient deprivation in different developmental stages of *C.*

elegans. This was accomplished through the analysis of nematodes containing transgenes otIs117[unc-33p::GFP], otIs118[unc-33::GFP] via protein extractions, gel electrophoresis, and western blots. Preliminary results show the expression of *unc-33* is induced under conditions of starvation. Further investigations include the analysis of the subcellular localization of UNC-33 in nematodes under nutrient deprivation.

Disclosures: F. Hernandez: None. **B. Rosas:** None. **H. Trombley:** None. **A. Holgado:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.04/B30

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant 1ZIAMH002768-20

Title: Proteins associated with the RNA sequences regulating axonal trafficking of TH mRNA

Authors: *A. J. BERNDT[1], A. ASCHRAFI[1], J. KOWALAK[3], M. COLT[4], C.-Y. CHEN[4], A. E. GIOIO[5], B. B. KAPLAN[2]
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Abstract: Prior work with the 3' untranslated region (UTR) of the tyrosine hydroxylase (TH) mRNA transcript revealed a 50bp region both necessary and sufficient for TH mRNA localization to distal axons of rat primary superior cervical ganglia (SCG) neurons. To explore proteins potentially involved in axonal trafficking and local translation of TH, we produced a biotinylated version of the 50-nucleotide regulatory sequence we termed the TH trafficking "zipcode". This zipcode and a scrambled zipcode sequence used as negative control, were combined separately with 3-day old SCG protein lysates from either central (somatic & axonal), or lateral compartments (axonal) of Campenot multicompartment cell culture chambers. Unique binding reactions were then further incubated with streptavidin magnetic beads in triplicate to immunopurify zipcode-protein complexes and complete the affinity assay. Mass spectrometry analyses of bead-bound proteins using PEAKS software, yielded a list of zipcode-bead associated proteins. Analyses of zipcode associated proteins with Ingenuity software produced a filtered list of 33 trafficking complex candidate proteins implicated in wide-ranging cellular processes including RNA transcription, transport, and degradation. Interestingly, dopamine β-hydroxylase mRNA was also identified amongst mRNA in TH zipcode immunopurifications, but

not in negative control samples, implying that the TH mRNA trafficking complex may contain other components that regulate the same neurotransmitter biosynthetic pathway.

Disclosures: A.J. Berndt: None. **A. Aschrafi:** None. **J. Kowalak:** None. **M. Colt:** None. **C. Chen:** None. **A.E. Gioio:** None. **B.B. Kaplan:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.05/B31

Topic: A.05. Axon and Dendrite Development

Title: JNK-dependent phosphorylation sites of GAP-43 is a marker of axon growth/regeneration, revealed by growth cone phosphoproteomics

Authors: *A. KAWASAKI[1], A. TAMADA[1], M. OKADA[3], S. OKUDA[2], M. IGARASHI[1]
[1]Departments of Neurochemistry and Mol. Cell Biol., [2]Lab. of Bioinformatics, Niigata Univ. Grad Sch. Med. Dent. Sci., Niigata, Japan; [3]Departments of Neurosurgery, and Cell. Neurobio., Brain Res. Institute. Niigata Univ., Niigata, Japan

Abstract: Axonal growth is a fundamental process to build the functional neural circuits in brain. Toward the comprehensive understanding of the molecular mechanisms of axonal growth in neurons, we performed an unbiased phosphoproteomic approach to identify the whole phosphorylation sites involved in this event. Phosphoproteomic analysis of growth cone membranes prepared from postnatal day 1 rat forebrain identified more than 6,000 phosphorylation sites from 1,223 proteins, most of which were Ser/Thr. The most frequently phosphorylated site was Ser96 of GAP-43 (growth-associated protein 43-kDa), a vertebrate-specific protein involved in axon growth. Bioinformatic analysis revealed that more than 60% of phosphorylation sites identified by phosphoproteomics were proline-directed Ser/Thr. Such types of phosphorylation are known to be mediated by kinases, including the mitogen activated protein kinases (MAPKs). Pharmacological analysis showed that the phosphorylation of Ser96 of GAP-43 was dependent on JNK, a member of MAPK family. Consistently, this phosphorylation was dramatically suppressed in knockout mice of MKK7, a MAP kinase kinase for JNK. In addition, the Ser96 phosphorylation was specifically detected in growing and regenerating axons in mice by immunofluorescence staining. Taken together, Ser96 phosphorylation of GAP-43 is the most frequent target of proline-directed phosphorylation, and represents a promising new molecular marker for mammalian axonal growth/regeneration.

Disclosures: A. Kawasaki: None. **A. Tamada:** None. **M. Okada:** None. **S. Okuda:** None. **M. Igarashi:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.06/B32

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant NS036232

Title: The effects of AHI1 mutations on optic nerve projection in zebrafish

Authors: *L. ZHU[1,2], S. LI[1], X.-J. LI[1], H. XU[2]
[1]Dept. of Human Genetics, Emory Univ. Sch., Atlanta, GA; [2]Nanchang Univ., Inst. of life science, Nanchang, China

Abstract: Joubert Syndrome (JBTS) is a rare inherited autosomal recessive disorder associated with cerebellum and brainstem malformation. The JBTS patients often show motor and behavioral disorders with the absence of the cerebellar vermis. Mutation in the Abelson-helper integration site-1 (AHI1) gene have been found to cause JBTS. Although over 80% of AHI1 mutantations can result in truncated AHI1 proteins, it remains unclear whether these mutant AHI1 elicite toxicity via a gain-of-function mechanism.Recent studies have reported cerebellar hypoplasia with a vermis and midline fusion in the early developmental stage of Ahi1 knockout mice. However, the disruption of axonal decussation that affects the corticospinal tract and superior cerebellar peduncles could not be found in Ahi1 knockout mice. It is also noticed that the coiled-coil structure in N-terminal of AHI1 protein is absent in the mouse Ahi1, though it is present in both fish and humans. Thus, we used zebrafish as a model to investigate whether Ahi1 mutations can affect axonal decussation by examining the the supra-optic tract (SOT) projection. Using in-situ hybridization, we found that ahi1 was specifically and highly expressed in the whole brain in zebrafish. We injected the morpholin to zebrafish embryos to knockdown ahi1 expression and found that ahi1 knockdown led to optic nerve misprojection and dysplasia at 4dpf (days post fertilization) larva. Considering that ahi1 is a ciliary gene, we examined the axons projection in zebrafish larva and found the supra-optic tract (SOT) exhibits defasciculation and anterior commissure (AC) unclosed in forebrain at 60hpf (hours post fertilization) larva. In addition, the motor nerves showed slightly defusion and shorten compared to wild type. We are currently using CRISPR/Cas9 to generate truncated ahi1 to test their roles in the supra-optic tract (SOT) projection.

Disclosures: L. Zhu: None. **S. Li:** None. **X. Li:** None. **H. Xu:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.07/C1

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant R01NS081333
NIH Grant 4T32GM007367

Title: Decreased axonal caspase-9 activity in neurons dysregulates mitochondrial dynamics and affects axon outgrowth *in vitro*

Authors: *J. A. BELARDE[1], S. J. SNIPAS[4], G. S. SALVESEN[4], U. HENGST[2], C. M. TROY[3]
[1]Med. Scientist Training Program, Col. of Physicians & Surgeons, [2]Pathology & Cell Biol., [3]Pathology & Cell Biology, Neurol., Columbia Univ., New York, NY; [4]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA

Abstract: The nervous system depends on stable connections among neurons to function appropriately. A major task in achieving this goal is maintaining viable axons, which require a carefully regulated local environment. This is especially important in the central nervous system, where neurons lack the ability to regenerate their axons following injury. However, the regulatory mechanisms involved in this stable health and maintenance remain largely unknown and require more detailed investigation. We have found that caspase-9 is an important regulator of axonal health. As a member of the caspase family of cell death proteases, caspase-9 activity is essential for the normal development of the brain. However, after development, active caspase-9 remains detectable in non-dying neurons, hinting at the possibility of additional non-apoptotic roles. Specifically, given that caspase-9 can be detected in stable axons, a highly specialized and tightly regulated cellular compartment, it is reasonable to ask if the protease is required in any way to support that stability. To explore this question, we employ a microfluidic model of neuronal culturing, using a chamber that capitalizes on the unique qualities of fluid dynamics on a microscale (channels ~3μm thick) to establish isolated compartments that allow for localized treatment of axons without affecting the cell body. After culturing embryonic neurons (from either dorsal root ganglion or cortices) in these chambers and allowing them sufficient time to grow and establish isolated axonal processes, we show presence of active caspase-9 in the axons that is not accompanied by cell death or degradation of the neurites. Furthermore, we show that by decreasing activity of caspase-9 in the axons using a novel, highly specific caspase-9 inhibitor developed by our lab, we see significant perturbations to the outgrowth of processes in the axonal compartment without an associated effect on the cell body compartment. Taken together these results suggest a functional role for caspase-9 activity in maintaining the health and

stability of axons, and ongoing work is exploring the mechanism behind this role. One possibility emerging from this work involves mitochondrial fusion and fission dynamics. These homeostatic processes are vital to ensuring functional mitochondria in axons and thus maintaining axonal viability. Our early data suggests a dysregulation of this balance when we reduce caspase-9 activity in the axons, and we are currently exploring potential candidate proteins that mediate this suspected effect.

Disclosures: J.A. Belarde: None. **S.J. Snipas:** None. **G.S. Salvesen:** None. **U. Hengst:** None. **C.M. Troy:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.08/C2

Topic: A.05. Axon and Dendrite Development

Title: Role of canonical wnt/β-catenin signaling in commissural neuron development

Authors: *R. TIAN, K. ONISHI, Y. ZOU
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Abstract: In embryonic rodent spinal cord, commissural neurons first extent axons ventrally from the dorsal spinal cord to reach and cross the ventral midline. After midline crossing, they turn anteriorly to continue to grow towards the brain. Our lab found that an anterior-high and posterior-low gradient of Wnt family secreted signaling proteins along the midline floor plate cells controls the direction of this turning. We then found that this sharp anterior turning is directly regulated by a non-canonical Wnt signaling pathway, the planar cell polarity (PCP) pathway. Recently, canonical Wnt/β-catenin pathway was shown to be required for anterior-posterior guidance of commissural axons in chick embryonic spinal cord. We tested this in rodents and found that canonical Wnt/β-catenin signaling is in fact required for several aspects of the development of commissural neurons. Blocking canonical Wnt signaling leads to alterations of cell body positioning and disoriented growth of commissural axons before they reach the floor plate. A few axons did reach the midline. They either did not turn at all or turned either anterior or posterior randomly after they crossed the midline. Therefore, we propose that canonical Wnt signaling is involved in multiple steps of the development of commissural neurons, including their migration, differentiation and axon guidance. We propose that their migration and axon guidance defects may be caused by disruption of their cell fate or differentiation program.

Disclosures: R. Tian: None. **K. Onishi:** None. **Y. Zou:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.09/C3

Topic: A.05. Axon and Dendrite Development

Title: Intrinsic expression of G protein-coupled receptor 3 facilitates formation of neuronal polarity in hippocampal neurons

Authors: *S. TANAKA, N. SHIMADA, H. SHIRAKI, T. MIYAGI, I. HIDE, N. SAKAI
Hiroshima Univ. Sch. of Biomed. Sci., Hiroshima, Japan

Abstract: G protein-coupled receptor 3 (GPR3) is a member of the class A rhodopsin-like GPCR family and is highly expressed in various neurons. GPR3 is unique in its ability to constitutively activate the Gαs protein without the addition of ligands, which elevates the basal level of intracellular cyclic adenosine monophosphate (cAMP). Here, we report that neuronal expression of GPR3 enhances neurite outgrowth and modulates neuronal survival. Recently, our time-lapse experiments of GPR3-transfected cerebellar granular neurons revealed that GPR3 was transported along the neurite and was predominantly distributed at the neurite tips, which were highly correlated with local protein kinase A (PKA) activation. Meanwhile, during the course of neuronal development, an immature neuron forms an axon and a dendrite, and neuronal polarity is subsequently established. Several intracellular signaling pathways, such as Rac1, Ras, cAMP-LKB1-SAD kinase, and the Ca2+/Calmodulin-dependent signaling pathway are responsible for the establishment and maintenance of neuronal polarity; however, the upstream signaling that modulates the activity of these factors has not been completely elucidated. In the present study, using rat hippocampal neurons, we focused on the possible involvement of GPR3 in the formation of neuronal polarity. When the endogenous expression of GPR3 was suppressed by siRNA, the number of neurons with Tau-1-positive neurites significantly decreased at 48-60 h after siRNA transfection. Conversely, the upregulated expression of GPR3 resulted in an accelerated formation of Tau-1-positive neurites at 24-36 h after transfection. GPR3-mediated acceleration of axon formation significantly reduced when the PI3-kinase inhibitor LY294002 (10 μM) or the PI3-kinase gamma specific inhibitor AS252424 (200 nM) was administered; the PKA inhibitor KT5720 (2 μM) was not significant. Finally, we asked if GPR3 expression affects the de-phosphorylation of CRMP2, which is downstream in the PI3-kinase signaling pathway. When the endogenous expression of GPR3 was suppressed by siRNA, the number of neurons with pCRMP2-negative neurites significantly decreased 60 h after GPR3 siRNA transfection. Furthermore, the staining intensity of pCRMP2 at the neurite tip was significantly stronger in GPR3-knockout mice than in the wild-type mice. These results suggest a potential role of GPR3 in the formation of neuronal polarity in hippocampal neurons.

Disclosures: S. Tanaka: None. **N. Shimada:** None. **H. Shiraki:** None. **T. Miyagi:** None. **I. Hide:** None. **N. Sakai:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.10/C4

Topic: A.05. Axon and Dendrite Development

Support: Academy of Finland
Brain and Mind graduate school

Title: Tropomyosin Tpm3.1 is required to maintain the structure and function of the axon initial segment

Authors: *P. HOTULAINEN[1], A. ABOUELEZZ[1], H. STEFEN[2], C. C. HOOGENRAAD[3], P. W. GUNNING[4], T. FATH[2]
[1]Minerva Inst. for Med. Res., Helsinki, Finland; [2]Sch. of Med. Sci., Univ. of New South Wales, Sydney, Australia; [3]Utrecht Univ., Utrecht, Netherlands; [4]3Oncology Res. Unit, Sch. of Med. Sci., Sydney, Australia

Abstract: The axon initial segment (AIS) is the site of action potential initiation and serves as a diffusion barrier that helps maintain neuronal polarity. Recent studies have revealed details about a specialized structural complex in the AIS. The specific role of actin in the AIS, however, remains unclear. While an intact actin cytoskeleton is required for AIS formation, pharmacological disruption of actin compromises the AIS diffusion barrier but does not affect overall AIS structure. In this study, we examined the dynamics and regulation of the AIS actin cytoskeleton. We found a population of relatively stable actin filaments decorated by tropomyosin isoform Tpm3.1 in the AIS. These filaments are part of the periodic sub-membranous AIS complex and AIS actin patches. Inhibiting Tpm3.1 in cultured hippocampal neurons led to the loss of AIS structure, the AIS diffusion barrier, and the clustering of sodium ion channels. This suggests that the role the actin cytoskeleton plays in the AIS is more important than previously appreciated.

Disclosures: P. Hotulainen: None. **A. AbouElezz:** None. **H. Stefen:** None. **C.C. Hoogenraad:** None. **P.W. Gunning:** None. **T. Fath:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.11/C5

Topic: A.05. Axon and Dendrite Development

Support: Samsung Science and Technology Foundation under Project Number SSTF-BA1602-11

Title: Dynamics of axonal β-actin mRNA in live hippocampal neurons

Authors: *B. LEE[1], S. BANG[2], S. LEE[2], N. JEON[2], H. PARK[1]
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Abstract: Local translation of mRNA is essential to facilitate neuronal function by regulating protein synthesis in a spatiotemporal manner. Yet it is not clearly understood how abundantly mRNA molecules are present in axons and how the axonal mRNAs are transported into their target sites. To address these questions, we investigated mRNA motion in live axons using a transgenic mouse that expresses fluorescently labeled endogenous β-actin mRNA. To identify axons in cultured neurons, we utilized either a microfluidic device or sparse transfection of fluorescent proteins. We found that β-actin mRNAs frequently localize at the neck of filopodia which can grow as an axon collateral branch and at varicosities where synapses typically occur. Furthermore, using high-speed dual-color imaging, we investigated the dynamics of actin filaments and β-actin mRNAs simultaneously. We found the axonal β-actin mRNAs are likely to localize in the actin-rich regions and show sub-diffusive movement. In contrast, β-actin mRNAs that do not localize in the actin-rich regions show super-diffusive directed motion. Based on these findings, we are developing a model for the transport and localization process to understand how axonal mRNAs are targeted to the actin hot spots. The novel findings on the dynamics of β-actin mRNA will shed important light on the biophysical mechanisms of mRNA transport and localization in axons.

Disclosures: B. Lee: None. **S. Bang:** None. **S. Lee:** None. **N. Jeon:** None. **H. Park:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.12/C6

Topic: A.05. Axon and Dendrite Development

Support: Project no.LQ1605 from the National Program of Sustainability II (MEYS CR)

Title: Identifying regulators of axonal (intracellular) transport

Authors: *M. FEOLE[1], V. POZO DEVOTO[2], M. NOVAKOVA[2], V. LACOVICH[2], G. STOKIN[2]
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Abstract: The intracellular transport is a regulated process, involving several proteins controlling molecular trafficking in all the cells, particularly in neurons. The onset of several neurodegenerative diseases, such as Alzheimer's, Parkinson's or Amyotrophic Lateral Sclerosis, exhibits significant axonal pathology where transport impairment plays a crucial role. However, the mechanisms underlying the disruption of neuronal transport are still unclear. In the present work we aim to characterize transport dynamics of specific proteins and the molecular machinery that is regulating this complex process. Human Neural Stem Cells derived neurons were terminally differentiated in multichannel μ-Slide VI (ibidi®) after 30 DIV. Several GFP-coupled cargos involved in different processes (neurotrophins, pre- and post-synaptic proteins, disease signaling) were transfected in neurons, in order to evaluate and describe possible differences in movement. Time-lapse movies of the different cargos were acquired, and then analyzed with Image Pro Premier®, and a thorough description of motion parameters was obtained: mean velocity, directionality, segmental velocity, average run length, pauses, and reversions. In addition, immunocytochemistry was performed after imaging, in order to describe the specific compartmentalization of cargos in neurons.Our results showed different behaviors during transport, mainly in velocities and directionality. In particular, APP showed an high velocity both in anterograde and retrograde movement, with a small stationary particle proportion; a similar pattern was also visible for Synaptophysin, an important protein involved in synapses maturation, while Rab5 (involved in endosomes biogenesis) displayed the lowest velocity pattern compared with the previous ones. Moreover, as expected BDNF showed high particle proportion in the retrograde direction. Relying on this comprehensive description of movement dynamics in human neurons, we decided to screen for their specific protein-protein interactions by a combination of GFP-trap and Mass Spectrometry. After obtaining the lysate from transfected neurons, we performed immunoprecipitation to trap the GFP-tagged proteins.

The isolated fractions were then analyzed by mass-spec to highlight the population of specific interactors for each cargo. In summary, our results describe for the first time the movement behavior in human neurons of several proteins involved in the crucial physiological pathway of transport. Ongoing studies will shed light on the regulation of these dynamics and will open a road to understand the pathophysiology of neurodegenerative diseases.

Disclosures: M. Feole: None. **V. Pozo Devoto:** None. **M. Novakova:** None. **V. Lacovich:** None. **G. Stokin:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.13/C7

Topic: A.05. Axon and Dendrite Development

Support: DoD/US Army Medical Research and Dev: W81XWH-13-1-0308)
NIH Grant R01-NS041596
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
Univ. of South Carolina SmartState Center for Childhood Neurotherapeutics

Title: Regulation of axonal mRNA storage depots to accelerate axon regeneration post injury: A novel therapeutic approach

Authors: *P. K. SAHOO[1], S. J. LEE[1], P. B. JAISWAL[2], S. ALBER[3], A. N. KAR[1], S. M. RANDOLPH[1], T. SMITH[1], B. SINGH[4], S. Y. HO[4], U. ANATOLY[5], S. CHAND[5], A. L. BURLINGAME[5], C. J. WOOLF[4], M. FAINZILBER[3], A. W. ENGLISH[2], J. L. TWISS[1]
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Abstract: Critical functions of intra-axonally synthesized proteins are thought to depend on regulated recruitment of mRNA from storage depots in axons. Here we show that axotomy induces translation of stored axonal mRNAs via regulation of the stress granule protein G3BP1, to support regeneration of peripheral nerves. G3BP1 aggregates in axons of peripheral nerves in stress granule-like structures that increase immediately after nerve injury and decrease during regeneration, with a commensurate increase in phosphorylated G3BP1. Colocalization and association of G3BP1 with axonal mRNAs is also correlated with the growth state of the neuron. Disrupting G3BP functions by overexpressing a dominant-negative protein activates intra-axonal mRNA translation, increases axon growth in cultured neurons, disassembles axonal stress

granule-like structures, and accelerates nerve regeneration in PNS and CNS *in vivo*. Casein Kinase 2 (CK2) phopshorylates G3BP1 in non-neuronal cells. We find *CK2* mRNA to be present in axons and gets locally translated This raises the interesting possibility that axonally synthesized CK2 regulates G3BP1 aggregation and releases G3BP1 associating mRNAs for translation.

Disclosures: P.K. Sahoo: None. **S.J. Lee:** None. **P.B. Jaiswal:** None. **S. Alber:** None. **A.N. Kar:** None. **S.M. Randolph:** None. **T. Smith:** None. **B. Singh:** None. **S.Y. Ho:** None. **U. Anatoly:** None. **S. Chand:** None. **A.L. Burlingame:** None. **C.J. Woolf:** None. **M. Fainzilber:** None. **A.W. English:** None. **J.L. Twiss:** None.

Poster

197. Axon and Dendrite Development: Axon Growth and Guidance: Axonal Transport and Trafficking

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 197.14/C8

Topic: A.05. Axon and Dendrite Development

Support: NIH/NINDS F31-NS103262-02

Title: Subcellular growth cone molecular machinery in subtype-specific cortical circuit formation

Authors: *J. HATCH[1], A. POULOPOULOS[3], J. D. MACKLIS[2]
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Abstract: During development, growth cones (GCs) of diverse cortical or other projection neuron (PN) subtypes navigate complex extracellular environments to reach distant, subtype-specific targets. These axon-terminal structures must respond to substrate-bound and diffusible signals in a subtype- and stage/context-specific fashion to construct specific functional circuitry. Recent studies strongly indicate that subcellular localization of specific molecular machinery to GCs might underlie the precise behaviors of these structures during circuit "wiring." While great progress has been made toward identifying diffusible and substrate-bound signals that guide axon growth, it is becoming increasingly clear that intracellular, local growth cone biology underlies the distinct behaviors of specific neuronal subtypes at specific developmental stages. Molecular determinants of these critical processes remain largely unstudied with respect to distinct neuronal subtypes under physiological conditions. Because most current knowledge of growth cone biology was identified *in vitro,* often with heterogeneous populations, access to subtype-specific growth cones in their native environment during normal development will

substantially elucidate molecular bases of cortical and other neural circuit formation.
Our laboratory has recently developed an integrated approach that enables high-throughput, high-depth proteomic and transcriptomic investigation of purified GCs from fluorescently labeled subtype-specific cortical projection neurons. This approach has already revealed unanticipated depth of GC molecular machinery, subtype-specificity, and GC enrichment of hundreds of transcripts and proteins. Building on this foundational work, GCs have been isolated from closely-related PN subtypes with distinct axonal trajectories at critical developmental stages to investigate whether and how subtype-specific GC molecular machinery might functionally enable specific subtypes to build and maintain specific circuitry. In particular, we investigate dynamic regulation of GC transcriptomes before and after midline crossing in interhemispheric callosal PN (CPN), and investigate whether and how local molecular machinery might implement a subcortical vs. intracortical trajectory in closely related subtypes, including CPN, corticospinal neurons (CSN), and corticothalamic PN (CThPN).

Disclosures: J. Hatch: None. **A. Poulopoulos:** None. **J.D. Macklis:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.01/C9

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NSF EPSCoR RII-2 FEC OIA1632891

Title: Measuring glutamate uptake *in vitro* in real time with high-sensitivity microelectrode probe

Authors: T. A. MURRAY[1], C. TAN[2], J. L. SCOGGIN[1], N. NGYUEN[1], U. KANSAKAR[1], S. SIDDIQUI[1], P. U. ARUMUGAM[2], *M. A. DECOSTER[3]
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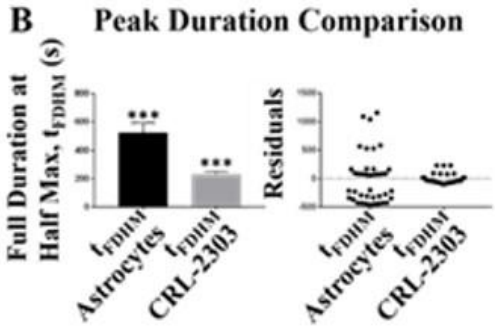
Abstract: Glutamate signaling is dysregulated in diseases such as epilepsy and gliomas. Enzyme-based platinum (Pt) microelectrode arrays (MEA) on ceramic probes have superior spatiotemporal resolution over microdialysis and single electrochemical probes. We created highly sensitive glutamate Pt-MEA probes (Glu microprobe) by applying L-glutamate oxidase, bovine serum albumin, and glutaraldehyde to Pt-MEAs (R1, CenMeT) and then depositing m-phenylenediamine by cycling between +0.25 V and +0.75 V, 50 mV/s, 20 min. In calibration tests, the microprobes had higher sensitivity, 4.6 ± 0.3 pA/μM (Fig. 1B), compared to the literature, due in part to an increased loading of enzymes onto MEA sites. The microsensor had long-term stability, up to 1 mo, with minimal change in Glu sensitivity when stored in DI water @ 22°C. *In vitro* performance was evaluated by discriminating differences in Glu uptake

between astrocytes (normal uptake) and CRL 2303 glioma cells (impaired uptake). We used the full duration at half maximum of the peak response (Fig. 1B) to additions of glutamate into cell culture media and the fall time, or clearance time (T_c), of the glutamate current, including analysis of residuals, to demonstrate that the probe had sufficient temporal resolution to discern differences between normal and impaired glutamate uptake. A significant difference was found between the clearance rate in astrocytes and glioma cells; $p < 0.0001$. The Tc (mean ± SEM) for astrocytes was 1.3 ± 0.2 pA s 1 (n = 36 tests) while the Tc for the glioma cells was 3.3 ± 0.3 pA s 1 (n = 38 tests). Given the long-term stability of the probes and their relatively high spatiotemporal resolution, these probes will be further developed for *in vivo* applications.
This work was supported by a grant from the NSF EPSCoR RII-2 FEC OIA1632891.
Figure 1. (A) Sensitivity from calibration tests to convert current to glutamate concentration. (B) Glu response differed ($p < 0.001$).

A. Sensitivity of Glu microprobes

	n	Sensitivity (pA/μM)
Site 1	4	4.9 ± 0.4
Site 2	7	5.0 ± 0.4
Site 3	7	3.5 ± 0.3
Site 4	7	5.3 ± 0.7
Mean ± SEM		4.6 ± 0.3

n, number of tests for a site.



Disclosures: T.A. Murray: None. **C. Tan:** None. **J.L. Scoggin:** None. **N. Ngyuen:** None. **U. Kansakar:** None. **S. Siddiqui:** None. **P.U. Arumugam:** None. **M.A. DeCoster:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.02/C10

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: International Graduate School in Molecular Medicine Ulm

Title: C-terminal truncation at serine 505 increases EAAT2 activity and is not involved in EAAT2 downregulation associated with staurosporine-induced caspase 3 activation

Authors: *T.-D. VOSS[1], J. LEWERENZ[2]
[1]Neurol., [2]Ulm Univ., Ulm, Germany

Abstract: *Introduction*: Downregulation of the excitatory amino acid transporter 2 (EAAT2) observed in diseases like amyotrophic lateral sclerosis, Alzheimer's and Huntington's disease is thought to contribute to glutamate (Glu) excitotoxicity. Post-transcriptional mechanisms have been proposed to underlie this downregulation, including caspase 3 (C3)-mediated cleavage of the EAAT2 protein at the C-terminus. *Aim: To study the mechanisms that regulate activity and protein stability of the EAAT2 protein. Methods*: A172 and HT22 cells were transiently co-transfected with VSV-G-tagged wild-type ($EAAT2^{wt}$), C3-cleavage site mutant ($EAAT2^{D504N}$) or C-terminal truncated (Δ505-572) EAAT2 (tEAAT2) cloned into pBI-5 and tetracycline transactivator to allow doxycycline(Dox)-inhibitable EAAT2 expression. EAAT2 activity was measured as DL-threo-β-benzyloxyaspartate-inhibitable ^{3}H-Glu uptake in A172 cells. C3 was activated in HT22 cells by staurosporine (STR). EAAT2 protein levels and C3 activation in HT22 cells were semiquantitatively assessed by immunoblotting. *Results*: When expressed in A172 cells, $EAAT2^{D504N}$ showed 19% higher activity than $EAAT2^{wt}$. In addition, in HT22 cells $EAAT2^{wt}$ protein levels were downregulated to 48±9% upon STR-induced C3 activation (250 nM, 6h). This downregulation was partially reversed by the pan-caspase inhibitor Q-VD-OPh (5 μM). However, STR-induced C3 activation was also associated with decreased EAAT2 protein levels upon $EAAT2^{D504N}$ overexpression (40±12%). Moreover, the size shift of $EAAT2^{wt}$ protein expected upon C3 cleavage could not be observed. In addition, the ubiquitin-activating enzyme E1 inhibitor PYR-41 (250 μM) rescued STR-mediated $EAAT2^{wt}$ protein downregulation more effectively than Q-VD-OPh. Finally, tEAAT2 overexpression compared to $EAAT2^{wt}$ revealed that the truncated protein leads to 20% higher EAAT2 activity. As ubiquitinated lysines are reportedly located at the EAAT2 C-terminus, we evaluated the half-life of EAAT2 activity after blocking transcription by Dox. While EAAT2 activity was downregulated to 61±3 and 32±2% in $EAAT2^{wt}$-overexpressing A172 cells after 24h and 48h, respectively, it was only reduced to 72±5% and 43±1% upon tEAAT2 expression. *Conclusion*: We found no evidence that EAAT2 downregulation associated with STR-induced C3 activation is mediated by cleavage at the EAAT2 C-terminus in our cell models. In contrast, mimicking C3 cleavage of the EAAT2 protein increased its activity, most possibly by stabilizing the protein as C-terminal deletion removes lysines reportedly involved in EAAT2 ubiquitination. Thus, how the D504N mutation increases EAAT2 activity remains to be explored.

Disclosures: T. Voss: None. **J. Lewerenz:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.03/C11

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Nordihidroguairaetic acid (NDGA) increases hippocampal synaptic density and enhances excitatory amino acid transporter 2 (EAAT2) function

Authors: *L. FOURGEAUD, A. W. HARRINGTON, Q. WANG, G. WOODRUFF, N. PHILLIPS, P. BONAVENTURE, A. BHATTACHARYA
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Abstract: Formation, maintenance and regulation of synapses is key to proper tuning of brain circuitry. However, synaptic loss is a common pathological hallmark of most brain disorders. To identify novel molecules able to increase synaptic density in mature neurons, we conducted a phenotypic screen using the Phenix Opera high content imaging system and rodent's primary neurons in culture (hippocampal and cortical). One of the molecule that we identified is a natural compound called Nordihidroguairaetic acid (NDGA). NDGA is a general lipoxygenase inhibitor found in the creosote bush (*larrea tridentate*) known for its antioxidant and anti-inflammatory properties. 24h of NDGA (200nM) treatment leads to 1.5 to 2-fold increase in synapse density in both hippocampal and cortical neurons. To assess the functional consequences of NGDA on synaptic activity, we recorded neuronal network properties using multielectrode array (MEA). Consistent with an increase in synapse density we observed an increase in firing rate upon NDGA treatment. One of the known well described neuronal properties of NDGA is to increase glutamate uptake. To evaluate the effect of NDGA on glutamate transport, we generated inducible recombinant cell lines overexpressing the human EAAT1 and EAAT2; and utilized the electrogenic properties of the EAATs to establish a membrane potential (Vm) assay. Acute and overnight NDGA treatment leads to an increase in hEAAT2 Emax while there is no change in the EC50 of the transporter. However, neither acute or chronic NDGA affects hEAAT1 mediated transport. In addition, 24h of NDGA treatment causes an increase in C^{14} glutamate flux in mouse synaptosomes enriched fraction. NDGA has also been shown to dominantly inhibit the 5-Lipoxygenase (5-Lox) enzyme over the other lipoxygenases isoforms. To confirm that the effect of NDGA on EAAT2 is mediated through inhibition of the 5-Lox pathway, we tested other known 5-Lox inhibitors. 24h treatment with Zileuton and BW-B70C also leads to increased glutamate mediated responses in cells overexpressing hEAAT2. Together, our results confirm that inhibition of the 5-Lox pathway by NDGA leads to an increase in EAAT2 mediated glutamate transport. We hypothesize that changes in synapse density and function upon 24h NDGA treatment is linked to changes in ambient glutamate levels impacting tonic activation of extra-synaptic receptors.

Disclosures: L. Fourgeaud: None. **A.W. Harrington:** None. **Q. Wang:** None. **G. Woodruff:** None. **N. Phillips:** None. **P. Bonaventure:** None. **A. Bhattacharya:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.04/C12

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Hope College Neuroscience Program
Hope College Biology Department
Hope College Chemistry Department

Title: Disruption of C-terminal tyrosine-based internalization motifs and putative N-terminal ubiquitination sites increase the cell surface expression and activity of System xc-

Authors: *M. A. SCHMIDT, A. GIBSON, J. LARSON, L. CHASE
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Abstract: System x_c^- exchanges intracellular glutamate for extracellular cystine across the membrane of many cell types, including astrocytes. Its activity directly regulates the synthesis of the antioxidant glutathione and the extracellular concentration of glutamate in some areas of the brain. Dysregulation of the transporter can lead to excessive glutamate release and excitotoxic cell death or the depletion of glutathione stores and the development of oxidative stress. We recently demonstrated that oxidants acutely upregulate System x_c^- activity by triggering the rapid redistribution of the transporter from intracellular compartments to the cell surface. However, little is known about the mechanisms which govern the constitutive and regulated trafficking of xCT. In the present study, we sought to identify trafficking motifs within the C-terminus of xCT that are important in regulating the delivery and internalization of xCT from the membrane. Specifically, using site-directed mutagenesis, we assessed putative trafficking motifs between positions 464 -486 containing the sequence GVPAYYFLI that might contribute to the constitutive trafficking of xCT to the plasma membrane. Using a radioisotope uptake assay and cell surface biotinylation assay, we demonstrated that disruption of either tyrosine-based internalization motif (YxxΦ) leads to an increase in transport activity and cell surface expression. However, we also recognized that the VPAYY motif could serve as a putative binding site for the ubiquitinating enzyme, Nedd4-2, suggesting that cell surface expression xCT may also be regulated by ubiquitination. Therefore, we also assessed whether disruption of putative ubiquitination sites may alter transport activity and cell surface expression. There are seven highly conserved lysine residues within xCT that are located on the cytoplasmic side of the membrane. These residues are located at positions 4, 37, 41, 43, 422, 472, and 473. We created multiple mutants of xCT containing single or multiple lysine to arginine mutations so that we could also assess the effect of these mutations on cell surface expression of System x_c^-. We found that mutation of the N-terminal lysine residues (K4, K41 and K43, but not K37) increases

transport activity and cell surface expression of the transporter. However, mutation of the C-terminal lysine residues (K 422, 472 and 473) did not disrupt transporter activity or cell surface expression. We are currently assessing the ubiquitination status of the VPAYY domain and N-terminal lysine mutants so that we may potentially be able to establish a link between ubiquitination status and cell surface expression of the transporter.

Disclosures: M.A. Schmidt: None. **A. Gibson:** None. **J. Larson:** None. **L. Chase:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.05/C13

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Conacyt Fellowship 456284

Title: Short-term exposure to manganese on Bergmann glial cells: Relevance to the Glu/Gln cycle

Authors: *J. SOTO-VERDUGO, L. HERNANDEZ-KELLY, E. LOPEZ-BAYGHEN, A. ORTEGA
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Abstract: Glutamate (Glu), the main excitatory neurotransmitter in the mammalian brain, it is cleared from the synaptic cleft by a family of sodium-dependent Glu transporters. Inside the glial cell, it is metabolized by glutamine (Gln) synthetase to Gln and released to the neurons through sodium-dependent neutral amino acid carriers of the N system. Gln is taken up by neurons completing the Glu/Gln cycle. Bergmann glial cells (BGC) are a type of specialized radial glia that reside in the cerebellum. In this context, recent studies have shown that one of the targets for manganese accumulation is the cerebellum. Manganese (Mn) is an essential trace element that in high doses can exert serious oxidative and neurotoxic effects. Mn neurotoxicity is characterized by astrocytic impairment both in the expression and activity of Gln transporters. The N system is a major facilitator of Gln efflux from glial cells. Also, altered intracellular mitogen-activated protein kinases (MAPK) signaling pathways represent an early event linked to Mn exposure in the immature brain. The molecular mechanisms mediating Mn-induced neurotoxicity, particularly in the context of the Glu/Gln cycle, have yet to be completely understood. Hence, we decided to investigate the role of Mn short-term exposure on BGC, as a well-established model of glia/neuronal interactions. To this end, primary cultures of chick cerebellar BGC were exposed to subtoxic concentrations of Mn ($MnCl_2$; 50-500 μM) from 15 minutes to 2 hours. The [^{3}H]-L-Gln release, as well as the extracellular signal-regulated kinase (ERK) 1/2 phosphorylation pattern were evaluated. Mn treatment caused a reduction in the Gln release

after, although this effect was not sustained under a background of aspartate (Asp). Mn exposure increased ERK1/2 phosphorylation, from the lowest time and concentration tested. The effect was not potentiated on a co-exposure with Asp. Overall, these findings suggest that altered intracellular MAPKs signaling pathways may represent an early event concerning the effects of Mn and that the disruption of Glu homeostasis may lead to impairment of the glutamatergic neurotransmission.

Disclosures: L. Hernandez-Kelly: None. **E. Lopez-Bayghen:** None. **A. Ortega:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.06/C14

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: CONACyT Grant 255087

Title: Modafinil regulates glutamine synthetase in cerebellum

Authors: *J. SILVA, L. MENDEZ, E. BEJARANO-PÉREZ, L. C. R. HERNÁNDEZ-KELLY, A. ORTEGA
Ctr. de Investigación y de Estudios Avanzados de, Ciudad de Mexico, Mexico

Abstract: Glutamate is the major excitatory transmitter in the Central Nervous System of vertebrates and exerts its actions through the activation of specific membrane receptors and transporters. Over-stimulation of glutamatergic receptors results in neuronal death, phenomena known as excitotoxicity. Extracellular glutamate levels have to be tightly regulated a family by high-affinity uptake systems expressed in neurons and glia cells. Most of the uptake process occurs in the glial compartment in a biochemical coupling known as glutamate/glutamine shuttle involved in the turnover of this neurotransmitter. Once internalized in the glial cells, glutamate is rapidly metabolized to glutamine *via*glutamine synthetase to be released to the vicinity of the presynaptic terminal, which takes it up and converts it back to glutamate to refill the synaptic vesicles, completing the cycle. Inhibition of Glutamine synthetase blocks glutamatergic transmission highlighting the importance of this glia-enriched enzyme. Among the great variety of Central Nervous System stimulants to which we have access daily, modafinil is widely used as a wakefulness agent although recently also been recommended for the treatment of excessive daytime sleepiness, fatigue and impaired cognition, and in that sense has become a popular drug among youngsters. Despite of the fact that the mechanism of action of this stimulant is still unclear, it increases glutamate extracellular levels. In order to establish a plausible involvement of glutamine synthetase in the effects of modafinil, we used the well-established model of chick cerebellar Bergmann glia primary cultures. Acute treatment with modafinil results in an increase

in glutamine synthetase activity as determined by γ-glutamyl hydroxamate production. Moreover, i.p. administration of 9, 90 and 900 mg/kg of modafinil in 8-day old rat pups increased the protein levels of glutamine synthetase as determined by Western blot analysis in cerebral cortex. These results strengthen the notion of an important role of glia cells in glutamate-dependent neurotransmission through the regulation of its compulsory glia-mediated turnover.

Disclosures: J. Silva: None. **L. Mendez:** None. **E. Bejarano-Pérez:** None. **L.C.R. Hernández-Kelly:** None. **A. Ortega:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.07/C15

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: CONACYT Grant 255087

Title: Modafinil regulates SNAT3 and the translation process in Bergman Glial Cells

Authors: *L. I. MENDEZ
CINVESTAV, CDMX, Mexico

Abstract: Glutamate (Glu) is the major excitatory amino acid in the vertebrate Central Nervous System (CNS), it is involved in several pathways and mechanisms after its release from the presynaptic terminal. It is removed from the synaptic cleft by a family of sodium-dependent excitatory amino acid transporters (EAATs) expressed both in neurons and glial cells. More than 80% of the released Glu is taken up by glial cells through either EAAT1 (also known as GLAST) or via EAAT 2 (Glt-1). Once internalized, Glu is metabolized to Glutamine (Gln) by Gln synthetase and released to the vicinity of the presynaptic terminal by the reverse function of the Na^+-dependent neutral amino acid transporter 3 (SNAT3). The presynaptic neurons take up Gln through SNAT2, converts it back to Glu and packed in the synaptic vesicles completing the recycling of the neurotransmitter in what is known as the Glu/Gln shuttle. Modafinil is a CNS stimulant that has gained popularity among college students although its molecular mechanism(s) of action has not been completely established. Through the use of the well-characterized model of chick cerebellar Bergmann glia cells culture (BGC), we undertook the characterization of the effect of Modafinil in SNAT3 function. We were able to find a time and dose-dependent decrease of [^{3}H] Gln uptake in BGC culture exposed to Modafinil. These results suggest that the stimulant enhances Gln release and therefore, augments Glu turnover. In order to gain insight into a plausible modulation by Modafinil in the protein repertoire of BGC, we explored the phosphorylation levels of the eukaryotic elongation factor 2, a factor that once

phosphorylated halts the translation process. The exposure of the cultured cells to a 100 µM concentration of Modafinil for 1 h, results in an increase in the phosphorylation pattern of eEF2. Our results suggest that Modafinil targets glial components of the Glu/Gln cycle in glial cells and it increases Glu turnover.

Disclosures: L.I. Mendez: None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.08/C16

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant R01AA019458 (Y.S.)

Title: Ceftriaxone attenuates alcohol drinking behavior and hydrocodone reinstatement: Role of modulating astroglial glutamate transporters in alcohol-preferring P rats

Authors: *F. ALSHEHRI[1], A. Y. HAKAMI[2], Y. ALTHOBAITI[3], Y. SARI[4]
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Abstract: Simultaneous abuse of ethanol and opioids is a common practice among drug users. Several studies demonstrated that dependence and relapse to several drugs of abuse, including ethanol and opioids affect the glutamatergic system. Chronic ethanol consumption and opioids use can lead to increase in extracellular glutamate concentrations in several brain regions. High levels of extracellular glutamate were associated with reduction in the expression of glutamate transporter 1 (GLT-1). The glutamate homeostasis is regulated by several glutamate transporters, including the GLT-1, cystine-glutamate transporter (xCT), and glutamate-aspartate transporter (GLAST). Changes in the expression of these transporters can lead to dysregulation of glutamate clearance and homeostasis. In this study, we investigated the effects of ceftriaxone (CEF) on hydrocodone (HYD) reinstatement and ethanol intake in alcohol-preferring (P) rats using the conditioned place preference (CPP) paradigm. The CPP procedure was performed in four phases: a habituation phase for three days, a conditioning phase with four sessions of HYD (5 mg/kg, i.p.), an extinction phase with four sessions of CEF (200 mg/kg, i.p.), and a reinstatement phase with one priming session of HYD. Animals had free access to ethanol (15% and 30%) for five weeks prior to the CPP paradigm, and continued through the end of the study. One prime dose of HYD (5 mg/kg, i.p.) produced a significant increase in time spent in the HYD-paired chamber in the reinstatement test. We found that CEF attenuated HYD-reinstatement and reduced ethanol drinking. Western blot analysis showed a reduction in GLT-1 and xCT expression in nucleus

accumbens (NAc), dorsomedial prefrontal cortex (dmPFC) and hippocampus (HIP) in rats simultaneously exposed to ethanol and HYD. CEF treatment attenuated these effects. No changes were observed in the expression of GLAST. These data show that CEF attenuated HYD-reinstatement and ethanol drinking behavior, in part, through upregulation of GLT-1 and xCT expression in central reward brain regions.

Disclosures: A.Y. Hakami: None. **Y. Althobaiti:** None. **Y. Sari:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.09/C17

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: CIHR

Title: GLT-1 regulates distinct glutamate receptor activation during excitatory transmission to MCH neurons

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Abstract: Increased excitability of melanin-concentrating hormone (MCH) neurons are known to promote sleep and weight gain. Glutamatergic afferents provide an excitatory drive to MCH neurons and may mediate plastic changes in response to homeostatic challenges. Our recent study showed that sleep deprivation induces plasticity of astrocytic glutamate transporter-1 (GLT-1), resulting in reduced excitatory transmission to these neurons (Briggs et al. 2018 J Neurosci). This suggests an important role of glutamate transport in controlling excitatory transmission to MCH neurons. However, it remains unknown which types of glutamate receptors mediate excitatory transmission to these neurons and how their activities are regulated by GLT-1. To answer these questions, whole cell patch clamp recordings were performed on MCH neurons in acute brain slices from male Sprague-Dawley rats. We identified three modes of glutamatergic transmission to these neurons with distinct time courses: fast EPSC induced by single afferent stimulation, pronounced slow EPSC evident following high frequency train stimulation, and tonic inward current which appears in the presence of the GLT-1 blocker DHK. DHK has no effect on fast EPSCs while paradoxically suppressing slow EPSC amplitude and area. Using specific receptor antagonists we found that fast EPSCs are mediated by AMPA receptors, slow EPSCs are mediated by kainate receptors (KARs) and possibly by group I metabotropic glutamate receptors (mGluR), and tonic currents are largely mediated by KARs. These results suggest that different glutamate receptors mediate distinct modes of glutamate

signaling in MCH neurons. Specifically, ambient glutamate induces tonic current in these neurons via KARs and this is tightly regulated by GLT-1, while AMPAR-mediated fast EPSCs are not influenced by GLT-1 activity. During intense synaptic activity, glutamate spillover may occur and lead to slow EPSCs, which is mediated by KAR and group I mGluR, and modulated by GLT-1. In conclusion, our study shows a complex mechanism of excitatory transmission mediated by multiple glutamate receptors that are differentially regulated by glutamate transport activity. Given the known role of MCH neurons, this may have functional implications on sleep and energy homeostasis.

Disclosures: S.C. Bowes: None. **C.L. Briggs:** None. **K. Semba:** None. **M. Hirasawa:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.10/C18

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH-NIMHD-G12-MD007583
UCC RISE R25GM110513
Title V P031S130068

Title: Translational activation of GLT-1 in astrocytes decreases the infarct size after focal ischemia

Authors: *F. A. TEJEDA[1], D. E. RIVERA-APONTE[2], C. J. MALPICA NIEVES[3], Y. HERNÁNDEZ[4], S. N. SKATCHKOV[5], M. J. EATON[2]
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Abstract: Ischemic stroke is defined as the interruption of nutrients and oxygen rich blood flow to the brain. Cells fail to generate sufficient ATP resulting in energy failure which leads to loss of ionic gradients and dysregulation of neurotransmitter release. In particular, glutamate is released, reuptake processes are impaired, and glutamate binds to its postsynaptic receptors and promotes excitotoxic neuronal death after an ischemic insult. Astrocytic GLT-1 is the major glutamate transporter responsible for removing excess glutamate from the extracellular space. A possible neuroprotective compound LDN/OSU 0212320 (LDN; a translational activator of the GLT-1) has been developed recently with beneficial outcomes in epileptic animal models. Similar to stroke, glutamate is released during epileptic seizures. The goal of this study is to evaluate the effects of LDN in stroke-associated brain injury. To study ischemic brain damage, mice were subjected to unilateral focal ischemia induced in the sensorimotor cortex using the

photothrombotic method. Male C57BL/6 mice (8-10 weeks of age) were injected i.p. with 75 mg/kg of 1% Rose Bengal and the area of the skull over the sensorimotor cortex was illuminated using a 150 watt X-Cite series 120 (at 12% power) to create the focal lesion. The study compared two groups: a) animals receiving 40mg/kg of LDN (i.p.) 24 hours before surgery and b) animals which received an i.p. vehicle injection (1% DMSO, 1% polyethylene glycol, 0.2% TWEEN 80, 10% hydroxypropyl-cyclodextran in 0.9% saline) 24 hours before surgery. Prior to receiving the focal lesion, mouse performance on the rung ladder walk was assessed. After these baseline data were determined, the mice received the focal lesion and 24 hours later their behavioral performance on the rung ladder walk was re-evaluated. The animals were then decapitated, brains were removed and 1mm sections were obtained using a mouse brain matrix. The sections were stained in a 5% solution of Tetrazolioum chloride (TTC) and the size of the lesion was measured using ImageJ. The area of the infarct for vehicle treated mice was 40.4 ± 8.8 mm^2 (mean ± SEM; n=3), whereas those pretreated with LDN had a reduced infarct size (20.4 ± 2.5 mm^2; n=3). Surprisingly, both groups had similar deficits in sensorimotor function 24 hours after surgery. In summary, we found that LDN reduced the infarct size after focal ischemia but did not alter the acute sensorimotor deficits at 24 hours. Experiments are in progress to determine if the decreased infarct size seen in LDN treated animals will result in increased recovery of sensorimotor function over time after stroke.

Disclosures: F.A. Tejeda: None. **D.E. Rivera-Aponte:** None. **C.J. Malpica Nieves:** None. **Y. Hernández:** None. **S.N. Skatchkov:** None. **M.J. Eaton:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.11/C19

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant NS102822

Title: Circadian regulation of astrocyte morphology and glutamate uptake

Authors: *J. MCCAULEY[1], A. SCIMEMI[2]
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Abstract: Multiple aspects of rodent and human behavior show circadian rhythmicity. Circadian rhythms are initiated by the supra-chiasmatic nucleus (SCN), located within the hypothalamus. The SCN is entrained by light through glutamatergic afferents from the retina. The SCN, in turn, resets the function of numerous brain regions, either through direct synaptic connections or indirectly via hormone release. The hippocampus is one of these target regions, implicated with memory consolidation and spatial navigation. Fast glutamatergic transmission in the

hippocampus is powerfully controlled by glutamate transporters, expressed at high levels in astrocytes. What is currently unknown is how exactly light exposure affects glutamate uptake, one of the main functions of astrocytes. Here, we address this question using a combination of high-resolution imaging and patch-clamp electrophysiology approaches. Our findings indicate that astrocytes undergo major remodeling during circadian rhythms. These structural changes are associated with altered rates of glutamate uptake, which, in turn, shapes the time course of excitatory synaptic transmission. Taken together, these findings identify astrocytes as major players in brain remodeling during circadian rhythmicity.

Disclosures: J. McCauley: None. **A. Scimemi:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.12/C20

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant R01AA019458 (Y.S.)

Title: Role of astroglial glutamate transporters in P rats co-exposed to alcohol and cannabinoid receptor agonist, CP 55,940

Authors: *A. Y. HAKAMI[1], F. S. ALSHEHRI[1], Y. S. ALTHOBAITI[2], Y. SARI[1]
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Abstract: Evidence supports the important role of the glutamatergic transmission in seeking behavior of several drugs of abuse. Studies have demonstrated that exposure to ethanol, cocaine, and/or methamphetamine dysregulated glutamate homeostasis in several reward brain regions, including the nucleus accumbens (NAc). However, less is known about the effects of co-exposure to polysubstance use on astroglial glutamate transporters, such as glutamate transporter 1 (GLT-1), cystine/glutamate exchanger (xCT) and glutamate/aspartate transporter (GLAST). In this study, we tested the effects of co-exposure to ethanol and CP 55,940 (CP), cannabinoid receptor 1 (CB1R) agonist, on ethanol intake and CP-induced reinstatement in alcohol-preferring (P) rats using an established conditioned place preference (CPP) paradigm. We revealed that one prime dose of CP induced a reinstatement behavior in P rats exposed to ethanol. Moreover, we revealed a significant downregulation in GLT-1 and xCT expression in the NAc, Amygdala (Amg) and Hippocampus (Hipp) in ethanol-vehicle and ethanol-CP as compared to control. Moreover, we revealed a significant downregulation in xCT expression in the dorsomedial prefrontal cortex (dmPFC) of ethanol-vehicle and ethanol-CP as compared to control. Administration of β-lactam compounds, Ampicillin/ sulbactam (A/S), known to upregulate GLT-1 and xCT, during extinction phase attenuated the CP-seeking behavior and reduced ethanol

consumption. This effect was associated, in part, with restoration of GLT-1 and xCT expression in tested brain regions. These findings demonstrate the potential role of upregulating GLT-1 and xCT expression to attenuate cannabinoids-seeking behavior and ethanol intake in animal model of polysubstance use.

Disclosures: A.Y. Hakami: None. **F.S. Alshehri:** None. **Y.S. Althobaiti:** None. **Y. Sari:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.13/C21

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: LISBOA-01-0145-FEDER-007391, project cofunded by FEDER, through POR Lisboa 2020 - Programa Operacional Regional de Lisboa, PORTUGAL 2020, and Fundação para a Ciência e a Tecnologia
SynaNet – Twinning Action funded by H2020 (GA-692340)
Fundação para a Ciência e a Tecnologia(SFRH/BPD/81627/2011)
Fundação para a Ciência e a Tecnologia(PTDC/DTP-FTO/3346/2014)

Title: CB1R activation increases GLAST activity in a PLC dependent pathway

Authors: *J. RIBEIRO[1,2], T. P. MORAIS[3], A. SEBASTIÃO[1,2], S. H. VAZ[1,2]
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Abstract: In the central nervous system, astrocytes regulate synaptic transmission in many aspects, including the control of extracellular glutamate levels, through GLAST and GLT-1 transporters (Perego et al.,2000), being this crucial process for the normal function of synaptic transmission. For fine control of the extracellular levels of glutamate, these transporters require a tight modulation. Astrocytes also express cannabinoid type-1 receptors (CB1Rs), which are activated by endocannabinoids released by neurons. Not much is known about the mechanism of action of these receptors in astrocytes, but it has been reported that they led to enhanced astrocytic calcium signaling in a phospholipase C (PLC)-dependent way. Since neurotransmitter transporters can be modulated by phosphorylation-coupled signaling cascades, we now assessed the influence of CB1Rs upon the glutamate transporter GLAST. Primary astrocytic cultures were prepared from Sprague Dawley pups (0-2days) as described by Vaz et al., 2011. [^{3}H]-glutamate uptake was performed with 18-23 div astrocytes. The specific transport mediated by GLAST was accessed by subtracting total transport from that detected in the presence of UCPH-101, a specific blocker of GLAST transporter. Glutamate transport in the primary cultured astrocytes

mainly performed by GLAST (about 70% of total transport). The presence of ACEA, a synthetic cannabinoid, upregulated this transporter activity through a significant increase in Vmax. The effect of ACEA upon transport was lost in the presence of AM-251 (1µM), a selective CB1R antagonist. Moreover, modulation of GLAST by CB1R activation occurs through a PLC-dependent but PKC independent pathway. These results indicate that CB1R activation increases the activity of glutamate transporter into astrocytes, thus disclosing a novel role for CB1Rs in glial cells. This may represent a protective feed-back mechanism to facilitate removal of glutamate from the synaptic cleft that could result from enhanced astrocytic calcium signaling and astrocytic glutamate release. Work supported by: SynaNet - Twinning Action funded by H2020 (GA-692340); LISBOA-01-0145-FEDER-007391, project cofunded by FEDER, through POR Lisboa 2020 - Programa Operacional Regional de Lisboa, PORTUGAL 2020, and Fundação para a Ciência e a Tecnologia (SFRH/BPD/81627/2011 and PTDC/DTP-FTO/3346/2014)."

Disclosures: J. Ribeiro: None. **T.P. Morais:** None. **A. Sebastião:** None. **S.H. Vaz:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.14/C22

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: ZDSYS201504301539161
KQTD2015032709315529
JCYJ20170412150845848

Title: Higher ambient synaptic glutamate at inhibitory versus excitatory neurons differentially impacts NMDA receptor activity

Authors: *L. YAO[1], J. HANSON[2], P. PAOLETTI[3], Q. ZHOU[1]
[1]Peking Univ., Shenzhen City, China; [2]Genentech, Inc, South San Francisco, CA; [3]PSL Res. Univ., Paris, France

Abstract: Identifying differences between excitatory and inhibitory neurons is important for both basic science and translational studies, as these differences are critical to the proper functions of the brain and may also underlie the pathogenesis of major brain diseases. In our previous study, we identified a GluN2A-selective positive allosteric modulator, GNE-8324, that selectively enhances N-methyl-D-aspartate (NMDA) receptor-mediated synaptic responses in inhibitory neurons but not excitatory neurons. Here, we demonstrated that a higher resting glutamate level in the synaptic cleft of excitatory synapses on inhibitory neurons is a key factor underlying this differential potentiation. We showed that increasing expression of glutamate

transporter 1 (GLT-1) eliminated GNE-8324 potentiation in inhibitory neurons while decreasing GLT-1 activity enabled potentiation in excitatory neurons. Our results reveal an unsuspected difference between excitatory synapses onto different neuronal types, and a more prominent activation of synaptic NMDARs by ambient glutamate in inhibitory neurons than excitatory neurons. This difference has implications for tonic NMDAR activity/signaling and can be exploited for selective modulation of inhibitory neuron activity in order to target various brain disorders especially those with reduced inhibition.

Disclosures: L. Yao: None. **J. Hanson:** None. **P. Paoletti:** None. **Q. Zhou:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.15/C23

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant Z1A-HD001205-24

Title: Developmental NMDA receptor ablation specific to a subset of interneurons confers schizophrenia-like impairments

Authors: *V. MAHADEVAN, R. CHITTAJALLU, K. A. PELKEY, D. ABEBE, X. YUAN, S. HUNT, C. J. MCBAIN
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Abstract: Schizophrenia (SCZ) is a debilitating neurodevelopmental psychiatric disorder affecting ~1% of the world's population. People diagnosed with SCZ experience a heterogeneous combination of symptoms. These include psychosis, social withdrawal, anxiety, cognitive and motor impairments, reflecting a dysfunction across many brain regions. Numerous studies have consistently indicated a deficiency of neurotransmitter systems - glutamate, GABA and dopamine in SCZ, particularly in the forebrain (neocortex and hippocampus), and other subcortical structures. Moreover, converging lines of data now support an integrated hypothesis that NMDA receptor hypofunction (NMDAR, a glutamate receptor mediating synaptic excitation), could underlie both GABAergic and dopaminergic dysfunctions in SCZ.
In the present study, using a Cre-lox approach involving *Nkx2.1*-cre and floxed-*GRIN1* (a requisite NMDAR subunit) mice, we ablated NMDAR function in GABAergic interneurons that arise from the medial ganglionic eminence and occupy different brain regions relevant to SCZ. Electrophysiological analyses in these animals from the ventral hippocampus, an important structure involved in SCZ-related behavioral abnormalities, indicate that NMDAR-hypofunction in a discrete interneuron class results in aberrant short-term plasticity, AMPA receptor function,

and dendrite patterning. Moreover, behavioral analyses indicate that these mutant animals exhibit novelty-induced hyperlocomotion, risk-taking and motor abnormalities reminiscent of SCZ-like impairments.
NMDARs are a key source of calcium entry into neurons regulating the transcription of new genes. To test whether the interneuron-specific loss of NMDARs results in aberrant excitation-transcription coupling and its centrality to SCZ etiology, we turned to next-gen RNAsequencing. By performing cell-type specific translatome analyses, we have recently discovered differential expression of several classes of genes spanning different neurotransmitter systems relevant to SCZ, in a brain region-specific manner. Overall, our comprehensive brain-wide interrogation of molecular, cellular, electrophysiological and behavioral approaches has allowed a systematic interrogation of the NMDAR-hypofunction hypothesis of SCZ. This, in turn, has revealed novel insights into disease etiology that could open new doors to developing new therapeutic strategies.

Disclosures: R. Chittajallu: None. **K.A. Pelkey:** None. **D. Abebe:** None. **X. Yuan:** None. **S. Hunt:** None. **C.J. McBain:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.16/C24

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant R01MH085666
NIH Grant R21MH111609

Title: Cell type specific input from mediodorsal thalamus to prefrontal cortical interneurons

Authors: *S. YANG, W.-J. GAO
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Abstract: The mediodorsal thalamus (MD) plays a critical role in cognition through its extensive glutamatergic innervation on both excitatory and inhibitory neurons in the medial prefrontal cortex (mPFC). Vasoactive intestinal peptide positive (VIP+) and somatostatin-positive (SOM+/SST+) are two type of non-fast spiking interneurons. Both of them are reportedly involved in PFC-dependent function and social behaviors, as well as mental disorders such as schizophrenia. However, whether and how these cells are influenced by the MD afferents remains unknown. In this study, by combining optogenetic technique with transgenic Cre mouse lines and whole cell patch-clamp recording, we aim to characterize the synaptic properties of the potential projection from the MD to VIP+ and SOM+ interneurons in the mouse PFC. We found that SOM+ interneurons receive direct monosynaptic inputs from the MD. Optogenetic stimulation of MD afferent terminals evoked more AMPA-mediated current than the NMDA-

mediated current in SOM+ interneurons. The NMDA/AMPA ratio was 0.43, which was smaller than the one recorded in pyramidal neurons (and possibly PV+ interneurons). In contrast, VIP+ interneurons do not receive direct innervation from the MD but were influenced by MD inputs through the polysynaptic transmission. Stimulating MD axon terminals induced multi-peak AMPA- and NMDA-mediated currents in VIP+ interneurons. These results suggest that SOM+ interneurons, but not VIP+ interneurons, may play important roles in mediating the effect of MD afferent on PFC-dependent function.

Disclosures: S. Yang: None. **W. Gao:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.17/C25

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DA042943 to VMP
NIH Grant DA43982 to KM

Title: Chronic adolescent exposure to Delta9-tetrahydrocannabinoil decreases neuronal responses to NMDA and GluN1 expression in region-specific dendrites defined by size and input from axon terminals containing CB1 receptors in the medial prefrontal cortex of adult mice

Authors: *V. M. PICKEL[1], J. CHAN[1], K. MACKIE[2], G. WANG[1]
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Abstract: Chronic repeated exposure to marijuana's major psychoactive compound, Δ9-tetrahydro-cannabinol (THC) during adolescence results in complex cognitive abnormalities that are reminiscent of those produced by NMDA receptor hypofunction in the medial prefrontal cortex (mPFC). The prelimbic (PL) and infralimbic (IL) mPFC are respectively implicated in endocannabinoid-regulated NMDA receptor-mediated synaptic plasticity that enables gain in impulse control and fear extinction during adolescence. This suggests that THC occupancy of CB1 receptors during this sensitive period of development results in functional down regulation of GluN1 containing NMDA receptors in PL- and/or IL-mPFC neurons receiving synaptic input from axon terminals that express CB1receptors. We tested this hypothesis using quantitative electron microscopic dual labeling and whole-cell current-clamp recording in the mPFC of adult C57Bl/6J male mice that had received once-daily intraperitoneal injections of vehicle or THC at escalating doses of 2.5-10 mg/kg through adolescence, postnatal day 30-44. GluN1 immunogold was localized on endomembranes and both synaptic and non-synaptic plasma membranes of many dendritic profiles and seen in select axonal and glial profiles throughout the mPFC. The

impact of THC pretreatment on GluN1 distribution relative to synaptic input varied substantially in the mPFC compartments. In the PL-PFC cortex of THC-pretreated mice, the cytoplasmic and total GluN1 density was significantly (1) decreased in small dendritic profiles receiving input from excitatory- and CB1R-labeled inhibitory-type terminals, and (2) increased in large glial ensheathed dendrites without synaptic contact. The current-clamp recording also showed a more negative resting membrane potential (RMP) and increased current-induced firing threshold, decreased spontaneous firing rate and reduction in depolarizing response to NMDA in PL-PFC neurons of THC pretreated mice. In contrast with the PL-PFC, chronic adolescent administration of THC increased the cytoplasmic density of GluN1 exclusively in large dendrites receptive to terminals expressing CB1 receptors in the IL-PFC. These results provide new evidence that THC occupancy of presynaptic CB1 receptors during adolescence produces functional depression of NMDA receptors and increased cytoplasmic accumulation of GluN1 subunits in large proximal dendrites influenced by glial-derived and CB1 regulated modulators in PL and IL-PFC, respectively. They have implications for understanding and treating psychiatric disorders worsened by early use of marijuana.

Disclosures: V.M. Pickel: None. **J. Chan:** None. **K. Mackie:** None. **G. Wang:** None.

Poster

198. Glutamate Transport and Signaling

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 198.18/C26

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIGMS R35 GM122573

Title: Regulation of glutamatergic neurotransmission in a *C. elegans* chemotaxis circuit by a novel vesicular transporter

Authors: *J.-H. CHOI, L. BAYER-HOROWITZ, N. RINGSTAD
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Abstract: Vesicular glutamate transporters (VGLUTs) package glutamate into synaptic vesicles and are essential for glutamatergic neurotransmission. Whether synapse and circuit function can be modulated through VGLUT-dependent mechanisms that determine the amount of glutamate released per exocytic event remains a fascinating and unresolved question. Through molecular dissection of a *C. elegans* sensory neuron that mediates a simple avoidance behavior, we have discovered a novel vesicular transporter that is co-expressed with VGLUT and functionally interacts with VGLUT to regulate glutamate release. Mutants lacking this transporter display excess glutamate release from sensory neurons. The resulting behavior defects are ameliorated by attenuation of post-synaptic AMPA-type glutamate receptors, and high-resolution behavioral

analysis suggests that specific synapses in a chemosensory circuit are affected by mutation of this novel vesicular transporter. We propose a model in which different vesicular transporters compete for access to a common electrochemical gradient to set the amount of glutamate stored in a vesicle. This model predicts that the substrate of the transporter we have discovered will be a potent endogenous regulator of glutamatergic neurotransmission. Our model further predicts qualitatively different functional interactions between other types of vesicular transporters, *e.g.* the vesicular acetylcholine transporter and the vesicular monoamine transporters, and this novel vesicular transporter, which is enriched in glutamatergic neurons but is also expressed in many non-glutamatergic neurons.

Disclosures: J. Choi: None. **L. Bayer-Horowitz:** None. **N. Ringstad:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.01/C27

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: MEXT/JSPS KAKENHI Grant Number JP16H05133

Title: SKF-10047, a prototype sigma-1 receptor agonist, facilitated the membrane trafficking and uptake activity of serotonin transporter and its mutant through the sigma-1 receptor-independent mechanism

Authors: *N. SAKAI[1], M. ASANO[2], H. YAMAMOTO[3], I. HIDE[2], S. TANAKA[2]
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Abstract: The function of serotonin transporter (SERT) is regulated via its membrane trafficking. Our previous studies have revealed that the SERT C-terminal deletion mutant (SERTΔCT) showed the robust decrease in its membrane trafficking and was retained at endoplasmic reticulum (ER), suggesting that SERTΔCT would be an unfolded protein. The accumulation of unfolded membrane protein in ER could be the cause of ER stress. It has been reported that the Sigma-1 receptor (SigR1) attenuates the ER stress via its chaperone activity when the SigR1 agonists bind to the receptor. In order to find the drugs that accelerate the membrane trafficking and relieve the ER stress, we focused on the SigR1 agonists. We investigated the effects of SKF-10047, a prototype SigR1 agonist, on the membrane trafficking and uptake activity of SERT and SERTΔCT expressed in COS-7 cells. The 24hr-treatment of SKF-10047 (> 200 μM) accelerated the SERT membrane trafficking, and robustly upregulated the activity of SERTΔCT. Interestingly, these effects of SKF-10047 on SERT functions also

remained in the cells in which the SigR1 expression was knocked-down by shRNA, suggesting that SKF-10047 exerted these effects on SERT via a mechanism independent of SigR1. In addition, PRE-084, a more specific SigR1 agonist than SKF-10047, did not influence on the SERT activity. These findings gave a rise to the idea that SKF-10047 would act on the other target than SigR1. To elucidate the novel mechanism underlying the effects of SKF-10047, we performed the cDNA array for the SKF-10047-treated and non-treated control cells. We identified several candidate genes, which is involved in the membrane trafficking. Among them, syntaxin 3 (STX3), a member of SNARE protein which participate in the exocytosis of vesicle and vesicular proteins, was significantly up-regulated by the treatment of 200 μM SKF-10047 for 48 hours. This leads to the possibility that STX3 is a target of SKF-10047, which facilitates the trafficking of SERT or SERTΔCT, thereby relieving the SERTΔCT-induced ER stress. Taken together, SKF-10047 would be a candidate drug for the relief of ER stress caused by the accumulation of unfolded membrane proteins.

Disclosures: N. Sakai: None. **M. Asano:** None. **H. Yamamoto:** None. **I. Hide:** None. **S. Tanaka:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.02/C28

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Fast analysis of dopamine and serotonin for high time resolution in microdialysis experiments

Authors: *M. EYSBERG[1], H.-J. BROUWER[2], L. M. VAN HEERWAARDEN[2], N. J. REINHOUD[2]
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Abstract: Microdialysis of neurotransmitters in vivo has become an invaluable tool to study neurotransmission in the living brain. Extracellular fluid of the brain is sampled through a semipermeable membrane with a microdialysis probe. HPLC analysis requires fractionation of the sample stream, and the size of the fractions will affect time resolution. To accurately measure fast responses, a high time resolution is necessary. Typical flow rates in microdialysis are 1 - 2 μL/min, and decreasing the fraction size to a few microliters enables a temporal resolution of a few minutes. We developed a robust commercially available on-line solution for the simultaneous analysis of DA and 5-HT with high time resolution in microdialysis experiments. The solution is based on a UHPLC system equipped with a dual loop sampling valve in combination with the new DECADE Elite electrochemical detector and SenCell (see fig 1) . Small samples with a volume of 1.5 μL were collected online into the dual loop sampling valve

and simultaneously analyzed. With this approach a temporal resolution of less than 2 minutes can be reached, with a detection limit of 100 pmol/L for both DA and 5-HT. Furthermore, it was demonstrated that by increasing the separation temperature from 35 °C to 60°C, the analysis time could be shortened to less than 1 minute allowing an even higher temporal resolution of in vivo experiments (see fig 2).

Figure 1. Schematic drawing of the set-up for online sampling & LC analysis.

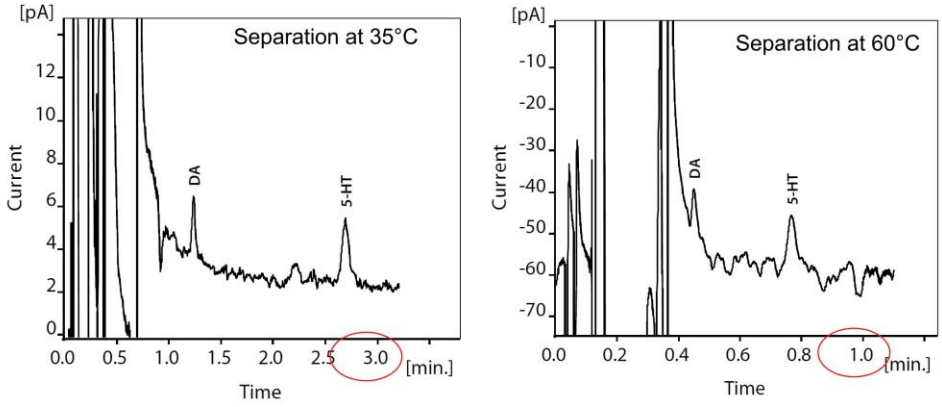

Figure 2. Chromatograms of a 100 pmol/L standard recorded at 35°C and 60°C.

Disclosures: M. Eysberg: None. **H. Brouwer:** None. **L.M. van Heerwaarden:** None. **N.J. Reinhoud:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.03/C29

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Dopamine neuron-derived IGF-1 controls dopamine neuron firing, skill learning and exploration

Authors: *A. PRISTERA[1], C. BLOMELEY[1], S. THRELFELL[2], D. BURDAKOV[1], S. CRAGG[2], F. GUILLEMOT[1], S.-L. ANG[1]
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Abstract: Midbrain dopamine (mDA) neurons in the ventral tegmental area (VTA) and substantia nigra compacta (SNc) play a fundamental role in cognitive processes, including reward processing, learning, motivation to engage in goal-orientated behaviours and regulate motor control. Dysfunctional mDA neurons in humans are associated with schizophrenia, anxiety, depression and drug addiction. In addition, SNc neurons degeneration leads to Parkinson's disease. Given that DA transmission is central to many cognitive processes and motor functions, it is pivotal that we develop a full understanding of mDA neuron regulation. Insulin-like growth factor 1 (IGF-1) is a hormone mainly secreted from the liver. It has been discovered that neurons within the brain are also able to synthesise and secrete IGF-1, which acts locally in a paracrine/autocrine manner. *Igf-1* transcripts have been found in mDA neurons, but functional information of mDA neuron-derived IGF-1 is virtually absent. We hypothesised that mDA neuron-derived IGF-1 acts as a neuropeptide, secreted in an activity dependent manner, able to shape mDA neuron functional properties and ultimately DA dependent-behaviours. We found, using *in situ* hybridisation and immunofluorescence on mouse midbrain sections, that mDA neurons expressing IGF-1 are distributed in salt-and-pepper fashion within the SNc and VTA. IGF-1 protein was found localised in cell bodies but not in axons. By functional studies on mDA neuron primary cultures we demonstrated that IGF-1 is secreted in an activity dependent manner. In addition, by employing false fluorescent neurotransmitter imaging on brain slices, we found that IGF-1 exposure to the ventral midbrain reduces DA release from mDA neurons. Using conditional knock-out (cKO) strategy, we addressed the role of mDA neuron-derived IGF-1 in adult mice. *Igf-1* cKO mice showed reduced IGF-1 signalling in the ventral midbrain, lower levels of phosphorylated tyrosine hydroxylase and DA content. mDA neurons in *Igf-1* cKO mice were less excitable, with decreased spontaneous firing, increased latency to fire action potentials and reduced number of action potentials fired in bursts. *Igf-1* cKO mice were hypoactive, showed reduced motor skill learning and lack of exploration in a novel environment. Together these data demonstrate that mDA neuron-derived IGF-1 is a modulator of mDA neurons activity and has a relevant role in controlling DA-mediated behaviours. Our results suggest that IGF-1 signaling in mDA neurons could represent a positive feedback loop to enhance DA transmission and facilitate DA-mediated behaviours.

Disclosures: A. Pristera: None. **C. Blomeley:** None. **S. Threlfell:** None. **D. Burdakov:** None. **S. Cragg:** None. **F. Guillemot:** None. **S. Ang:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.04/C30

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Fast and sensitive analysis of acetylcholine, GABA, glutamate, monoamines and metabolites using the UHPLC ALEXYS neurotransmitter analyzer

Authors: *L. M. VAN HEERWAARDEN[1], H.-J. BROUWER[1], M. EYSBERG[2], N. J. REINHOUD[1]
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Abstract: In the field of neurotransmitter analysis, there is a continuing demand for faster and more sensitive detection of analytes in microdialysis samples. The requirement to quantify picomolar concentration levels of neurotransmitters with good reproducibility and accuracy in small sample fractions (< 5 uL) is an analytical challenge.
The UHPLC ALEXYS™ Neurotransmitter Analyzer, based on the DECADE Elite (electrochemical detector) and SenCell (electrochemical flow cell), has been designed to meet the highest demands for detection sensitivity and performance. It comprises of a number of integrated system solutions, which have been developed for trace analysis of neurotransmitters. Parallel and serial detection schemes using multiple flow cells have been used instead of running sequential trials for different neurotransmitters. Dual or triple loop injection valves are applied with minimum sample consumption on parallel UHPLC systems under completely different conditions. Getting more information out of fewer samples is not only saving time and money but - in the end - also test animals.
Several examples of optimized assays for the analysis of acetylcholine, GABA, glutamate, monoamines and metabolites are shown to demonstrate the performance of the UHPLC ALEXYS™ Neurotransmitter Analyzer. Some features of these methods:
• Fast and efficient separations using sub-2µm particle columns
• Reproducible results (response RSD <2%)
• Detection limits down to 0.15 fmol monomoamines (30 pM; 5 µL), 3 fmol acetylcholine (0.3 nM; 10 µL), and 15 fmol GABA (10 nM; 1.5 µL)
• Basal levels of neurotransmitters can be quantified accurately (Fig. 1)

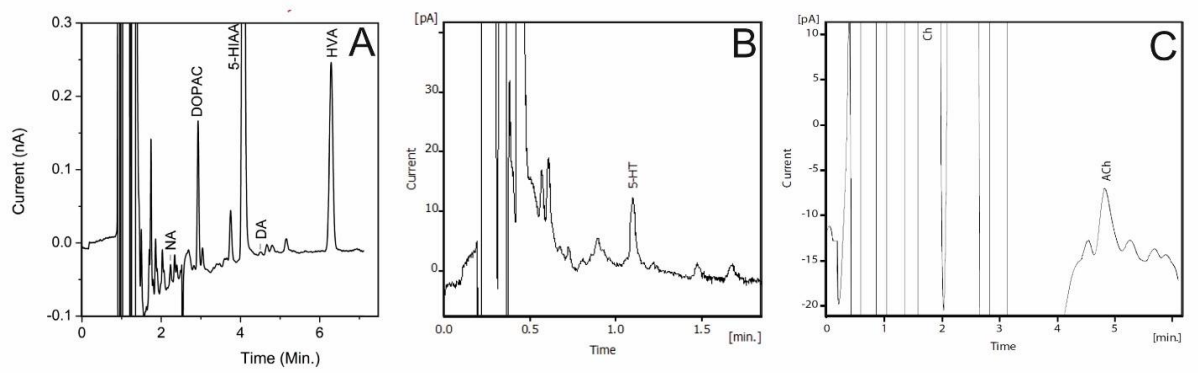

Figure 1. Example chromatograms of basal level rat dialysate samples using the ALEXYS Neurotransmitter analyzer:

(A) Analysis of monoamines and metabolites (2 µL injection volume).
Calculated concentrations in the dialysate sample 0.4 nmol/L NA, 5.8 nmol/L DOPAC, 55.5 nmol/L 5-HIAA, 0.1 nmol/L DA, 10.7 nmol/L HVA and 0.9 nmol/L 5-HT.

(B) Fast analysis of 5-HT (1.5 µL injection volume). Calculated concentration in the dialysate sample 0.54 nmol/L 5-HT.

(C) Analysis of acetylcholine (10 µL injection volume). Calculated concentration in the dialysate sample 1 nmol/L ACh.

Disclosures: H. Brouwer: None. **M. Eysberg:** None. **N.J. Reinhoud:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.05/C31

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Study was funded by Pierre Fabre Médicament

Title: Serotonin 5-HT_{1A} receptor biased agonists differentially facilitate rat social interaction under high luminosity conditions

Authors: M. A. VARNEY[1], R. DEPOORTÈRE[2], L. BARDIN[3], *A. NEWMAN-TANCREDI[2]
[1]Neurolixis, Dana Point, CA; [2]Neurolixis, Castres, France; [3]Pierre Fabre Médicament, Toulouse, France

Abstract: When placed in an unfamiliar and brightly-lit arena, two adult male rats that have not previously interacted display a low level of social interaction attributed to an anxiety-like state. The test has therefore been used to explore anxiolytic/anti-stress activity and we investigated the effects of serotonin 5-HT_{1A} receptor agonists displaying various activity profiles i.e. partial vs full agonist efficacy; and pre- vs post-synaptic 5-HT_{1A} receptor preferential activation by 'biased agonists'.
Adult, male, Sprague-Dawley rats were housed singly before starting the social interaction session. Thirty min before being placed in a Plexiglas arena, a pair of rats were injected with either vehicle or a given dose of diazepam (as a reference compound) or of one of the six 5-HT_{1A} receptor agonists listed in the Table. Time spent in social interaction (following, sniffing, playing) was recorded.
Time spent in social interaction was inversely correlated with light intensity, with values dropping nearly by half (212.6 +/- 18.8 vs 113.7 +/- 7.0 s) between 10 and 300 lux (measured at floor level). Under the high light intensity conditions (300 lux), diazepam showed a bell-shaped curve, with significant and mild effect (78% increase in interaction time above control) at 1 mg/kg i.p. only. Effects of the 5-HT_{1A} receptor agonists are summarized in the Table.
Full agonists, whether non-preferential (flesinoxan, 8-OH-DPAT) or preferential for pre-synaptic receptors (F13714), showed the strongest activity in this model. The preferential pre-synaptic receptor partial agonist, S15535, was active over a wide dose-range. In contrast, F15599 (a.k.a. NLX-101), a high-efficacy biased agonist that preferentially activates post-synaptic 5-HT_{1A} receptors, exhibited little activity. The clinical anxiolytic, buspirone, showed a marked effect despite its partial agonist activity at 5-HT_{1A} receptors, possibly due to other mechanisms (dopamine $D_{2/3}$ antagonism by buspirone or alpha2 antagonism by its principal metabolite, 1-PP). These data support the hypothesis that activity in this model is mediated by preferential full agonist activation of pre-synaptic 5-HT_{1A} receptors.

Effects of 5-HT1A agonists on rat social interaction under high luminosity conditions						
	F13714	F15599	S15535	Flesinoxan	8-OH-DPAT	Buspirone
Full or partial agonist	full	full	partial	full	full	partial
Pre- or post-synaptic	pre	post	(pre)	both	both	both
Dose-range (route)	0.0025-0.04 (ip)	0.01-0.63 (ip)	0.01-2.5 (ip)	0.04-0.63 (ip)	0.03-0.125 (sc)	0.3-1 (sc)
Active doses (mg/kg)	0.04	0.16	0.04 to 2.5	0.63	0.06, 0.125	0.63, 1
Max. effect vs control (dose)	117% (0.04)	59% (0.16)	74% (0.63)	117% (0.63)	158% (0.06)	159% (1)

Disclosures: **M.A. Varney:** A. Employment/Salary (full or part-time):; NEUROLIXIS. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PIERRE FABRE MEDICAMENT. Other; STUDY WAS FUNDED BY PIERRE FABRE MÉDICAMENT. **R. Depoortère:** A. Employment/Salary (full or part-time):; NEUROLIXIS. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PIERRE FABRE MEDICAMENT. Other; AUTHOR WAS EMPLOYED AT PIERRE FABRE MÉDICAMENT AT TIME OF EXPERIMENTS, STUDY WAS FUNDED BY PIERRE FABRE MÉDICAMENT. **L. Bardin:** A. Employment/Salary (full or part-time):; PIERRE FABRE MEDICAMENT. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PIERRE FABRE MEDICAMENT. Other; STUDY WAS FUNDED BY PIERRE FABRE MÉDICAMENT. **A. Newman-Tancredi:** A. Employment/Salary (full or part-time):; NEUROLIXIS. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PIERRE FABRE MEDICAMENT. Other; AUTHOR WAS EMPLOYED AT PIERRE FABRE MÉDICAMENT AT TIME OF EXPERIMENTS, STUDY WAS FUNDED BY PIERRE FABRE MÉDICAMENT.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.06/C32

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: DA043331-02

Title: RGS12 modulates dopamine transporter (DAT) function in ventral striatum via a kappa-opioid receptor (KOR)-dependent mechanism

Authors: *J. D. GROSS[1,2], S. W. KASKI[2], A. B. SCHROER[2], D. P. SIDEROVSKI[2], V. SETOLA[2,3]
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Abstract: RGS ("Regulator of G protein Signaling") proteins are best known for their activity on Gα-GTP subunits; *i.e.*, RGS proteins increase the rate of GTP hydrolysis and, thus, reassociation of Gα-GDP and Gβγ subunits. However, some RGS proteins exert additional functions on G protein-coupled receptor signal transduction pathways. RGS12 is one of the most complex RGS proteins known, with five distinct functional/protein-binding motifs. We recently reported (Gross *et al. Journal of Psychopharmacology*, 2018) that mice lacking RGS12 exhibit increased dopamine transporter (DAT) expression and dopamine uptake in ventral striatal tissue. However, the mechanism underlying this increased expression and function of DAT was unclear. Given previous reports that kappa-opioid receptor (KOR) activation positively regulates DAT activity, RGS12 is capable of inhibiting G protein activation downstream of KOR activation, and marked overlap of *Oprk1* and *Rgs12* mRNA expression, we investigated whether alterations in KOR activity and/or sensitivity might be responsible for the effect of RGS12 on DAT. We established that KOR antagonism reversed the augmented DAT uptake observed in RGS12-null ventral striatal synaptosomes. Further assays revealed that KOR expression and sensitivity are both increased in RGS12-null mice. Our new data establish a KOR-RGS12-DAT functional link in the ventral striatum.

Disclosures: J.D. Gross: None. **S.W. Kaski:** None. **A.B. Schroer:** None. **D.P. Siderovski:** None. **V. Setola:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.07/C33

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Stanford Neurosciences Institute NeuroChoice (RCM)
P50 DA042012 (KD, RCM)
F32 MH115668 (PH)

Title: Selective filtering of accumbal inputs by neuromodulators

Authors: *P. HOERBELT[1,2], D. J. CHRISTOFFEL[2], J. J. WALSH[2], B. D. HEIFETS[2,3], K. DEISSEROTH[4], C. RAMAKRISHNAN[4], L. KING-ADAS[2], R. C. MALENKA[2]
[1]Stanford Univ., Stanford, CA; [2]Dept. of Psychiatry and Behavioral Sci., Nancy Pritzker Lab., Stanford University School of Medicine, CA; [3]Dept. of Anesthesiology, Perioperative and Pain

Med., Stanford Univ. Sch. of Med., Stanford, CA; [4]Stanford Univ. Sch. of Med., Dept. of Bioengineering, Dept. of Psychiatry and Behavioral Sciences, and Howard Hughes Med. Inst., Stanford, CA

Abstract: The neuromodulators dopamine (DA) and serotonin (5-HT) influence a wide range of motivated behaviors but the detailed mechanisms by which they modify critical neural circuits remain largely unknown. The nucleus accumbens (NAc) is a key node for reward processing and receives dense DA and 5-HT innervation. To determine whether DA and 5-HT selectively modulate synaptic transmission in the NAc in an input-specific manner, we examined how these neuromodulators influence excitatory postsynaptic currents (EPSCs) generated by four of the major glutamatergic inputs to the NAc. In mice in which D1-MSNs are labelled by tdTomato, we injected two different adeno-associated viruses each encoding one of two optogenetic constructs (blue light-activated Chronos or red light-activated ChrimsonR) into pairs of the major NAc input areas: the ventral hippocampus, the medial prefrontal cortex, the basolateral amygdala, or the periventricular thalamus. After 5-6 weeks of incubation, we made whole cell voltage clamp recordings from NAc MSNs in acute slices prepared from these animals while optogenetically activating two independent sets of inputs. EPSCs generated by these different inputs were selectively depressed by DA or 5-HT in an input specific manner. Specifically, DA and 5-HT differentially regulated EPSCs generated by inputs from medial prefrontal cortex and periventricular thalamus compared to other inputs. These findings are recapitulated during drug-induced release of endogenous DA or 5-HT. Preliminary results suggest that the input-specific neuromodulator-evoked regulation of excitatory inputs occurs in either D1- or D2-MSN subpopulations. Moreover, consistent with previous work, measurement of EPSC paired pulse ratios suggests a presynaptic mechanism of neuromodulator action. Taken together, our findings suggest that DA and 5-HT selectively filter incoming excitatory input to the NAc. This input-specific modulation of excitatory synaptic transmission in the NAc may contribute to the discrete behavioral consequences of DA and 5-HT release in the NAc and provide insights that may prove useful for novel therapeutic approaches to the treatment of disorders involving pathological motivations.

Disclosures: P. Hoerbelt: None. **D.J. Christoffel:** None. **J.J. Walsh:** None. **B.D. Heifets:** None. **K. Deisseroth:** None. **C. Ramakrishnan:** None. **L. King-Adas:** None. **R.C. Malenka:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.08/C34

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH grant R01 DA019921 (GLF)
NSF grant IOS 0921969 (CAL)
NSF grant IOS 0921874 (KJR)

Title: Sex-steroid mediation of OCT3s as a mechanism for regulation of serotonin in the female rat medial hypothalamus and related behaviors

Authors: *J. L. SCHOLL[1,2], J. T. ROGERS[3], N. FENG[3], G. L. FORSTER[2,4], M. J. WATT[2,4], J. D. W. YAEGER[3], M. W. BUCHANAN[3], C. A. LOWRY[5], K. J. RENNER[3,1]
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Abstract: The dorsomedial hypothalamus (DMH) is believed to modulate stress through the integration of autonomic and neuroendocrine responses that mediate appropriate changes in behavior. Local delivery of corticosterone (200 ng/mL) combined with progesterone (P, (120 ng/mL) into the mediobasal hypothalamus, which includes the DMH and ventromedial hypothalamus, of adult, ovariectomized rats systemically primed with estradiol (E_2, 5 µg) markedly and rapidly increases extracellular serotonin (5-HT) concentrations. Corticosterone may exert rapid effects on 5-HT by blocking organic cation transporter 3 (OCT3), membrane transporters that are highly expressed in the DMH. Since OCT3 is believed to function as a clearance mechanism for monoamines, including 5-HT, it is possible that stress-induced increases in corticosterone may exert behavioral effects by prolonging 5-HT signaling. Normetanephrine (NM), a norepinephrine metabolite that blocks OCT3, was delivered via reverse microdialysis to determine if the effect on DMH 5-HT was similar to corticosterone in adult, ovariectomized rats primed with E_2 and P. Consistent with the corticosterone effect, 5-HT was significantly increased by NM perfusion within the first post-treatment dialysate sample. We then tested behavioral effects of corticosterone and NM in the DMH, hypothesizing that blocking OCT3 would increase the expression of fear- and anxiety-related behaviors and, as a result, acutely suppress the expression of the lordosis reflex. Anxiety-like behavior was tested using the open-field test and the elevated plus-maze (EPM). Ovariectomized rats primed with E_2 and P were treated with bilateral infusions of corticosterone (48 pg/0.5 µL), NM (45 ng/0.5 µL) or vehicle (V) into the DMH 10 min prior to behavioral evaluation. Surprisingly, neither corticosterone nor NM infusions into the DMH affected anxiety-like behaviors. However, infusions of both OCT3 blockers into the DMH reversibly suppressed sexual behavior. To examine the role of steroid-priming on OCT3, western blots were performed on DMH tissue. OCT3 was upregulated in the DMH of rats primed with E_2 + P when compared to E_2 +V and V + V controls. Taken together, these results suggest that steroid modulation of OCT3-mediated neurotransmitter clearance can rapidly and reversibly alter the expression of behavior.

Disclosures: J.L. Scholl: None. **J.T. Rogers:** None. **N. Feng:** None. **G.L. Forster:** None. **M.J. Watt:** None. **J.D.W. Yaeger:** None. **M.W. Buchanan:** None. **C.A. Lowry:** None. **K.J. Renner:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.09/C35

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Intramural Research

Title: An intracellular trace amine-associated receptor 1 (TAAR1) couples to different G-protein pathways in distinct subcellular compartments to initiate the changes in neurotransmitter transporter trafficking elicited by amphetamines

Authors: *S. M. UNDERHILL[1], S. S. SCOTT[3], S. G. AMARA[2]
[1]Lab. of Mol. and Cell. Neurobio., [2]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Natl. Inst. of Mental Hlth., Natl. Instittues of Hlth., Bethesda, MD

Abstract: Amphetamine, amphetamine-derivatives and trace amines can modulate dopaminergic and glutamatergic signaling through internalization of the dopamine and glutamate transporters, DAT and EAAT3. Amphetamine enters dopamine neurons through the DAT and once in the cytoplasm it activates the intracellular G-protein-coupled receptor (GPCR) TAAR1. Near the endoplasmic reticulum, TAAR1 signals through a Gα-subunit, G13, which leads to the activation of the small GTPase, RhoA, stimulation of the Rho-associated protein kinase, ROCK, and internalization of the plasma-membrane transporters DAT and EAAT3. Amphetamine also activates TAAR1 receptors coupled to Gs, activating PKA which in turn phosphorylates RhoA at a serine residue to inactivate RhoA. Through this mechanism, TAAR1 mediates amphetamine-mediated RhoA activation, inactivation and transporter internalization. We used FRET sensors for PKA (AKAR4) as well as a new enhanced RhoA sensor to investigate amphetamine-mediated signaling through these two biochemical cascades. Using targeting motifs, we were able to distinguish signaling near the ER, golgi, nucleus, cytoplasm, mitochondria, synaptic vesicles and lipid-raft and non-lipid-raft membranes. RhoA and PKA pathways activated by TAAR1 display distinct subcellular profiles of activation and reveal a striking compartmentalization of amphetamine effects within the cell.

Disclosures: S.M. Underhill: None. **S.S. Scott:** None. **S.G. Amara:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.10/C36

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: O-glycosylation of β2-adrenergic receptor regulates agonist-mediated signalingin hek293 cells

Authors: *S. RYU, T. SHIM, C. MOON
Dept. of Cognitive & Brain Sci., DGIST, Daegu, Korea, Republic of

Abstract: The β_2-adrenergic receptor (β_2AR) is a G protein-coupled receptor (GPCR) that binds to norepinephrine and epinephrine to mediate the diverse physiological responses in the sympathetic nervous system. A majority of the β_2AR known as a glycoprotein which possess N-glycosylation at its N-terminal, and these β_2AR also undergoes other reversible post translational modifications (PTMs) upon agonist stimulation. O-glycosylation of GPCRs also have been suggested, but rarely studied about its effects on GPCR mediated signaling. Here, we examined agonist mediated signal transduction of O-glycosylation modified β_2AR in HEK293 cells. Eventually, we are interested in a transient stage which is followed by “switch-on” to “switch-off” state in PTM-dependent receptor cycling. To identify a novel regulatory mechanism of reversible receptor cycling, we suggested O-glycosylation as a regulator considering its competitive modules with phosphorylation. By regulating key enzymes of O-glycosylation cycling, we demonstrated that elevated intracellular O-glycosylation levels delays receptor internalization from the plasma membrane. In addition, the receptor expressed in O-glycosylation deficient cells showed destabilized within the membrane. This finding of O-glycosylation of β_2ARs is unprecedented and hints a possibility of specific biological roles in GPCR signaling such as signal termination; desensitization, receptor internalization, and receptor stability.

Disclosures: S. Ryu: None. **T. Shim:** None. **C. Moon:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.11/C37

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Serotonin 5-HT1B receptors decrease lateral inhibition in the mouse striatum by reducing the probability of GABA release from spiny projection neurons

Authors: *S. POMMER, J. R. WICKENS
Neurobio. Res. Unit, Okinawa Inst. of Sci. and Technol., Onna-son, Japan

Abstract: Striatal spiny projection neurons (SPNs) make inhibitory synaptic connections with each other via collaterals of their main axon, forming a local lateral inhibition network. Previous studies have shown that serotonin, acting via the 5-HT1B receptor, modulates neurotransmitter release from terminals in the target nuclei of SPN projections. Despite this well accepted function, the role of 5-HT1B receptors in lateral inhibition locally among SPNs remains poorly understood. To address this issue, whole-cell patch clamp recordings were made from SPNs in acute brain slices, while optogenetically stimulating presynaptic SPNs. Inhibitory postsynaptic currents (iPSCs) mediated by GABA were measured before and after application of a 5-HT1B receptor agonist. Activation of 5-HT1B receptors significantly reduced the amplitude of postsynaptic iPSCs in SPNs (Fig. 1, ***: p = 0.0003, **: p = 0.005, *: p = 0.0179). This effect was due to a reduced presynaptic release probability of GABA (Fig. 2). Collectively, these results suggest a prominent role of serotonin in modulating lateral inhibition among striatal neurons.

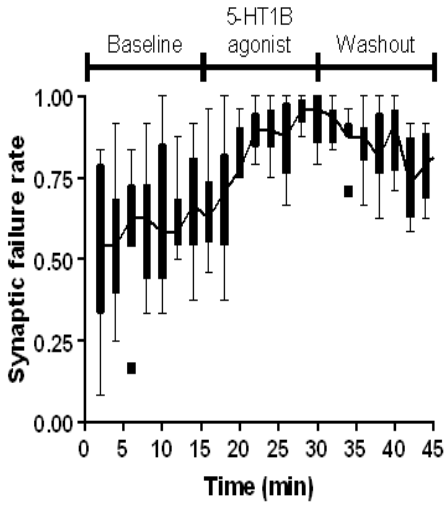

Figure 2: Effect of 5-HT1B activation on failure rate of presynaptic SPNs terminals

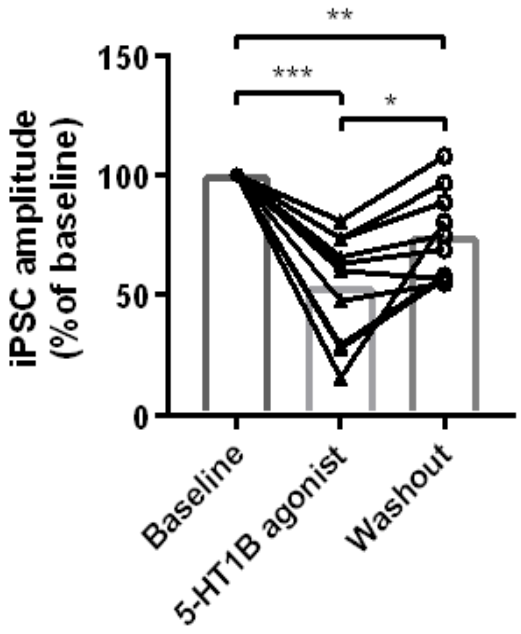

Figure 1: Effect of 5-HT1B activation on the amplitude of SPN-SPN iPSCs.

Disclosures: S. Pommer: None. **J.R. Wickens:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.12/C38

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DA042737

Title: Cholesterol-independent effects on serotonin transporter regulation: Role of simvastatin

Authors: *C. M. MITCHELL[1], A. SCHROERING[2], B. K. YAMAMOTO[3]
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Abstract: The serotonin transporter (SERT) is localized in cholesterol-rich microdomains within the plasma membrane. These microdomains are thought to modulate SERT protein-protein interactions and post translational modifications. However, the mechanism of membrane

cholesterol on SERT function in the brain has yielded conflicting results. No studies have examined the role for cholesterol biosynthetic intermediates in regulating SERT function. To investigate the role of cholesterol and its biosynthetic intermediates on neuronal SERT function, serotonergic RN46A-B14 cells were stably overexpressed with myc-tagged SERT. Simvastatin was used to block synthesis of cholesterol and cholesterol biosynthetic intermediates by blocking the rate limiting enzyme HMGCoA reductase. Serotonin (5-HT) transport activity was assayed by measurement of intracellular 5-HT content after incubation of cells with 5-HT. Simvastatin decreased total cholesterol in the cells and disrupted lipid rafts within the plasma membrane but surprisingly, increased 5-HT uptake in a fluoxetine-sensitive manner. This was evidenced by a shift in the Km but not the Vmax for 5HT. To examine the role of biosynthetic intermediates downstream of HMGCoA reductase in the enhanced 5HT uptake, mevalonate was added to the medium in the presence of simvastatin and completely blocked the enhanced uptake, while repletion of cholesterol with squalene did not. The addition of the isoprenylation intermediate, farnesyl pyrophosphate also blocked the enhanced uptake. These results indicate that simvastatin enhances 5-HT uptake via SERT in a manner dependent on the inhibition of the farnesylation pathway but independent of cholesterol *per se*. In addition, further *in vivo* studies showed enhanced 5-HT uptake in the prefrontal cortex of rats administered 10 mg/kg/day simvastatin intraperitoneal for 7 days. Collectively, these data support a role for the farnesylation pathway in regulating SERT in the brain.

Disclosures: C.M. Mitchell: None. **A. Schroering:** None. **B.K. Yamamoto:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.13/D1

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: UC Riverside IC funds
NIH R01NS089652
NIH 1R01NS104834

Title: Noradrenergic modulation of somatosensory cortex during tactile detection

Authors: *H. YANG[1], B. A. BARI[2], J. Y. COHEN[3], D. H. O'CONNOR[4]
[1]Univ. of California, Riverside, Riverside, CA; [2]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [3]Neurosci., Johns Hopkins Univ., Baltimore, MD; [4]Dept. of Neurosci., The Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Understanding the variability associated with perception and decision-making remains a fundamental challenge for neuroscience. Neurons in mouse primary somatosensory (S1) cortex

exhibit choice-related activity during simple tactile detection tasks (Sachidhanandam et al., 2013; Yang et al., 2016). What are the underlying neural processes that influence the occurrence of successes and failures of stimulus detection? The neuromodulator norepinephrine (NE), whose ascending inputs to cortex arise mainly from the brainstem nucleus locus coeruleus (LC), has been proposed to have a critical role in regulating multiple aspects of behavior, including perception, attentiveness and decision-making. However, we have limited understanding of its function in modulating even simple aspects of sensory processing during perceptual behaviors. Here, we address this issue by performing single-unit recordings from optogenetically identified LC-NE neurons (n = 38) during a tactile detection task. Applying an ideal observer, receiver-operating characteristic analysis, we found that ~70% of our recorded LC neurons showed spiking that discriminated successes vs. failures of tactile stimulus detection, i.e. Hits vs Misses. Specifically, lower pre-stimulus "tonic" activity (LC spike rate measured prior to stimulus onset) predicted successful detection, as did higher stimulus-evoked "phasic" activity (spike rate measured in a brief window immediately after stimulus onset). In separate experiments, we performed simultaneous intracellular (whole-cell) recordings in S1 and extracellular recordings in LC (n = 26 paired recordings). We found that LC spiking was positively correlated with membrane potential fluctuations of S1 neurons, with LC spikes preceding the peaks of S1 depolarizations by ~100 ms. Our results suggest that the LC-NE system modulates somatosensory information processing during touch perception.

Disclosures: H. Yang: None. **B.A. Bari:** None. **J.Y. Cohen:** None. **D.H. O'Connor:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.14/D2

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant AG043458

Title: Validating PET dopamine receptor imaging with microPET and microdialysis

Authors: *M. AUMANN, M. BUBSER, A. SHEKARA, C. JONES, D. ZALD
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Abstract: Dopamine (DA) is implicated in neuropsychiatric disorders ranging from Parkinson's disease to schizophrenia and addiction. DA receptors are the primary target of endogenous DA, and as such, are a key determinant of DA functioning in different brain regions. DA D2-like receptors are widely expressed throughout the brain, with the highest levels in the striatum. Unfortunately, current [18F]-Fallypride Positron Emission Tomography (PET) data interpretation is constrained by limitations in our understanding of the extent to which

endogenous DA influences D2-like DA receptor availability. In this study, we have addressed the methodological problem in interpretation of [18F]-Fallypride data by using a combination of *in vivo* microdialysis to measure endogenous DA and microPET to measure D2 receptor availability (binding potential). Measurement of DA D2-like binding potential using microPET and the high affinity D2 radioligand [18F]-Fallypride was performed at baseline and following pharmacological depletion of DA with intraperitoneal resperine and alpha-methyl-para-tyrosine (AMPT) allowing assessment of the level of D2 receptor availability, both with, and in the absence of, endogenous DA. Further, microdialysis was performed to measure levels of endogenous DA levels, both at baseline and in the depleted state, to estimate the extent to which extracellular DA was depleted, and the extent to which changes in binding potential were associated with the extent of DA depletion . The goal of this research project is to develop a translational model using microPET to link the precision of preclinical pharmacological manipulation of the mesolimbic DA system to human clinical PET research measuring DA effects. This work has potential for drug development, and, by moving directly between an animal and human model, can further facilitate the ability to use measurable individual differences in D2 receptor availability between patients to help optimize individualized treatment plans.

Disclosures: M. Aumann: None. **M. Bubser:** None. **A. Shekara:** None. **C. Jones:** None. **D. Zald:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.15/D3

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant MH093567
NIH Grant U54HD083211

Title: Steady-state monoamine measures reveal diverse neuromodulatory compartments across macaque cortex

Authors: *N. J. WARD, W. ZINKE, J. J. COPPOLA, A. A. DISNEY
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Abstract: Early views of how subcortical neuromodulatory nuclei exert influence over cortex assert that these modulatory systems provide a global rather than local signal across cortex. The ability to examine hypotheses related to global vs. local signaling require measurement of these neuromodulatory molecules across cortical regions. Here we present steady-state data for monoamine concentrations measured from multiple regions of the macaque monkey cortex. We

collected postmortem tissue punches from the unfixed, frozen brains of four adult, male macaques. Using liquid chromatography/mass spectrometry, we analyzed samples from visual, parietal, and somatomotor cortical regions for concentrations of dopamine, noradrenaline, and serotonin. Our data indicate that measured monoamine tissue concentrations cannot be predicted simply by univariate proxies such as prior monoaminergic innervation and receptor pattern data. Across our selected cortical regions, dopamine and noradrenaline exhibit a rostral-to-caudal gradient while serotonin does not. Using hierarchical clustering of our monoamine concentration data, we find that areas cluster by related function: visual and parietal areas comprise one cluster, while sensorimotor areas comprise a second cluster. By plotting our three-dimensional monoamine concentration data, we similarly see that regions group in this multidimensional, multimodulator space, with functionally-related cortical regions grouping together. To test whether neuromodulatory signaling truly exhibits local variations, we propose supplementing this data with future in vivo studies to determine how much our steady-state data is reflected by concentrations measured extracellularly in awake, behaving animals. We also propose that these studies should be conducted with concurrent behavior so as to construct neurochemical state-spaces that define brain or behavioral states using multidimensional, dynamical concentration data.

Disclosures: N.J. Ward: None. **W. Zinke:** None. **J.J. Coppola:** None. **A.A. Disney:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.16/D4

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: California NanoSystems Institute Challenge Grant

Title: The deep structure of the brain serotonergic matrix

Authors: M. T. HINGORANI[1], K. C. MAYS[1], N. DETERING[2], *S. JANUSONIS[1]
[1]Dept. of Psychological and Brain Sci., [2]Dept. of Statistics and Applied Probability, Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Nearly all neural processes in vertebrate brains are physically embedded in a dense matrix of axons (fibers) that release 5-hydroxytryptamine (5-HT, serotonin). Many studies have investigated densities of these fibers in the healthy and diseased brain, but the deep structure of the serotonergic matrix remains poorly understood. Our research focuses on its three aspects: (1) the stochastic properties of single serotonergic fibers, (2) the potential contribution of blood platelets to serotonergic signaling, and (3) the interaction of serotonergic fibers with microglia. Analysis 1: We immunolabeled serotonergic fibers in the mouse brain, traced them in the

primary somatosensory cortex (in Fiji ImageJ), and modeled their trajectories as a random walk based on the von Mises-Fisher probability distribution (with the concentration parameter κ). We obtained a robust estimate of the concentration parameter and also showed that its value can vary across brain regions. Analysis 2: We selectively depleted platelets in adult mice and measured (with quantitative RT-PCR) the mRNA levels of several 5-HT receptors and glia-specific proteins in the cerebral cortex and basal nuclei one day after the depletion. The analysis showed that the expression of some of the genes may be affected by the lack of platelets, suggesting that peripheral 5-HT may contribute to brain serotonergic signaling. Analysis 3: Using multiple-label immunohistochemistry with confocal and super-resolution (Stimulated Emission Depletion (STED)) microscopy, we investigated colocalization of serotonergic varicosities and microglial processes in the mouse brain. We found contacts between these two ubiquitous brain elements and obtained information about their spatial arrangements with nanometer resolution. These findings advance the current understanding of the fine organization of the serotonergic matrix, a key structure in the biology of several mental disorders, including Autism Spectrum Disorder, Major Depressive Disorder, and schizophrenia.

Disclosures: M.T. Hingorani: None. **K.C. Mays:** None. **N. Detering:** None. **S. Janusonis:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.17/D5

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: FONDECYT grant N° 1150244

Title: Orexin regulates the increase in dopamine extracellular levels in the ventral tegmental area induced by the stimulation of the lateral septum

Authors: I. M. VEGA-QUIROGA, H. E. YARUR, *K. GYSLING
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Abstract: Dopaminergic neurons of the ventral tegmental area (VTA) are important in goal directed behavior. These neurons are highly controlled by GABAergic interneurons and by glutamatergic and GABAergic inputs from several brain areas. In addition, neuropeptides have a modulatory role on the activity of dopaminergic neurons, such orexin (OX). Previously, we have shown that the lateral septum (LS) connects with the antero-ventral region of the VTA and that LS stimulation inhibits GABAergic interneurons, inducing the activation of VTA dopaminergic neurons (Vega-Quiroga et al, 2017). The LS has also projects to the OX neurons of the lateral hypothalamus (Yoshida et al, 2006). Thus, we decided to study whether orexin plays a role in the

increase in VTA dopamine extracellular levels induced by lateral septum stimulation. To this end, we performed dual probe *in vivo* microdialysis experiments in anesthetized rats. One probe was installed in the LS to stimulate it with high potassium solution and the other probe was installed in the VTA to measure glutamate, GABA and dopamine extracellular levels. The results show that intra VTA infusion of SB-334867 (orexin-A antagonist) significantly decreased VTA dopamine extracellular levels and blocked the activation of dopaminergic neurons induced by LS stimulation. The block in the VTA dopamine increase by LS stimulation was also observed in the presence of indiplon (an alpha1 subunit GABA-A allosteric modulator), which has been described to increase VTA dopamine extracellular levels induced by LS stimulation (Vega-Quiroga et al, 2017). Our results suggest that OX modulation of VTA dopaminergic neurons is part of a complex interaction of the LS activity over the VTA. Further studies should address whether the observed changes in VTA dopamine extracellular levels induced by the OX antagonist are due to its effect in the direct connection of the LS to VTA or they depend on the connection of the LS through the lateral hypothalamus.

Disclosures: I.M. Vega-Quiroga: None. **H.E. Yarur:** None. **K. Gysling:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.19/D7

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Canadian Institutes of Health Research (CIHR)
Parkinson Canada Society
Fonds de Recherche en Santé du Québec (FRQS)

Title: Molecular and neurochemical heterogeneity of dopaminergic terminals

Authors: *C. DUCROT[1], C. MICHAUD-TARDIF[1], A.-S. RACINE[1], S. BURKE NANI[1], M.-J. BOURQUE[1], B. G. ROBINSON[2], J. T. WILLIAMS[2], L.-E. TRUDEAU[1]
[1]Départements de Pharmacologie et Physiologie et de Neurosciences, GRSNC, Univ. de Montréal, Montreal, QC, Canada; [2]Vollum Inst., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Dopamine (DA) neurons of the substantia nigra compacta (SNc) and ventral tegmental area (VTA) establish a complex axonal arborization comprising axon terminals that appear to be mainly non-synaptic in structure, as revealed by ultrastructural observations. Our objective was to test the hypothesis that the molecular make-up of synaptic and non-synaptic terminals established by DA neurons is different. To address this question, we developed an efficient *in vitro* system in which primary DA neurons prepared from the SNc or VTA of TH-GFP transgenic mice were placed in co-culture with striatal neurons. Considering previous work

showing that subsets of DAergic neurons are able to package and release glutamate or GABA at some of their terminals, we took advantage of the postsynaptic markers PSD95 and gephyrin to characterize the axonal domain of these neurons. Using a transgenic mouse with a GFP-tagged D2 receptor (D2R-KI) we also evaluated the proportion of DAergic terminals close to D2R clusters. Furthermore, considering that the development of synaptic contacts in most neuron implicates trans-synaptic proteins such as neurexins and PTPsigma, we used overexpression and downregulation strategies to specifically examine the contribution of such proteins to synapse formation by DA neurons. Immunocytochemistry and confocal microscopy were used to examine the colocalization of presynaptic markers including synaptotagmin 1 (SYT1), VMAT2 or Bassoon and postsynaptic markers including PSD95 or Gephyrin and D2R. Our results show that *in vitro*, DA neurons of the SNc and VTA establish a large density of axonal varicosities, the majority of which contain the presynaptic markers SYT1 and VMAT2. Using FM1-43, an activity-dependent marker of vesicular cycling, we found that the majority of such varicosities were active. However, only a minority were found to be associated with the presynaptic active zone marker Bassoon or with the postsynaptic markers PSD95 or gephyrin. Lentiviral overexpression of Neurexin 1α but not Neurexin 3α increased the formation of excitatory and inhibitory synapses established by DA neurons by approximately 50%. We also found that downregulation of PTPsigma decreased the proportion of excitatory synapses established by DA neurons by approximately 40%.

Disclosures: C. Ducrot: None. **C. Michaud-Tardif:** None. **A. Racine:** None. **S. Burke Nani:** None. **M. Bourque:** None. **B.G. Robinson:** None. **J.T. Williams:** None. **L. Trudeau:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.20/D8

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Functional domains in the dopamine transporter intracellular C-terminus

Authors: *J. GARCIA-OLIVARES, S. A. WASSERMAN, C. FENOLLAR-FERRER, S. G. AMARA
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Abstract: Neurotransmission by monoamines (dopamine, serotonin, and norepinephrine) is altered in complex neurologic and psychiatric conditions such as Parkinson's disease, depression, attention-deficit hyperactivity disorder and substance use disorders. For dopamine, the dopamine transporter (DAT, SLC6A3) clears extracellular dopamine through a sodium-coupled transport mechanism. The functions of DAT are regulated by different mechanisms including phosphorylation, ubiquitination, and protein-protein interactions to the intracellular N-

and C-termini. In the past five years, several high-resolution structures of members of this family of transporters have been resolved, including those for Drosophila DAT (dDAT) and the human serotonin transporter (hSERT). These structures have provided relevant information about ligand and antidepressant binding sites, but have provided no structural information on the intracellular N- and C- termini. To explore the possible structural arrangements of the intracellular regions, we used an in *silica* approach to model the cytosolic domains of hDAT. The full-length models were built using a specific designed protocol in which ab initio and template-based molecular modelling techniques were combined. Here, we present evidence that the DAT C-terminus contains structural domains that control transporter function. We performed systematic alanine scanning along the C-terminus using site-directed mutagenesis. To study the role of these residues in transport and trafficking events these hDAT mutants were transfected into HEK-293 cells and tested in a radiolabeled uptake assay using [3H]-DA in parallel with surface-labeling using biotin reagents. First, we found that alanine substitutions in the C-terminus (from E598 to D605) produced only modest alterations in function and with no changes in surface expression levels. Second, we found that charge reversal mutations such as D600K, R601D and E602R exhibit a significant loss in function when compared to substitutions where the charge was neutralized (D600N, R601N, E602N). Our data suggest that the C-terminus may interact with transmembrane regions of the transporter or other interacting proteins through a dipole-dipole interaction that is critical for uptake activity. The study presented here shows that intracellular regions such as the C-terminus are not only sites for recruitment of kinases or regulatory proteins, but they also contain structural information that in coordination with the transmembrane core regulates transport activity.

Disclosures: J. Garcia-Olivares: None. **S.A. Wasserman:** None. **C. Fenollar-Ferrer:** None. **S.G. Amara:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.21/D9

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: CIHR

Title: Investigation of the developmental downregulation of Vglut2 expression in developing DA neurons: Implication of the dorsal striatum

Authors: *W. M. KOUWENHOVEN[1], C. DUCROT[2], M.-J. BOURQUE[1], J.-F. POULIN[3], R. AWATRAMANI[4], L.-E. TRUDEAU[2]
[1]Dept. of pharmacology and physiology, Univ. de Montréal, Montreal, QC, Canada;
[2]Departments of pharmacology and neurosciences, GRSNC, Univ. De Montréal, Montreal, QC,

Canada; [3]Neurosciences, Northwestern Univ. - Chicago, Chicago, IL; [4]Northwestern Univ., Chicago, IL

Abstract: In Parkinson's disease, the most vulnerable neurons are found in the ventral tier of the substantia nigra (SN), while the adjacent dopamine (DA) neurons of the ventral tegmental area (VTA) are mostly spared.
Although a large proportion of adult VTA DA neurons express Vglut2, a vesicular glutamate transporter, and release glutamate as a second neurotransmitter in the striatum, adult SN DA neurons typically do not have this capacity. To better understand the contribution of Vglut2 expression to the functions and vulnerability of DA neurons, we aim to better understand the developmental expression pattern of Vglut2 in DA neurons and the mechanisms that regulate expression of this transporter in DA neurons.
Using an intersectional genetic approach based on Vglut2-Cre and TH-Flpo drivers, we first find that a large majority of dopaminergic neurons expressed Vglut2 at some point in their development. Using fluorescent in situ hybridization, we found that already at E14.5, subset-specific differences can be found, with Vglut2 transcript still found in caudomedial DA neurons, but with very limited expression in rostrolateral DA neurons. We are presently looking at the time course of this developmental downregulation of Vglut2. Together, these data suggest that the glutamatergic neurotransmitter identity of DA neurons is gradually suppressed during late embryonic development a finding that is in line with our previous observations showing that the percentage of DA neurons expressing Vglut2 decreases from E16.5 to P0 (Fortin et al., 2012).
Intriguingly, a substantial component of the innervation of the striatum by DA neurons develops just before birth, and as such temporally overlaps with the repression of Vglut2 expression in a large portion of DA neurons. We therefore hypothesize that innervation of the striatum by DA neurons provides a signal required for postnatal repression of Vglut2.
To test this hypothesis, we are presently taking advantage of a primary DA neuron striatal co-culture system, in combination with single-cell qPCR or fluorescence-activated cell sorting and population-based qPCR to examine signals that regulate Vglut2 expression. We find that Vglut2 expression is globally repressed when DA neurons are co-cultured with dorsal striatal cells, but not with ventral striatal cells.
The contribution of contact-dependent and secreted signals is presently being investigated.
These experiments shed new light on the mechanisms that regulate the neurochemical identity of DA neurons during development. Ongoing experiments might also provide new insights into the plasticity of the neurochemical identity of DA neurons during pathological conditions.

Disclosures: C. Ducrot: None. **M. Bourque:** None. **J. Poulin:** None. **R. Awatramani:** None. **L. Trudeau:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.22/D10

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant R01AA016022
NIH Grant K99AA025991
DICBR ZIA AA000407
NIH Grant U01NS090604

Title: Direct simultaneous comparison of a novel fluorescent dopamine sensor (dLight) with fast-scan cyclic voltammetry in cortex and striatum

Authors: *A. G. SALINAS[1,2], Y. MATEO[1], S. M. AUGUSTIN[1], J. O. LEE[1], T. PATRIARCHI[3], L. TIAN[3], D. M. LOVINGER[1]
[1]Natl. Inst. On Alcohol Abuse and Alcoholism, Rockville, MD; [2]Dept. of Bioengineering, George Mason Univ., Fairfax, VA; [3]Dept. of Biochem. and Mol. Med., Univ. of California Davis, Davis, CA

Abstract: Dopamine (DA) is critically involved in several neurobiological processes and disorders including movement, learning, schizophrenia, and substance use disorders. Thus, the ability to monitor DA release during behavioral tasks or in response to salient stimuli is of the utmost importance. Fast-scan cyclic voltammetry (FSCV) is an electrochemical method used to detect DA on a subsecond time scale. A limitation of FSCV is the inability to distinguish between monoamine neurotransmitters (MNTs) with similar electrochemical signatures (e.g. DA and norepinephrine). This limitation has precluded FSCV examination of brain regions where different MNTs are present (e.g. cortex). To address these limitations, intensity-based genetically-encoded indicators with specific binding for different MNTs have been developed, including a dopamine sensor, dLight1. Sensitive optical readout of changes in DA were achieved by directly coupling the DA binding-induced conformational changes in human DA receptors to changes in fluorescence intensity of circularly permuted GFP. We have characterized the utility of dLight1, by comparing fluorescent photometric and FSCV responses in brain slices. We found that dLight1 detects lower levels of DA relative to FSCV in striatal brain slices. This may facilitate in vivo recording of DA activity in regions with low DA release levels. We also found that with low frequency burst stimulations, dLight1 could more faithfully track individual stimulations than FSCV. Application of cocaine increased the decay time of single-stimulus induced responses measured with both dLight1 and FSCV (reflecting dopamine uptake inhibition) but did not affect the peak height of the dLight1 signal. This cocaine effect difference is likely due to dLight1 trafficking to synaptic and extrasynaptic sites and thus reflects synaptic

and extrasynaptic DA levels. In contrast, FSCV is a measurement of DA overflow out of synapses and is thus more affected by drugs that influence DA uptake without affecting DA release. We also assessed DA release in M1 and M2 cortical regions (areas where DA release is difficult to assess with FSCV) and found that the release properties of cortical DA terminals differ from those of striatal DA terminals in that a single stimulation was not sufficient to induce DA release. However, burst stimulation reliably induced DA release. Further studies characterizing cortical DA release are underway. In both cortex and striatum, we verified the molecular and pharmacological specificity of dLight1 by applying a D1 receptor antagonist to abolish the dLight1 signal. Altogether, results suggest that dLight1 may serve as a viable alternative to FSCV.

Disclosures: A.G. Salinas: None. **Y. Mateo:** None. **S.M. Augustin:** None. **J.O. Lee:** None. **T. Patriarchi:** None. **L. Tian:** None. **D.M. Lovinger:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.23/D11

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: DA021213

Title: Identification of residues involved in the dopamine transporter-Gbetagamma functional interaction

Authors: *J. A. PINO, G. M. HIDALGO, M. QUIROZ, G. E. TORRES
Dept. of Pharmacol. and Therapeut., Univ. of Florida, Gainesville, FL

Abstract: The dopamine transporter (DAT) plays a crucial role in the regulation of brain dopamine (DA) homeostasis. Through re-uptake of DA, DAT serves two important functions: the termination of synaptic transmission at dopaminergic terminals, and the replenishment of vesicular DA pools. In addition to uptake, DAT can also function to release DA. This process, which is referred to as DAT-mediated efflux, is the mechanism used by potent and highly addictive psychostimulants, such as amphetamine and its analogues, to increase extracellular DA levels in motivational and reward areas of the brain. It has long being recognized that DA neurons release DA through exocytotic and non-exocytotic processes. However, the exact mechanism by which physiological signals or psychostimulants, such as amphetamine, induce DA efflux through DAT still remains a complex and not completely understood area of research. Thus, examining the basic mechanism(s) that affect DA efflux through DAT is critical for both understanding fundamental aspects of DA regulation and clinical intervention in DA-related brain disorders associated with the therapeutic use and abuse of psychostimulants. Recently, we

discovered that the βγ subunits of G protein (Gβγ) bind to the intracellular carboxy-terminus of DAT and regulate transporter activity. More importantly, we have observed that activation of Gβγ promotes DAT-mediated DA efflux. However, the amino acid residues involved in Gβγ interaction site(s) in DAT and their role in transporter regulation remain largely unknown. Here, we used a combination of mutagenesis, immunoprecipitations, and functional assays to identify the Gβγ binding site on DAT and its role in transporter regulation. Preliminary functional studies are consistent with previous biochemical evidence indicating that the sequence FREKL located in the carboxy-terminus of DAT plays a role in Gβγ interaction with DAT and promotion of DA efflux. Thus, this study provides a starting point for a further detailed characterization of the DAT-Gβγ interaction and a better understanding of its contribution to DAT-mediated efflux

Disclosures: J.A. Pino: None. **G.M. Hidalgo:** None. **M. Quiroz:** None. **G.E. Torres:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.24/D12

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: GVSU-CLAS Microscopy Facility
GVSU-OURS travel grant to BV and LR

Title: Localization of histidine decarboxylase and histamine in peripheral and central neural tissues of *Drosophila melanogaster*

Authors: B. VANDENBERG[1], L. ROBB[2], J. HOWE[2], *M. G. BURG[3]
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Abstract: Histamine (HA) is the neurotransmitter used by photoreceptors in *Drosophila* and is synthesized by the enzyme histidine decarboxylase (HDC), encoded by the *Hdc* gene. The study of *Hdc* mutants in Drosophila that are defective in HA synthesis to understand the role of HA in a number of processes has relied on HA immuno-detection (or HPLC) to identify the presence or absence of HA. While it is known that HDC activity is initially needed by photoreceptors to synthesize HA, the regulation of HDC and the location of HA synthesis are not well understood. Determining the location of the HDC protein in *Drosophila* has been hampered by the inability to detect HDC immunologically, due to cross-reactivity with other decarboxylases and lack of a *Drosophila*-specific HDC antiserum. As the HDC protein is known (in other organisms) to be post-translationally modified through the removal of both the N- and C-termini, an internal epitope-labelling approach for the HDC protein was taken. We have previously shown that HDC with an internal FLAG epitope label can be detected in both the larval and adult stages, although

HA colocalization has not been accomplished in all cells, particularly photoreceptor cells. This *Hdc*-FLAG transgene was transformed into the Hdc^{JK910} mutant, which normally lacks endogenous HDC activity. The *Hdc*-FLAG transformant flies were analyzed for a functional HDC protein using HA immunofluorescence in a number of developmental stages, as the HA detected would be due to the activity of the transgenically-supplied HDC-FLAG protein. FLAG immunofluorescence was also used to detect the epitope-labeled HDC-FLAG protein using the M2 FLAG antibody. HDC-FLAG immunostaining yielded a staining pattern similar to the HA immunostaining in wildtype flies. Co-localization immunostaining for HA and HDC-FLAG has been completed in the adult and larval CNS using confocal microscopy, with some localization differences being detected. HDC-FLAG and HA appear to co-localize throughout central brain neuronal soma and processes in both larval and adult stages. In contrast, photoreceptor cells appear to localize HDC to discrete regions, separately from the photoreceptor cell terminal where HA is more concentrated. As a result of this subcellular localization difference, it is likely that HDC may be regulated in central brain neurons differently from that in photoreceptor cells. This difference in enzyme-neurotransmitter localization between photoreceptor cells and CNS neurons could also reflect differences in how HA is used and regulated by each cell type.

Disclosures: B. Vandenberg: None. **L. Robb:** None. **J. Howe:** None. **M.G. Burg:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.25/D13

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: *In utero* exposure to stress and SSRI antidepressant differentially affect serotonin-dependent developmental processes in the fetal mouse brain

Authors: *Q. ZHAO[1], J. C. VELASQUEZ[2], Y. CHAN[1], L. C. GALINDO NOVAES[3], I. BURD[4], A. M. ANDREWS[5], A. BONNIN[6]
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Abstract: Epidemiological and animal model studies suggest that exposure to either the stress of untreated depression or to selective serotonin (5-HT) reuptake inhibitors (SSRI) antidepressants during pregnancy increase risks for neurodevelopmental disorders in the offspring. Although SSRIs target 5-HT signaling, little is known about their effect, particularly in the context of maternal stress, on fetal brain development *in utero*. Pregnant mice were divided into chronic unpredictable stress (CUS), CUS+SSRI, SSRI-only and control groups. The dams were

subjected to CUS from gestational day (GD)8 through GD17. CUS+SSRI was defined as maternal CUS with the addition of the SSRI citalopram in the drinking water. On GD17, gross morphological development of the fetal brain was assessed by magnetic resonance imaging (MRI). Fetal brain 5-HT tissue concentration was measured by HPLC. The spatial distribution of 5-HT, cortical layers structure and formation of major axonal pathways were assessed by immunohistochemistry and iDISCO-based 3D-reconstructions. We found that *in utero* exposure to maternal CUS does not affect overall brain growth, but specifically increases 5-HT tissue concentration in the fetal forebrain. This effect is reversed by maternal oral administration of CIT during the same period. Mechanistically, CIT reverses neurochemical effects of stress by altering 5-HT distribution in fetal thalamocortical axons and neurons. Importantly in utero exposure to stress and CIT, individually and combined, disrupt fetal cortical layer formation. The data suggests that although the SSRI CIT reverses some effects of stress during pregnancy, both exposures differentially impact 5-HT-dependent fetal neurodevelopment.

Disclosures: Q. Zhao: None. **J.C. Velasquez:** None. **Y. Chan:** None. **L.C. Galindo novaes:** None. **I. Burd:** None. **A.M. Andrews:** None. **A. Bonnin:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.26/D14

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: Slc22a3, a potential second presynaptic serotonin transporter

Authors: *M. R. ARNOLD[1], A. O. WILLIAMS[2], A. AGRAWAL[2], H. E. DAY[3], J. S. TALBOOM[4], M. ORCHINIK[5], C. A. LOWRY[1]
[1]Integrative Physiol., [3]Psychology and Neurosci., [2]Univ. of Colorado Boulder, Boulder, CO; [4]Banner Hlth., Phoenix, AZ; [5]Sch. Life Sci., Arizona State Univ., Tempe, AZ

Abstract: Brain serotonergic systems play a role in cognitive and affective function and have been implicated in the pathophysiology of anxiety disorders, affective disorders, and trauma- and stressor-related disorders. Drugs that block serotonin reuptake into presynaptic terminals are used widely in the treatment of these disorders, and therefore understanding mechanisms underlying presynaptic clearance of serotonin is of major clinical interest. The neurotransmitter serotonin is cleared from brain synapses by the presynaptic sodium-dependent, high-affinity, low-capacity serotonin transporter, solute carrier family 6 (neurotransmitter transporter) member 4 (Slc6a4). However, evidence suggests possible expression of a second serotonin transporter, the sodium-independent, low-affinity, high-capacity serotonin transporter, organic cation transporter 3 (Oct3; Slc22a3, also known as the extraneuronal monoamine transporter (EMT)), in serotonergic neurons. However, it is unclear if Slc22a3 localizes to the presynaptic serotonergic

terminal, or to other cellular compartments within these cells, and, furthermore, if it co-localizes to the same presynaptic terminals as Slc6a4. For example, recent studies at the electron microscope level have identified Slc22a3 expression on neuronal and glial endomembranes, including Golgi, mitochondrial and nuclear membranes. Using a dual label fluorescence *in situ* hybridization histochemistry approach we demonstrated overlapping expression patterns of tryptophan hydroxylase 2 (Tph2), the rate-limiting enzyme in the biosynthesis of brain serotonin, and Slc22a3 mRNA expression within the rat dorsal raphe nucleus. To understand Slc22a3 protein location on the presynaptic terminals we used a quadruple label immunofluorescence for Slc6a4, Slc22a3, postsynaptic density protein 95 (Psd-95) and DAPI (4',6-diamidino-2-phenylindole), using an N-SIM Super-Resolution Microscope System. We were able to demonstrate that Slc22a3 and Slc6a4 co-localize in the same presynaptic terminals within the rat dorsal raphe nucleus, the main source of serotonergic projections to forebrain limbic structures. These findings highlight the need to understand the dynamic interactions between Slc6a4 and Slc22a3 in controlling serotonin reuptake and serotonergic signaling, physiology, and behavior in health and disease.

Disclosures: M.R. Arnold: None. **A.O. Williams:** A. Employment/Salary (full or part-time):; Double Helix LLC. **A. Agrawal:** A. Employment/Salary (full or part-time):; Double Helix Optics. **H.E. Day:** None. **J.S. Talboom:** None. **M. Orchinik:** None. **C.A. Lowry:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.28/D16

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: FAPESP
CNPq
CNPq Science without Borders
CIHR
WCHRI
AIHS

Title: Multiple mechanisms underlying the modulation of Locus coeruleus neuronal excitability by serotonin in the newborn rat

Authors: *V. BIANCARDI[1,4], T. S. ALVARES[1], L. H. GARGAGLIONI[4], G. D. FUNK[1,2,3]
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Abstract: Serotonergic (5HT) and noradrenergic (NA) neurons modulate neuronal and network excitability throughout the CNS in a manner that varies with development and arousal state. Of the multiple NA cell groups in the brain, the *Locus coeruleus* (LC) has the most extensive projection pattern and broadest influence on behavior, contributing to such diverse functions as sleep-awake cycling, appetite, learning and memory and cardiorespiratory control. LC neurons, like 5HT raphe neurons, are also CO_2/pH sensitive and, contribute to central respiratory chemoreception. 5HT neurons project to, and release 5HT, in the LC. However, the impact of this input on LC neuronal excitability, the underlying cellular mechanisms, and the consequences of this modulation for behavior remain to be fully characterized. Activation of $5HT_{1A}$, $5HT_{2A}$ and $5HT_3$ receptors reduce LC neuron excitability in juvenile and adult rats via presynaptic modulation of Glutamate, GABA and NE release, respectively. In addition, exposure of rats to 5HT reuptake inhibitors (SSRIs) postnatally (P1-10) results in adults with hyperexcitable LC neurons. In contrast, chronic delivery of SSRI to adult rats reduces the firing rate of LC neurons. These effects suggest developmental differences in the effect of 5HT on LC neuron excitability. Thus, the aim of this study was to assess in newborn rats the mechanisms by which 5HT affects LC neuron excitability. We examined the serotonergic responses of 150 LC neurons via whole-cell voltage clamp techniques. 101 neurons responded to 5HT (100 µM) with an inward current (-30 ± 3 pA), 18 responded with oscillations (freq of 0.4 ± 0.1 Hz), and 31 did not respond. $5HT_3$R agonists (mCPBG & SR57227; 100 µM) had no effect on membrane current. $5HT_2$R agonists (PNU22394 & TCB-2 together, 100 µM) evoked 3 types of responses: an 1124 ± 416% increase in the freq of glutamatergic mEPSCs (i.e., blocked by CNQX and AP5; 29/37 neurons); an inward current (-15 ± 2 pA) associated with a 21 ± 6% increase in input resistance (16/37 neurons) and a nitrendipine-sensitive (Ca^{2+} channel blocker), 0.1 Hz oscillation (5/37 neurons). The 5-HT_{1A}R agonist 8-OH-DPAT (50 µM) induced an inward current (-14 ± 3 pA, 6/11 neurons), while Sumatriptan (100 µM), a $5HT_{1ABD}$R agonist, had no effect. These data demonstrate in newborn rats that 5HT has multiple effects on LC neurons, including a presynaptic $5HT_2$-mediated increase in glutamatergic mEPSCs and a postsynaptic facilitation of Ca^{2+}-dependent membrane oscillations, as seen previously in adults. We have also described a novel postsynaptic, $5HT_2$/$5HT_{1A}$ receptor-mediated inward current, suggesting that the modulation of LC neurons by 5HT changes developmentally.

Disclosures: V. Biancardi: None. **T.S. Alvares:** None. **L.H. Gargaglioni:** None. **G.D. Funk:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.29/D17

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DA021213

Title: G protein βγ subunits play a critical role in the actions of amphetamine

Authors: *S. S. HARRIS[1], J. C. MAUNA[2], J. A. PINO[1], E. THIELS[3], G. E. TORRES[1]
[1]Pharmacol. and Therapeut., Univ. of Florida, Gainesville, FL; [2]Neurobio., Univ. of Pittsburgh Dept. of Neurobio., Pittsburgh, PA; [3]Natl. Sci. Fndn., Alexandria, VA

Abstract: Extracellular dopamine (DA) levels are primarily regulated via reuptake into the presynaptic terminal by the DA transporter (DAT). Addictive psychostimulants, such as amphetamine, target DAT and increase the levels of extracellular DA by inducing efflux through DAT. Recently, we discovered that G protein βγ subunits (Gβγ) interact with the intracellular carboxy terminus of DAT, and that *in vitro* activation of Gβγ promotes DA efflux through DAT similar to amphetamine. In this study, we investigated the role of Gβγ in the actions of amphetamine in DA neurons in culture, ex vivo striatal tissue, and in freely moving rats. Activation of Gβγ with the peptide mSIRK potentiated amphetamine-induced hyperlocomotion, but did not alter the effect of cocaine. Conversely, the Gβγ inhibitor gallein attenuated the hyperlocomotion induced by amphetamine, but not cocaine. Infusion of a TAT-fused peptide that targets the Gβγ-binding site on DAT (TAT-DATct1) in the nucleus accumbens also attenuated the amphetamine-induced hyperlocomotion. To examine the mechanism behind the locomotor effects of Gβγ on amphetamine actions, we measured DA efflux in DA neurons in culture, dorsal striatum and nucleus accumbens tissue, and *in vivo* using microdialysis. In DA neurons in culture, inhibition of Gβγ with gallein or blockade of the interaction between Gβγ and DAT with the TAT-DATct1 peptide decreased DA efflux. Moreover, activation of Gβγ with mSIRK potentiated, whereas inhibition of Gβγ with gallein reduced, amphetamine-induced increases in extracellular DA in the rat nucleus accumbens and dorsal striatal tissue, and *in vivo*. Finally, we showed that inhibition of Gβγ also altered the rewarding effects of amphetamine, as demonstrated by the blockade of amphetamine-induced place preference with gallein. Collectively, these results suggest that the interaction between DAT and Gβγ plays a critical role in the actions of amphetamine and therefore, represents a novel target for modulating amphetamine's actions *in vivo*.

Disclosures: S.S. Harris: None. **J.C. Mauna:** None. **J.A. Pino:** None. **E. Thiels:** None. **G.E. Torres:** None.

Poster

199. Monoamines I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 199.30/D18

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NHI Grant P50 AA022538
NIH Grant U01 AA020912

Title: Activation of estrogen receptor alpha enhances ethanol excitation of ventral tegmental area neurons in female mice

Authors: B. J. VANDEGRIFT[1], *M. S. BRODIE[1], A. W. LASEK[2]
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Abstract: The ventral tegmental area (VTA) plays a critical role in reward and reinforcement in alcohol addiction and the neurons of the VTA are estrogen-sensitive. Our prior work has shown that ethanol excites VTA dopaminergic (DA) neurons and that ethanol potency is increased during high estrogen states, both in ovariectomized (OVX) mice treated with estradiol (E2) and in gonadally intact females. Two estrogen receptors, ERα and ERβ, are expressed in the VTA, but thus far it is unknown which of these receptors mediates E2 modulation of ethanol-induced excitation of VTA DA neurons. To determine the receptor subtypes involved, OVX C57BL/6J mice were treated daily for 3 days with an ERα agonist (PPT, 1 mg/kg), ERβ agonist (DPN, 1 mg/kg), or vehicle prior to single unit extracellular electrophysiological recordings in brain slices containing the VTA. Neurons from mice treated with PPT had a significantly greater excitatory response to ethanol (40-120 mM) compared with DPN and vehicle-treated mice. We also characterized the ability of estrogen receptors in freely cycling females to modulate sensitivity to ethanol in VTA neurons. Brain slices were collected during diestrus II (high E2) or estrus (low E2), and ethanol excitation was assessed before and after administration of selective estrogen receptor antagonists. Ethanol excitation (80 mM) was greater in diestrus II than in estrus, consistent with our previous findings in gonadally-intact females. After treatment with the ERα antagonist (MPP dihydrochloride), the ethanol response in neurons from diestrus II mice was reduced by 53.3%, but the antagonist had no effect on the ethanol response in neurons from estrus mice. Treatment with an ERβ antagonist (PHTPP) did not affect ethanol excitation in neurons from mice in estrus or diestrus II. These results demonstrate that estrogen enhances ethanol excitation of VTA neurons through actions at ERα. Because acute treatment with an ERα antagonist reversed the enhanced ethanol excitation, ERα may mediate a rapid, non-genomic mechanism of estrogen action in the VTA. Our results imply that activation of ERα in the VTA could potentially promote high levels of drinking by females by enhancing the response of DA neurons to ethanol. Supported by NIAAA: P50 AA022538 (MSB and AWL) and U01 AA020912 (AWL).

Disclosures: B.J. Vandegrift: None. **M.S. Brodie:** None. **A.W. Lasek:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.01/D19

Topic: B.02. Ligand-Gated Ion Channels

Support: NHMRC (1058542 and 1080976)
ARC LIEF grant LE130100078

Title: Inhibitory synapse deficits caused by familial a1 $GABA_A$ receptor mutations in epilepsy

Authors: *X. CHEN, N. DURISIC, A. KERAMIDAS, J. LYNCH
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Abstract: Epilepsy is a spectrum of neurological disorders with many causal factors. The GABA type-A receptor ($GABA_AR$) is a major genetic target for some forms of heritable human epilepsies. Here we examine the functional effects of three mutations to the α1 subunit ($\alpha1^{T10'I}$, $\alpha1^{D192N}$ and $\alpha1^{A295D}$) on inhibitory postsynaptic currents (IPSCs) mediated by the major synaptic $GABA_AR$ isoform, α1β2γ2L. We employed a neuron - HEK293 cell heterosynapse preparation to record IPSCs mediated by mutant-containing $GABA_ARs$ in isolation. IPSCs were recorded in the presence of the anticonvulsant drugs, carbamazepine and midazolam, and at elevated temperatures (22, 37 and 40 ^oC) to gain insight into mechanisms of febrile seizures. The mutant subunits were also transfected into cultured cortical neurons to investigate changes in synapse formation and neuronal morphology using fluorescence microscopy. We found that IPSCs mediated by $\alpha1^{T265I}\beta2\gamma2L$, $\alpha1^{D192N}\beta2\gamma2L$ $GABA_ARs$ decay faster than those mediated by α1β2γ2L receptors. IPSCs mediated by $\alpha1^{D192N}\beta2\gamma2L$ and $\alpha1^{A295D}\beta2\gamma2L$ receptors also exhibit a heightened temperature sensitivity. In addition, the $\alpha1^{T265I}\beta2\gamma2L$ $GABA_ARs$ were refractory to modulation by carbamazepine or midazolam. In agreement with previous studies, we found that $\alpha1^{A295D}\beta2\gamma2L$ $GABA_ARs$ expressed poorly in HEK293 cells and neurons. However, pre-incubation with 100 nM suberanilohydroxamic acid (SAHA) resulted in $\alpha1^{A295D}\beta2\gamma2L$ $GABA_ARs$ mediating IPSCs that were indistinguishable in magnitude and waveform to those mediated by α1β2γ2L receptors. Finally, mutant-specific changes to synaptic bouton size, synapse number and neurite branching were also observed. These results provide new insights into the mechanisms of epileptogenesis of α1 epilepsy mutations and suggest possible leads for optimising treatment options for patients harbouring these mutations.

Disclosures: X. Chen: None. **N. Durisic:** None. **A. Keramidas:** None. **J. Lynch:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.02/D20

Topic: B.02. Ligand-Gated Ion Channels

Support: NCN Grant 2013/11/B/NZ3/00983
NCN Grant 2015/18/A/NZ1/00395

Title: Flurazepam modulation of $GABA_A$receptor gating depends on the receptor ligation

Authors: *M. JATCZAK-SLIWA[1,2], K. TEREJKO[1], M. BRODZKI[2,1], M. A. MICHAŁOWSKI[2,1], M. M. CZYZEWSKA[1], J. M. NOWICKA[1], A. ANDRZEJCZAK[2], R. SRINIVASAN[2], J. W. MOZRZYMAS[1]
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Abstract: In the mammalian brain the $GABA_A$ receptors are essential mediators of inhibitory neurotransmission that can be modulated by several clinically used drugs such as benzodiazepines (BDZs). However, the mechanism underlying this modulation remains still obscure. In our study we focused not only on BDZ - flurazepam (FLU) effect on ligand-evoked $GABA_A$ receptor activation but also on receptor spontaneous activity. To address this issue, we used patch-clamp technique to record macroscopic and microscopic currents mediated by wild-type $\alpha_1\beta_2\gamma_{2L}$ or mutated receptors (L,A,C substitution of α_1F64 residue which is located at the GABA-binding site and is involved in receptor binding and gating - primarily preactivation transition). As a result, we have found that mutation increases spontaneous activity and FLU upregulated it at the macroscopic and single-channel level to the same extent as for WT receptors. Our model simulations indicate BDZ effect on the opening/closing transition in unliganded gating process. On the other hand, FLU modulation of agonist (GABA) and partial agonist (P4S) evoked activity concerned preactivation and desensitization step. Moreover, we demonstrate for the first time that unliganded $GABA_A$ receptors may undergo desensitization which depended on BDZ modulation. Finally, we show that spontaneous activity may affect the time course of agonist-induced current in the form of an “overshoot” after agonist removal which represents cross-desensitization of bound and unbound rceptors. Summarizing, receptor $GABA_A$ is modulated by FLU differently for unliganded and liganded state. Supported by NCN grants: 2013/11/B/NZ3/00983 and 2015/18/A/NZ1/00395.

Disclosures: M. Jatczak-Sliwa: None. **K. Terejko:** None. **M. Brodzki:** None. **M.A. Michałowski:** None. **M.M. Czyzewska:** A. Employment/Salary (full or part-time):; Wroclaw Medical University. **J.M. Nowicka:** None. **A. Andrzejczak:** None. **R. Srinivasan:** None. **J.W.**

Mozrzymas: A. Employment/Salary (full or part-time):; Wroclaw Medical University, University of Wroclaw.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.03/D21

Topic: B.02. Ligand-Gated Ion Channels

Support: National Natural Science Foundation of China 81571125
National Natural Science Foundation of China 81571088
National Natural Science Foundation of China 81770839

Title: Single ethanol withdrawal regulates extrasynaptic delta-$GABA_A$receptors via PKCdelta activation

Authors: J. CHEN[1], Y. HE[1], Y. WU[1], H. ZHOU[1], L.-D. SU[2], W.-N. LI[1], R. W. OLSEN[3], J. LIANG[4], Y.-D. ZHOU[1], *Y. SHEN[1]
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Abstract: Alcohol (ethanol, EtOH) is one of the most widely abused drugs with profound effects on brain function and behavior. $GABA_A$ receptors ($GABA_A$Rs) are one of the major targets for EtOH in the brain. Temporary plastic changes in $GABA_A$Rs after withdrawal from a single EtOH exposure occur both *in vivo* and *in vitro*, which may be the basis for chronic EtOH addiction, tolerance and withdrawal symptoms. Extrasynaptic δ-$GABA_A$R endocytosis is implicated in EtOH-induced $GABA_A$R plasticity, but the mechanisms by which the relative abundance and localization of specific $GABA_A$Rs are altered by EtOH exposure and withdrawal remain unclear. In this study, we investigated the mechanisms underlying rapid regulation of extrasynaptic δ-$GABA_A$R by a single EtOH withdrawal in cultured rat hippocampal neurons. Thirty-min EtOH (60 mM) exposure increased extrasynaptic tonic current (I_{tonic}) amplitude without affecting synaptic $GABA_A$R function in neurons. In contrast, at 30 min after withdrawal, I_{tonic} amplitude and responsiveness to acute EtOH were both reduced. Similar results occurred in neurons with okadaic acid (OA) or phorbol 12,13-dibutyrate (PDBu) exposure. PKC inhibition prevented the reduction of I_{tonic} amplitude and the tolerance to acute EtOH, as well as the reduction of $GABA_A$R-δ subunit abundance induced by a single EtOH withdrawal. Moreover, EtOH withdrawal selectively increased PKCδ level, whereas PKCδ inhibition specifically rescued the EtOH-induced alterations in $GABA_A$R-δ subunit level and δ-$GABA_A$R function. Together, we provided strong evidence for the important roles of PKCδ in the rapid regulation of extrasynaptic

δ-$GABA_AR$ induced by a single EtOH withdrawal.
Key words: ethanol withdrawal; extrasynaptic δ-$GABA_AR$; tonic current; PKCδ; hippocampal neurons
Supported by Grants 81571125, 81571088, and 81770839.

Disclosures: J. Chen: None. **Y. He:** None. **Y. Wu:** None. **H. Zhou:** None. **L. Su:** None. **W. Li:** None. **R.W. Olsen:** None. **J. Liang:** None. **Y. Zhou:** None. **Y. Shen:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.04/D22

Topic: B.02. Ligand-Gated Ion Channels

Support: CIHR Grant PJT-153183
NSERC Grant RGPIN 436168

Title: GABA-evoked spike initiation in the central axon terminals of primary afferent neurons requires concurrent changes in chloride regulation and neuronal excitability: An *ex vivo* two-photon GCaMP imaging study

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Abstract: Primary afferent neurons transmit information as spikes from the periphery to the central nervous system via synapses formed by their central axon terminals in the spinal dorsal horn. However, abnormal (ectopic) spikes can be initiated at the central axon terminals, which then propagate antidromically. GABAergic interneurons in the dorsal horn innervate the central axon terminals. Primary afferent neurons are depolarized by GABAergic input due to their high intracellular Cl^- concentration. This primary afferent depolarization (PAD) normally has inhibitory effects because it causes shunting and sodium channel inactivation. However, PAD can become excitatory (i.e. evoke ectopic spiking) under pathological conditions. Indeed, GABA-evoked spikes that propagate antidromically to the periphery may contribute to neurogenic inflammation observed in chronic pain conditions. We investigate the pathological changes in primary afferent neurons that enable GABA to evoke spikes at the central axon terminals. We used GCaMP-based calcium imaging to detect spiking in an ex vivo dorsal root ganglion preparation in which the central axon terminals in the spinal cord were intact. A depolarizing shift in the GABA reversal potential (E_{GABA}) and/or an increase in intrinsic excitability were pharmacologically induced by aldosterone and 4-AP, respectively. The former

effect was determined to result from an NKCC1-dependent mechanism given its sensitivity to the NKCC1 inhibitor, bumetanide. PAD-evoked spiking following GABA application to central axon terminals was observed almost exclusively after both aldosterone and 4-AP were applied. Thus, PAD-evoked spiking in central axons terminals requires a joint change in E_{GABA} and intrinsic excitability. Imaging of calcium signals in somata following GABA application to central axon terminals also demonstrates that PAD-induced spikes propagate antidromically, away from their site of initiation. We found that inflammation impacts both E_{GABA} and intrinsic excitability such that the joint requirements for PAD-induced spiking are met under inflammatory conditions. Taken together, these results argue that two processes - chloride regulation and intrinsic excitability - interact to dictate the response of primary afferent neurons to $GABA_A$ receptor activation on their central axon terminals. Importantly, although inflammation induced both of the aforementioned biophysical changes, reversing either change is sufficient to prevent GABA-evoked spiking. The last observation, in particular, should facilitate the strategic design of therapeutic interventions.

Disclosures: S.A. Prescott: None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.05/D23

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01 NS101888

Title: Molecular mechanisms of $GABA_A$ receptor trafficking to the axon initial segment

Authors: *A. J. NATHANSON[1], R. M. HINES[2], T. Z. DEEB[3], P. A. DAVIES[1], S. J. MOSS[1,3]
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Abstract: The axon initial segment (AIS) is the site of action potential (AP) initiation in most neurons, and dysfunction in this crucial area is linked to the development of epileptic disorders in humans. While channelopathies associated with voltage-gated ion channels enriched at the AIS are fairly well studied, the role of the primary ligand-gated ion channel found at the AIS—the γ-aminobutyric acid type A receptor ($GABA_AR$)—has not been investigated. $GABA_ARs$ mediate fast inhibitory synaptic transmission in the brain, and are heteropentamers assembled from 2 α(1-3), 2 β(1-3), and 1 γ2 subunit. Even modest deficits in GABAergic signaling contribute to a variety of disorders, including epilepsy. For efficient synaptic inhibition to take place, $GABA_ARs$ must be precisely trafficked to and stabilized at the proper postsynaptic area. Interestingly, $GABA_ARs$ are known to have a subtype-specific localization pattern within

hippocampal pyramidal neurons: $GABA_ARs$ containing α1 subunits are concentrated in the dendritic compartments, while at the AIS, the vast majority of $GABA_ARs$ contain the α2 subunit. These α2-$GABA_ARs$ are exclusively innervated by GABAergic axo-axonic interneurons; each of these interneurons contacts hundreds of pyramidal cell AISes, and through inhibitory neurotransmission controls the timing of AP firing and the synchronization of large ensembles of excitatory neurons. Despite the putative importance of subtype specific inhibitory synapses at the AIS in controlling network excitability, the molecular mechanisms by which neurons construct these synapses within the tightly controlled AIS compartment remain unknown. Preliminary data from the Moss laboratory shows that an amino acid motif, consisting of amino acids 360-375, in the intracellular loop domains of the α subunits may be the key. This motif shows differential binding affinities to intracellular inhibitory synaptic proteins. Specifically, the 360-375 of α1 preferentially binds gephyrin, while the 360-375 of α2 has high affinity for collybistin. We will investigate the roles amino acids 360-375 and their associated intracellular interactors play in the targeting of $GABA_ARs$ to the AIS. To this end, we have developed a novel transgenic mouse, the Gabra1-2 mouse, in which residues 360-375 of the α1 subunit have been replaced with those of the α2 subunit. **Using this mouse, we will test the hypothesis that the ICD 360-375 α2 motif is sufficient to target $GABA_ARs$ to the AIS of hippocampal pyramidal neurons, and directing α1-$GABA_ARs$ to AIS synapses will enhance the efficacy of GABAergic inhibition and offer protection from induced seizures.**

Disclosures: A.J. Nathanson: None. **R.M. Hines:** None. **T.Z. Deeb:** None. **P.A. Davies:** None. **S.J. Moss:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.06/D24

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant MH-096463
NIH Grant HL-118561
NIH Grant NS-076517
Austrian Science Fund (FWF) W1232
Austrian Science Fund (FWF) P27746

Title: Different benzodiazepines bind with distinct binding modes to $GABA_A$-receptors

Authors: *P. SCHOLZE[1], A. A. ELGARF[1], D. C. B. SIEBERT[2], F. STEUDLE[1], A. DRAXLER[1], M. ERNST[1], G. LI[3], S. HUANG[3], J. M. COOK[3]
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Abstract: Benzodiazepines are clinically relevant drugs, which bind to $GABA_A$ neurotransmitter receptors at the alpha+/gamma2- interfaces and thereby enhance GABA induced chloride ion flux leading to neuronal hyperpolarization. However, the structural basis of benzodiazepine interactions with their high affinity site at $GABA_A$ receptors is controversially debated in the literature and *in silico* studies led to discrepant binding mode hypotheses. In the current study computational docking of diazepam into alpha+/gamma2- homology models suggested that a chiral methyl group, which is known to promote preferred binding to alpha5-containing $GABA_A$ receptors (position 3 of the 7-membered diazepine ring), could possibly provide experimental evidence in favor of or against the so far proposed binding modes. Thus, we investigated three pairs of R- and S-isomers of structurally different chemotypes, namely diazepam-, imidazobenzodiazepine- and triazolam-derivatives. We used radioligand displacement studies as well as two-electrode voltage clamp electrophysiology in alpha (1, 2, 3, and 5)-beta3-gamma2-containing $GABA_A$ receptors to determine ligand binding and functional activity of the three chemotypes. Interestingly, both imidazobenzodiazepine isomers displayed comparable binding affinities while for the other two chemotypes a discrepancy in binding affinities of the different isomers was observed. Specifically, the R-isomers displayed a loss of binding whereas the S-isomers remained active. These findings are in accordance with our *in silico* studies suggesting the usage of a different binding mode of imidazobenzodiazepines compared to the other two tested chemotypes. Hence, we conclude that different chemically related benzodiazepine ligands rather interact *via* distinct binding modes than using a common binding mode.

Disclosures: P. Scholze: None. **A.A. Elgarf:** None. **D.C.B. Siebert:** None. **F. Steudle:** None. **A. Draxler:** None. **M. Ernst:** None. **G. Li:** None. **S. Huang:** None. **J.M. Cook:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.07/D25

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01MH097082
NIH Grant R21MH113177
NIH Grant R21AG053740

Title: Global expression patterns of $GABA_A$ receptor subunits in humans differentiate brain regions into ontogenically related groups

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Abstract: Inhibitory signaling mediated by ionotropic $GABA_A$ receptors ($GABA_ARs$) is a fundamental pillar of brain function. However, comprehensive information about receptor subtypes across the healthy human brain is limited, which complicates the study of inhibitory remodeling in brain disorders. In this study we sought to determine major relationships between $GABA_ARs$ subunits across the human brain to understand better the typical variability expected during normal physiological states, and set a global framework to compare inhibitory remodeling during pathological states. Microarray datasets from the Allen Brain Institute were used to delineate major relationships between $GABA_AR$ subunits across 111 brain structures in six healthy human brains. We also used RNA sequencing-resolution datasets from the Aging, Dementia and Traumatic Brain injury study, which has a high number of subjects (n = 50) but is limited to four regions: the hippocampus, the temporal and parietal cortex, and the white matter of the forebrain (http://aging.brain-map.org/). By using these datasets in unsupervised data-driven analyses we found that patterns of expression of $GABA_AR$ subunits are topographically organized according to their ontogenic origin and show high consistency in brain regions characterized by recurrent, or repetitive, cytoarchitecture at the regional, and substructure levels. In contrast, subcortical regions composing the limbic and hypothalamic axis systems, which are affected in neurological and psychiatric disorders, show high differential enrichment of specific $GABA_AR$ subunits. Hippocampus, amygdala and hypothalamus show the most region-specific expression of $GABA_ARs$, underlining the opportunity to target specific regions of the brain to modulate GABA neurotransmission for precise pharmacological treatments targeting specific neuropsychiatric conditions. Additionally, regional differences in the strength, probability and directionality of correlations between $GABA_AR$ subunits suggests a global pattern of expression determined by anatomical developmental origin, and might be useful to determine the "organizational layout" of $GABA_AR$ subunits globaly and at structural levels. Future studies that include neurodegenerative and psychiatric RNA sequencing datasets should be useful to explore homeostatic rearrangements of $GABA_AR$ subunits after physiological, pharmacological or pathological challenges.

Disclosures: A. Limon: None. **P.A. Sequeira:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.08/D26

Topic: B.02. Ligand-Gated Ion Channels

Title: Importance of the $GABA_A$receptors from invertebrates to vertebrates

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Abstract: While chemical neurotransmission was identified more than a century ago, the importance of γ-amino-butyric acid (GABA) as a neurotransmitter in both invertebrates and vertebrates was discovered only about sixty years ago (Tauc, 1961). Moreover, whereas earlier intracellular recordings identified that activation of fast synaptic neurotransmission mediated by GABA was associated with an increase of the membrane conductance for chloride ions, it is only recently that similitudes and differences between vertebrates and invertebrates channel properties were identified.
The discovery that open channel blockers of the invertebrate $GABA_A$ receptors are efficient insecticides raised the question about potential toxicity in view of the fact that these compounds might act at vertebrate receptors. However, clear differences in affinities exist between the vertebrate and invertebrate receptors which allowed the development of powerful molecules (Hainzl, 1996; Ratra, 2001, Rufener, 2017). Our understanding of the precise biochemical determinants governing these significant differences remains limited. Moreover, open channel blockers also display significant differences in efficacy across invertebrate species.
The increasing availability of sequences encoding for the GABA-Cl from invertebrate and $GABA_A$ from vertebrate receptors offers novel possibilities to make comparisons across both target and off-target species. Functional studies conducted using recombinant expression in *Xenopus* oocytes represents a decisive complement to examine the function and pharmacological differences between chloride permeable receptors across species unravelling the role of critical amino acid residues in the mechanism of action of specific molecules. In summation, new possibilities arise to evaluate potential insecticidal activity in vitro, separate this activity from activity on vertebrate receptors, and distinguish sensitivity of receptors from insects and acarids considered pest species versus those generally considered beneficial.
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Disclosures: K. Kambara: 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.; Boehringer Ingelheim Animal Health. **D. Bertrand:** A. Employment/Salary (full or part-time):; HiQScreen Sàrl. **S. Bertrand:** A. Employment/Salary (full or part-time):; HiQScreen Sàrl. **Y. Moreno:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Animal Health. **J. Harrington:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Animal Health.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.09/D27

Topic: B.02. Ligand-Gated Ion Channels

Support: Career Development Award, United States Department of Veteran Affairs, Biomedical Laboratory Research and Development Service #BX00167
James S. McDonnell Foundation Grant #220023046

Title: Faster emergence and recovery from sevoflurane anesthesia in mice lacking the alpha-4 subunit of the gaba(a) receptor

Authors: *K. S. EDOKPOLOR[1], S. SCHWERIN[2], J. FIDLER[4], S. KRATZER[3], P. S. GARCIA[5]
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Abstract: GABA (γ -aminobutyric acid) type A receptors(GABA(A)Rs) are members ofthe Cys-loop ligand channel super-family. These pentameric receptors are heterogenous in their sub-unit composition. Most anesthetics used in the clinical setting augment current through the GABA(A)Rs to induce and maintain unconsciousness. Post-anesthetic cognitive effects such as memory deficits, and disorientation— can persist into the immediate recovery period. The appearance of these effects may predict cognitive decline.The alpha4-containing GABA(A)Rs mediate tonic current and are expressed extrasynaptically in several brain regions including the thalamus. We report on the restoration of arousal and the recovery of usual waking behaviors after exposure to general induced (6%) and maintained (3.2%) with the volatile anesthetic sevoflurane. Animals genetically modified to prevent expression of the alpha4-subunit were significantly faster to regain arousal and normal waking behaviors, such as, return of righting reflex (RORR), and spontaneous ambulation. End emergence was defined by a non-transient and consistent RORR. The end of the recovery period was determined by the first attempt to remove adhesive tape affixed to the forepaw of the animal while anesthetized (sticky dot test). To further examine the pharmacologic specificity of this phenomenon, an agonist specific for alpha4-containing GABA(A)Rs, gaboxadol, was administered to wild type mice prior to anesthesia. These data combined highlight that extra-synaptic GABA(A)Rs are important for emergence and recovery from general anesthesia. These data are also consistent with the notion that a depolarized thalamus functioning in processing of cortico-thalamic information is a critical part of the re-animation sequence after general anesthesia.

Disclosures: K.S. Edokpolor: None. **S. Schwerin:** None. **J. Fidler:** None. **S. Kratzer:** None. **P.S. Garcia:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.10/D28

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant 092809-01

Title: Enhancement of extrasynaptic $GABA_A$ receptors by $GABA_B$ receptors and L-type calcium channels

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Abstract: The γ-amino butyric acid A receptors ($GABA_A$Rs) are major contributors of cellular inhibition in the CNS, where synaptic $GABA_A$Rs mediate phasic inhibition and extrasynaptic $GABA_A$Rs are responsible for tonic inhibition. Extrasynaptic $GABA_A$Rs are composed of unique subunits that enable them to sense low ambient GABA concentrations, for example, delta subunit containing receptors in the cerebellum (α6, δ) and the hippocampus (α4/5, δ). The fascinating feature of tonic inhibition is that it provides access for bulk inhibition/modulation of cells in the vicinity of the source of ambient GABA, ultimately affecting the downstream neuronal network. Extrasynaptic receptors are also targets for alcohol, neurosteroids, sleep-aids, and anesthetics presenting their potential for being a therapeutic target. In cerebellar granule cells extrasynaptic $GABA_A$Rs are known to be under control of $GABA_B$ receptors, however, the mechanism of this regulation is unclear. We made whole-cell patch-clamp recordings from granule cells in acute cerebellar slices, and $GABA_A$R-mediated currents were recorded by photolytic release of RuBi-GABA. We found that blocking $GABA_B$ receptors by bath application of CGP55845 or 2hydroxy-saclofen reduced $GABA_A$R currents to ~60% of control, suggesting $GABA_A$R currents are tonically enhanced by $GABA_B$Rs. $GABA_B$R antagonists had no effect on $GABA_A$R currents in Purkinje or stellate cells, or on $GABA_A$R currents evoked by synaptic GABA release in granule cells. Enhancement of $GABA_A$R currents by $GABA_B$Rs requires G-protein signaling, adenylate cyclase, and Ca^{+2}/calmodulin-dependent protein kinase II (CaMKII). Non-stationary fluctuation analysis suggests the change in $GABA_A$R current results from a change in number of $GABA_A$Rs activated, and we did not find any change in the EC_{50} of $GABA_A$Rs. The reduction in $GABA_A$R current by $GABA_B$R antagonists was mimicked and occluded by bath application of EGTA-AM. Likewise, bath application of nifedipine reduced $GABA_A$R currents in granule cells,

raising the possibility that $GABA_BRs$ regulate $GABA_ARs$ through modulation of L-type Ca^{2+} channels.

Disclosures: S.N. Khatri: None. **W. Wu:** None. **J.R. Pugh:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.11/D29

Topic: B.02. Ligand-Gated Ion Channels

Support: Lundbeck Foundation R133-A12270
Lundbeck Foundation R192-2015-666
Lundbeck Foundation R230-2016-2562

Title: Kinase-dependent behaviour of delta-containing GABA-A receptors disguises the efficacy of orthosteric agonists and reveals agonistic effects of gabazine

Authors: *P. WELLENDORPH[1], U. LEURS[1], C. B. FALK-PETERSEN[1], P. SCHOLZE[2], B. FRØLUND[1], N. O. DALBY[1]
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Abstract: A subset of the $GABA_A$ receptors expressed in recombinant systems and in neurons is known to exhibit both constitutive- and agonist-induced gating. Two such receptors are the δ-subunit containing $GABA_A$ receptors $\alpha_4\beta_1\delta$ and $\alpha_4\beta_3\delta$, which are expressed in adult rodent hippocampal dentate gyrus granule cells (DGGCs) at peri- and extrasynaptic loci. The aim of the present study was to examine the role of protein kinase activity on the constitutive current, and further, to discern the relationship between constitutive and agonist-mediated gating in DGGCs. Towards this aim, we studied the $GABA_A$ receptor-mediated tonic current recorded in the presence of tetrodotoxin in adult rodent DGGCs by whole cell patch clamp in rodents.
We found that the tonic current is almost exclusively mediated by constitutively active δ-subunit containing $GABA_A$ receptors, and that the constitutive current is absent in recordings at 24 °C or in recordings at 34 °C including an intracellular inhibitor of protein kinase C or under calcium-free conditions. Using the β_1/β_3-selective compound thio-THIP we observed a four-fold increase in efficacy when measuring at constitutively silent receptors. This effect was absent in $\delta^{-/-}$ mice. When applying the classified neutral antagonist gabazine (GBZ) in the absence of constitutive activity, we surprisingly found that GBZ alone induces a current in DGGCs (EC_{50} =2.1 μM). The effect of GBZ was not seen in recording conditions of high constitutive activity, was inhibited by picrotoxin, potentiated by the δ-selective positive allosteric modulator, DS2, completely absent in $\delta^{-/-}$ mice and reduced in $\beta_1^{-/-}$ mice. However, this effect of GBZ could not be replicated in

human $\alpha_4\beta_{1/3}\delta$ receptors expressed recombinantly in HEK cells. We hypothesize that specific intracellular components in neurons interact with receptors to determine constitutive gating and receptor responsiveness to orthosteric ligands.
In conclusion, our data highlight how recording conditions for whole cell patch clamp analysis of $\alpha_4\beta_{1/3}\delta$ $GABA_A$ receptors may mask important pharmacological effects. Our data suggest that *in vivo* efficacy of δ-subunit specific agonists (i.e. THIP) in DGGCs is diminished in pathological conditions of increased PKC activity. Furthermore, we report that the well-known antagonist GBZ is not a neutral antagonist but displays a stimulatory effect at constitutively silent δ-containing $GABA_A$ receptors. We recommend that care is taken when performing *in vitro* characterization of ligands at constitutively active $\alpha_4\beta_{1/3}\delta$ $GABA_A$ receptors, which is easily achieved using recording conditions of reduced kinase activity.

Disclosures: P. Wellendorph: None. **U. Leurs:** None. **C.B. Falk-Petersen:** None. **P. Scholze:** None. **B. Frølund:** None. **N.O. Dalby:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.12/D30

Topic: B.02. Ligand-Gated Ion Channels

Support: National Natural Science Foundation of China [Grant No.81621003]

Title: GABR mutations identified in Chinese patients with major depressive disorder

Authors: W. KUANG[1], T. LU[3], J. LI[1], Q. GONG[1], Z. DONG[1], Y. LUO[1], *L. TIAN[2]
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Abstract: As a neuropsychiatric disorder with high prevalence and life-threatening possibility, major depressive disorder (MDD) is characterized by variety of symptoms, such as sadness, anhedonia and decreased interest in daily activities. Genetic analysis is a powerful tool to identify risk variants and to enhance understanding of etiology of MDD, leading to improved early diagnosis, and development of more effective therapies. The study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University, and patients were recruited from Mental Health Center of West China Hospital. DNA extracts of peripheral blood samples were collected from patients (age between 18 and 65) diagnosed with MDD according to the DSM-IV (American Psychiatric Association, 2000) by board certified and experienced psychiatrists. Quality and quantity of extracted DNA were first assessed, and samples with concentrations >20 ng/μL and 260/280nm absorbance ratios between 1.8 and 2.0 were selected for subsequent sequencing analysis. Whole exome sequencing was carried out with

high-throughput second-generation sequencing technique using Illumina HiSeq platform PE150. Only sequenced reads with $Q_{phred}30$ (indicating error rate of <0.1%) were used in further analysis. DNA samples collected in parallel from healthy participants served as controls. A total number of 64 patients and 36 healthy controls were included for whole exome sequencing analysis. Series of mutations in neurotransmitter γ-aminobutyric acid receptors (GABR) were identified in 28 patients with none discovered in healthy controls. Disease incidence was found highly correlated to the presence of GABR mutation (odds ratio 55.839, 95% confidence interval 3.2-974, *P*=0.0058). The 28 patients harbor several mutations in the genes encoding 18 subtypes of GABR. Among which, several single nucleotide polymorphisms (SNPs) were missense mutations located in exonic regions of GABR causing codon change and modification in amino acids. The most frequently identified SNPs were rs 832032 (GABR rho3, GABRR3, found in 26 patients), rs 1139916 (GABRE, found in 22 patients), rs 211035 (GABRG2, found in 17 patients), rs 1186902 (GABRR1, found in 12 patients), rs 282129 (GABRR2, found in 9 patients), and rs 10163310 (GABRP, found in 8 patients). Though multiple mutations were identified, number of mutations was not correlated to severity of the disease. Our preliminary data suggested a role of GABR in MDD pathology. Further analysis will combine other neuropsychological and psychoradiological (MRI) assessments in search for the relationships between its genotype and endophynotype of MDD.

Disclosures: W. Kuang: None. **T. Lu:** None. **J. Li:** None. **Q. Gong:** None. **Z. Dong:** None. **Y. Luo:** None. **L. Tian:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.13/D31

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant R01ES024064

Title: MeHg-induced cell death in the ventral lumbar spinal cord region of C57BL6J mice

Authors: *M. RIOS CABANILLAS[1], W. D. ATCHISON[2]
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Abstract: In the Renshaw Area, spinal cord α motor neurons (αMNs) send excitatory signals onto Renshaw interneurons, which in turn, send inhibitory neurotransmission back to the same αMNs, ultimately modulating their signaling. Ligand-gated ion channels, such as nicotinic acetylcholine receptors (nAChRs), glycine and $GABA_A$ receptors ($GABA_ARs$), are key mediators of synaptic transmission in the Renshaw Area. Methylmercury (MeHg) is an

environmental contaminant that affects brainstem MNs, causing an increased excitability and increased $[Ca^{2+}]_i$. Furthermore, MeHg causes marked reduction in $GABA_A$Rs function, thereby reducing circuit inhibition. αMN viability during and after MeHg exposure at the lumbar ventral spinal recurrent inhibitory pathway has never been studied. The purpose of these experiments was to determine the contribution of Renshaw Area ligand-gated ion channels to αMNs mortality following an acute *in vitro* MeHg exposure. Lumbar sections of adult C57BL6J mice (N = 5-8) were continuously exposed to 20 µM MeHg during 15 min through a real-time perfusion system. Viability measurements were recorded using calcein-AM at 15 min of MeHg exposure and 1 and 3 hrs post-MeHg in the absence or presence of the antagonists, bicuculline, mecamylamine, dihydro-ß-erythroidine or strychnine, which block $GABA_A$Rs, heteromeric nAChRs or glycine receptors, respectively. At 1 hr after a 15 min exposure to MeHg, there was no immediate cytotoxicity. However, by 3 hrs after exposure, viability was reduced significantly by 35% from control. Pretreatment with bicuculline (20 µM) significantly reduced cell mortality at 3 hrs post-MeHg by 22% relative change. Mecamylamine (α2 subunit specific blocker), dihydro-ß-erythroidine (α4 subunit specific blocker), or strychnine before and during MeHg exposure do not protect against cell mortality. In conclusion $GABA_A$Rs contribute to MeHg-induced cytotoxicity. Determining the role of MeHg-induced cell death through these receptors could potentially elucidate mechanisms that these receptors play to MeHg-induced cell death and may assist in identifying pathways by which MeHg causes αMN excitotoxicity and cell death. This project was supported by NIH grant: R01ES024064.

Disclosures: M. Rios Cabanillas: None. **W.D. Atchison:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.14/D32

Topic: B.02. Ligand-Gated Ion Channels

Support: Lundbeck Foundation Grant R230-2016-2562
Drug Research Academy
A.P. Møller Foundation of Advancement of Medical Science

Title: Identification of a novel scaffold with competitive antagonist activity at ionotropic $GABA_A$ receptors

Authors: *C. B. FALK-PETERSEN, T. M. TSONKOV, M. S. NIELSEN, K. HARPSØE, D. E. GLORIAM, P. WELLENDORPH
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Abstract: γ-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the mammalian brain working at both the ionotropic $GABA_A$ receptors ($GABA_AR$) and the metabotropic $GABA_BRs$. The $GABA_ARs$ are chloride conducting heteropentameric receptors composed from 19 different subunits. Receptors composed of $\alpha_{4/6}\beta\delta$ and $\alpha_5\beta\gamma_{2s}$ subunits are located outside the synapse mediating tonic inhibition in contrast to the synaptic receptors (primarily $\alpha_1\beta_2\gamma_{2s}$) mediating phasic inhibition. The number of selective compounds targeting the extrasynaptic receptors are limited and no truly selective antagonists exist. Finding an antagonist only targeting extrasynaptic receptors would help studying the physiological and pathophysiological role of tonic inhibition mediated by these receptor subtypes.
The aim of this study was to identify novel selective antagonists at $\alpha_4\beta_1\delta$ receptors by screening of a diverse small compound library (2112 compounds). Commercially available analogs of the hits would be purchased to improve potency and further studied to gain information on the binding site and selectivity profile.
The screening and follow up studies were performed using the FLIPR Membrane Potential (FMP) on recombinant human $GABA_ARs$ expressed in either a HEK-293 Flp-In cell line stably expressing the human δ-subunit in conjunction with transient expression of α_4 and β_1, or background HEK cell line.
From the initial screening using an EC_{80} value of GABA, we identified one hit, 2027 with an IC_{50} value of 0.33 μM (6.48±0.13, n=4) at $\alpha_4\beta_1\delta$. Further testing showed a similar potency at $\alpha_4\beta_1\gamma_{2s}$ receptors, IC_{50} of 0.13 μM (6.89±0.10, 3). However, upon follow-up testing of 53 analogs of 2027, a 10-fold gain in potency was obtained for the analogue CFP 018, IC_{50} of 88 nM (7.05±0.16, n=3) at $\alpha_4\beta_1\delta$. A Gaddum/Schild analysis of CFP 018 showed a competitive profile with a Schild slope of 1.01±0.062 and a K_B of 19 nM (n=3). This was further supported by preliminary radioligand binding experiments on cortical rat brain homogenate using [^{3}H]muscimol, showing that 2027 and CFP 018 can displace radioligand binding fully with IC_{50} values of 0.36 μM and 14 nM (n=1), respectively. Further selectivity testing at other related $GABA_AR$ subtypes showed a tendency toward a preference for $\alpha_{4/5}$ over $\alpha_{1/6}$ receptors but with no β-subunit or γ/δ-selectivity.
We have identified a novel scaffold with mid nanomolar range potency for ionotropic $GABA_ARs$. Intriguingly, although these ligands are not GABA analogs, they were shown to be competitive antagonists at the orthosteric site. These compounds - or derivatives thereof - may provide lead compounds to gain more insight into the function of selected subtypes of $GABA_ARs$.

Disclosures: C.B. Falk-Petersen: None. **T.M. Tsonkov:** None. **M.S. Nielsen:** None. **K. Harpsøe:** None. **D.E. Gloriam:** None. **P. Wellendorph:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.15/D33

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant MH111461
NIH Grant MH104506
NIH Grant GM108580
Center for the Investigation of Membrane Excitability Diseases at Washington University Grant CIMED-17-03
The Bantly Foundation

Title: Characteristics of delta-subunit containing $GABA_A$ IPSCs in dentate granule neurons

Authors: *M.-Y. SUN[1], S. MENNERICK[1,2,3]
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Abstract: Two major $GABA_A$ receptor classes mediate ionotropic GABA signaling, those containing a δ subunit (δ receptors) and those with a γ2 subunit. Using gene editing to confer picrotoxin resistance on the δ subunit in mice, we pharmacologically isolated δ receptors in dentate granule cells. This chemogenetic approach revealed previously underappreciated impact of δ- receptors on phasic inhibition and possibly unanticipated local actions of GABA rather than spillover-dominated effects. To test whether δ IPSCs are spillover mediated, we first varied recruitment of presynaptic fibers. Surprisingly, increasing stimulus intensity did not alter the relative δ contribution with postsynaptic charge as the output measure, suggesting δ receptors are recruited proportionally to synaptic γ2 receptors. However, the δ contribution to peak IPSC decreased and decay time constant of δ IPSCs increased with increased stimulus intensity, consistent with relative saturation of the peak IPSC and a spillover component that dictates δ IPSC decay time course. We examined whether δ IPSCs are more sensitive than γ2 IPSCs to altered presynaptic vesicle release at a given stimulus strength. With paired stimulation, δ peak IPSCs depressed more than γ2 IPSCs, consistent with higher sensitivity of δ IPSCs to reduced vesicle release. Reduced extracellular $[Ca^{2+}]$ also depressed δ IPSCs more than γ2 IPSCs, consistent with higher sensitivity of δ receptors to altered vesicle release probability. Moreover, the rapidly dissociating antagonist TPMPA exhibited slightly weaker δ IPSC antagonism in high (2.6 mM) $[Ca^{2+}]_o$ vs low (1.3 mM) $[Ca^{2+}]_o$. To differentiate the effects of GABA diffusion vs local synaptic GABA on δ IPSCs, we applied dextran to reduce GABA diffusion. Dextran accelerated δ IPSC decay but had little effect on peak IPSC, suggesting that peak δ IPSC is driven by local, near saturating GABA effects, while IPSC decay is driven by some GABA

escape to distal receptors. Overall, our results indicate that the δ contribution is sensitive to altered release probability, but actions of GABA have both a local and diffusional component. The diffusional component may be smaller than predicted from previous work.

Disclosures: M. Sun: None. **S. Mennerick:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.16/D34

Topic: B.02. Ligand-Gated Ion Channels

Support: NSF Grant IOS1655365

Title: Neuronal glutamate transporters control striatal inhibition

Authors: *M. A. PETROCCIONE[1], A. SCIMEMI[2]
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Abstract: The neuronal glutamate transporter EAAC1 is abundantly expressed in the striatum. Polymorphisms in the gene encoding EAAC1 are associated with neuropsychiatric disorders characterized by the repeated execution of stereotyped motor behaviors, like OCD. What is not known is exactly how EAAC1 regulates synaptic transmission in the striatum. One intriguing feature of EAAC1 is that it is expressed at both excitatory glutamatergic and inhibitory GABAergic synpases. Our previous work has shown that, at excitatory synapses in the striatum, EAAC1 limits activation of metabotropic glutamate receptors and controls long-term synaptic plasticity. Here we ask how EAAC1 shapes GABAergic transmission onto D1 and D2-receptor expressing medium spiny neurons (D1- and D2-MSNs, respectively), the two main output cells in the striatum. We first show that there is a larger co-localization of EAAC1 with D1- than D2-MSNs. Blocking glutamate transporters with the broad-spectrum, competitive glutamate transporter antagonist TFB-TBOA reduces the amplitude of miniature IPSCs (mIPSCs) in D1-MSNs in the presence of EAAC1. The same approach does not lead to significant changes in the mIPSC amplitude in D1-MSNs in the absence of EAAC1. Consistent with these findings, TFB-TBOA reduces the amplitude of evoked IPSCs more profoundly in D1-MSNs that express EAAC1. These findings are consistent with the pre-synaptic localization of EAAC1 at inhibitory synapses. They also indicate that EAAC1 might exert a cell-specific control of inhibition onto D1-MSNs that, in turn, might represent a powerful mechanism to regulate the activity of neuronal circuits that are dysfunctional in OCD.

Disclosures: M.A. Petroccione: None. **A. Scimemi:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.17/D35

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant MH111461

Title: Primary and secondary consequences of altered phasic $GABA_A$ inhibition

Authors: L. ZIOLKOWSKI, M.-Y. SUN, H.-J. SHU, A. BENZ, N. RENSING, M. WONG, *S. J. MENNERICK
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Abstract: Most $GABA_A$ receptors mediating fast inhibition in the CNS contain a single γ2 subunit, which combines with 2 α and 2 β subunits to form a functional receptor. Small changes to the amino acid sequence of the γ2 subunit can have apparently minor effects on the function of the channel but large clinical consequences, such as developmental disorders and epilepsy in humans. The pathology may be triggered by a primary change in $GABA_A$ signaling but probably also involves secondary developmental pathogenic changes. To test the effect of a disruption in inhibition via the γ2 subunit, we engineered a mutation in the γ2 gene (T6'Y) that results in a small change in channel kinetics as well as resistance to picrotoxin, thus providing a pharmacological signature of γ2 incorporation. Recombinant receptors expressed in N2a cells showed expected picrotoxin resistance, no change in steady-state EC_{50} for GABA, but fast deactivation kinetics, assessed by rapid GABA application to nucleated patches and by voltage-pulse relaxations. The lack of change to steady state GABA responses suggests that the γ2 T6'Y mutation can be used to selectively alter synaptic responses. P40-90 mice homozygous for the knock-in mutation in the γ2 locus displayed abnormal baseline EEG dominated by low-frequencies, seizures, and premature death. Abnormal EEG was not evident in heterozygotes or in P23-25 homozygotes. The latter observation is consistent with the possibility of a secondary developmental component driving pathology. In dentate granule neurons from P40-P60 hippocampal slices, γ2-containing mutant receptors exhibited faster mIPSC decays than WT mIPSCs. Faster mIPSC decays in native cells were not caused by γ2 exclusion or by substitution by another subunit, because mIPSCs exhibited resistance to picrotoxin. The primary genetic lesion led to secondary consequences, including reduced mIPSC frequency without a change in mIPSC peak amplitude in dentate granule neurons. These changes represent candidates for those driving eventual abnormal brain function. Results in mice partly phenocopy a mutation in the human γ2 gene (K328M), which results in febrile seizures and generalized epilepsy. Overall, our results demonstrate a well-controlled model system for investigating the developmental changes

triggered by selective mild disruption of phasic inhibition, with possible relevance to human epilepsies.

Disclosures: L. Ziolkowski: None. **M. Sun:** None. **H. Shu:** None. **A. Benz:** None. **N. Rensing:** None. **M. Wong:** None. **S.J. Mennerick:** 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.; SRA from Sage Therapeutics (not related to this study).

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.18/D36

Topic: B.02. Ligand-Gated Ion Channels

Support: Lambert Initiative for Cannabinoid Therapeutics

Title: Concatenated $GABA_A$ receptors reveal diverse molecular phenotype of epilepsy-causing mutations

Authors: *N. ABSALOM[1], V. W. Y. LIAO[2], P. K. AHRING[2], M. T. BOWEN[3], J. ARNOLD[4], I. MCGREGOR[3], M. CHEBIB[2]
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Abstract: Recent advances in whole genome sequence have enabled the identification of *de novo* mutations that cause a range of childhood epilepsies. Multiple mutations have been discovered in genes that encode for subunits of the γ-aminobutyric acid receptor type A ($GABA_A$), specifically GABRA1, GABRB3 and GABRG2 that encode the α1, β3 and γ2 subunits respectively. These mutations are dominant and will express both wild-type and mutant subunits, resulting in a mixture of receptors containing one, or two mutant subunits being expressed at the cell surface.
To determine the consequences on receptor function, we created a concatenated γ2-β3-α1-β3-α1 receptor and expressed it in *Xenopus* oocytes. The receptor responded to GABA at a similar concentration range to receptors created from free subunits and was positively modulated by the benzodiazepine clobazam. We then introduced the γ2(R323Q), β3(D120N), β3(T157M), β3(S254F) and β3(Y302C) mutations in either heterozygous or homozygous configurations. We measured the change in function by constructing concentration-response curves to GABA and estimating the maximum open probability (Est Po) by applying GABA, etomidate and diazepam. The potency of GABA at the γ2(R323Q) mutation was decreased while the maximum Est Po was unchanged. Similarly, when the β3(D120N) and β3(T157M) mutations were introduced at

either location the GABA potency was decreased, however when the mutations were introduced at both locations the activation by GABA was completely abolished. The β3(Y302C) mutation at either location decreased the maximum Est Po and reduced the potency of GABA, while mutations at both locations shifted the concentration-response curve to the right and further reduced the maximum Est Po. Introducing the β3(S254F) at different locations either reduced or increased the GABA potency depending on the location of the mutation. In most cases, introducing the epilepsy-causing mutations impaired GABA function, and the introduction of a mutation at one location caused an intermediate phenotype compared to the introduction of two mutations. These heterozygous receptors will contribute to impaired GABAergic signalling.

Disclosures: **N. Absalom:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lambert Initiative for Cannabinoid Therapeutics. **V.W.Y. Liao:** None. **P.K. Ahring:** None. **M.T. Bowen:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lambert Initiative for Cannabinoid Therapeutics. **J. Arnold:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lambert Initiative for Cannabinoid Therapeutics. **I. Mcgregor:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lambert Initiative for Cannabinoid Therapeutics. **M. Chebib:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lambert Initiative for Cannabinoid Therapeutics.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.19/D37

Topic: B.02. Ligand-Gated Ion Channels

Support: FONDECYT Postdoctoral Fellowship 3170108 to CFB
FONDECYT 1160851 to GM-C
FONDECYT 1170252 to GEY

Title: Screening for novel modulators of the GABA receptor insecticide-resistance using an in silico approach

Authors: *C. F. BURGOS, C. MUÑOZ, G. E. YÉVENES, G. MORAGA-CID
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Abstract: The GABA type A receptors ($GABA_ARs$) are members of the superfamily of ligand-activated pentameric ion channels (pLGICs). $GABA_ARs$ are widely expressed in the nervous system of vertebrates and invertebrates participating in the control of neuronal excitability. Although its function, topology and architecture are highly conserved in vertebrates and invertebrates, there are important differences in its sensitivity to allosteric modulators. This

differential modulation shown by the $GABA_AR$ in insects allows them to be classified in a subgroup and their differences have been widely exploited in the generation of drugs with insecticidal activity. Within this subgroup of receptors, the GABA Rdl (resistance to dieldrin) had been extensively used to study the mechanisms of action of several insecticidal drugs. However, the lack of structural information about the GABA Rdl receptors makes a hard challenge the design of more effective and specific compounds. In order to gain information about the putative binding pocket for several insecticidal drugs, we created homology models using the human beta3 $GABA_AR$ structure for the GABA Rdl receptorA302S/G mutants. Both models were used as a target for docking protein-ligand simulations using a group of selected insecticides. The interaction grid was placed in the binding site for non-competitive antagonist (NCA) IA defined by amino acids A2'(A302), T6'(T306) and L9'(L309) in the TM2 of each subunit. Thus, we predicted docking scores (DS) and theoretical $deltaG_{bind}$ in wild-type GABA receptor for the insecticides cyclodienes dieldrin, endosulfan and phenylpyrazole fipronil. In GABA Rdl receptors dieldrin and endosulfan showed a decrease of DS and $deltaG_{bind}$, while for fipronil were slightly modified. All these results are directly related to the experimental information reported and allow us to validate the GABA Rdl models for the following screening tests. The *in silico* screening was performed using these validated grids and molecules of diverse chemical properties, stored in subsets of the ZINC database, to identify those that would have the potential to modulate the GABA Rdl receptors. A total of 3176623 molecules were initially prepared and their physicochemical properties calculated for later use in this first stage of screening. All generated complexes were analyzed and ranked according to their DS and $deltaG_{bind}$ with a similar protocol to the insecticides. Overall, the *in silico* obtained data suggest that our homology model of the insecticide binding pocket is a viable tool for the screening of novel selective and effective compounds with a potential insecticidal activity.

Disclosures: C.F. Burgos: None. **C. Muñoz:** None. **G.E. Yévenes:** None. **G. Moraga-Cid:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.20/D38

Topic: B.02. Ligand-Gated Ion Channels

Support: APP1124567
LP160100560

Title: Concatenated γ-aminobutyric acid type A receptors revisited; creating order in chaos

Authors: *P. K. AHRING, V. W. Y. LIAO, H. C. CHUA, N. M. KOWAL, M. CHEBIB, T. BALLE
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Abstract: The method of subunit concatenation has been used extensively in defining $GABA_AR$ stoichiometry and subunit arrangement. Theoretically, this technique allows precise experimental control at the single subunit level that would not be possible otherwise. Wide application of the technique followed the systematic refinements performed by the Sigel group in the early 2000s [1]. Since then, a large number of studies have been performed based on the published constructs and the specific ruleset devised by the Sigel group for new construct creation. While the concatenation technique is powerful, there are also caveats associated with its use. Some of the potential pitfalls were discussed by Sigel, Kaur [2]. We speculated, however, that the most important caveat might have been overlooked. Recently, we discovered that the expression of published concatenated nicotinic acetylcholine receptor (nAChR) constructs in oocytes led to far more complex receptor pools than anticipated [3]. This was due to an ability of the linked nAChR subunits to orient themselves in both the clockwise and the counterclockwise directions. In the present study, we therefore evaluate whether the $GABA_AR$ constructs designed by the Sigel group give uniform resultant receptor pools. As expected, based on our previous work with nAChRs, this is not the case. Dimeric constructs and pentameric constructs thereof lead to dimers and pentamers, which have the inherent ability to assemble in both the clockwise and the counterclockwise orientations. In an attempt to constrain this flexibility, we designed a range of dimeric constructs with different linker lengths. Crucially, we find that it is possible to obtain a uniform receptor expression using some of these new concatenated constructs. Our work imply that previous conclusions based on data from concatenated constructs need to be re-examined. As a consequence, we further suggest that the science of $GABA_AR$ assembly may be less chaotic than previously proposed.
1. Minier, F. and E. Sigel. Trends Pharmacol Sci, 2004. **25**(9): p. 499-503.
2. Sigel, E., et al. Biochem Soc Trans, 2009. **37**(Pt 6): p. 1338-42.
3. Ahring, P.K., V.W.Y. Liao, and T. Balle. J Gen Physiol, 2018.

Disclosures: P.K. Ahring: None. **V.W.Y. Liao:** None. **H.C. Chua:** None. **N.M. Kowal:** None. **M. Chebib:** None. **T. Balle:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.21/D39

Topic: B.02. Ligand-Gated Ion Channels

Support: DANDRITE-R248-2016-2518

Title: SorCS1 regulates neurotransmission in the hippocampus and psychiatric disease-related behaviors in mice

Authors: *P. L. OVESEN[1], U. BOELCHO[2], M. M. HOLM[3], A. NYKJAER[2]
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Abstract: Introduction: A shift in the excitation/inhibition balance of the brain may lead to severe psychiatric diseases. The Vps10-p domain receptor SorCS1 has been genetically associated to ADHD and Autism, but so far no studies have addressed the functional relevance. Here we identify Sorcs1 as a critical regulator of inhibitory and excitatory synaptic transmission in the hippocampus. **Methods:** Brain slices from adult SorCS1 -/- mice were used to study evoked synaptic transmission, network inhibition and neuronal excitability in the dentate gyrus performant pathway. Neuronal oscillations were recorded in the pyramidal cell layer of the CA3-CA4. Hippocampal lysates were analysed for gene/protein expression of GABAergic-associated proteins. In-vitro and in-vivo structural properties of inhibitory synapses were studied in primary neuronal cultures (ICC) and hippocampal brain slices (IHC). RNA scope of SorCS1 was performed on E13.5, E15.5 and E17.5 embryos. Cognitive function and psychiatric-related behaviour of SorCS1 KO mice was analysed in a range of behavioural tasks. **Results:** Lack of SorCS1 resulted in impaired basal synaptic transmission, reduced long-term synaptic plasticity as well as enhanced neuronal excitability, reduced network inhibition and impaired γ-oscillation power. In line with this, IHC showed a 2-fold reduction in the density of inhibitory synapses in the dentate gyrus. Protein expression analysis revealed a 3-fold reduction of the $GABA_A$ Receptor α2 subunit in the hippocampus. Accordingly, SorCS1-/- mice displayed impaired working memory and showed psychiatric disease-like symptoms demonstrated by enhanced locomotion, repetitive behaviour and reduced social interaction. **Conclusion:** Our results identify SorCS1 as a key regulator of E/I balance in the hippocampus and suggests a role of SorCS1 in the pathology of psychiatric disorders.

Disclosures: P.L. Ovesen: None. **U. Boelcho:** None. **M.M. Holm:** None. **A. Nykjaer:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.22/D40

Topic: B.02. Ligand-Gated Ion Channels

Title: Ligand-activation of $gaba_a$ receptors on the automated patch clamp platforms qpatch and qube 384 using conventional electrophysiology and optopharmacology

Authors: *M. SCHUPP[1], K. BODDUM[1], D. R. SAUTER[2], P. SKAFTE-PEDERSEN[1], L. BLOMSTER[3], H. L. OLSEN[1], R. B. JACOBSEN[1]
[1]Sophion Biosci., Ballerup, Denmark; [2]Sophion Biosci., Woburn, MA; [3]Saniona, Ballerup, Denmark

Abstract: γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS) and the binding of GABA to GABA receptors ($GABA_AR$) is a crucial process in the healthy brain. An imbalance of GABA secretion or the malfunction of the receptor is associated with multiple disease areas like anxiety disorders, seizures and schizophrenia. Pharmacological manipulation of the receptor has therefore a large therapeutic potential, which is underscored by the amount of available treatment possibilities and the ongoing search for alternatives thereof. However, the progress of drug discovery targeting ion channels such as $GABA_AR$ is limited due to the challenges of manual patch clamp. Here, we show pharmacological modulation of the $GABA_AR$ using our high-throughput automated patch clamp (APC) systems QPatch and Qube 384. Our study includes a characterization of the heterogeneous $GABA_AR$ population of cultured primary hippocampal astrocytes and an evaluation of the $GABA_AR$ clone α5β3γ2. In addition, we utilize the well-characterized $GABA_AR$ response to establish a novel method for ligand release, namely the light-stimulated release of caged GABA using optogenetics on our Qube 384 platform. Our results demonstrate the feasibility of performing $GABA_AR$ targeted drug-screening on our ACP platforms and introduces optogenetics as a viable application for high-throughput pharmacological experiments.

Disclosures: M. Schupp: None. **K. Boddum:** None. **D.R. Sauter:** None. **P. Skafte-Pedersen:** None. **L. Blomster:** None. **H.L. Olsen:** None. **R.B. Jacobsen:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.23/D41

Topic: B.02. Ligand-Gated Ion Channels

Support: MRC

Title: Single transmembrane domain residues control cell surface expression of $GABA_A$ receptor subunits

Authors: *S. HANNAN, T. G. SMART
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Abstract: Cell surface expression of type-A γ-aminobutyric acid (GABA) receptors ($GABA_ARs$) determines the efficacy of inhibitory neurotransmission in the central nervous system. $GABA_ARs$ pentamers are assembled from a pool of 19 subunits (α1-6, β1-3, γ1-3, ρ1-3, δ, θ, ε and π) according to precise co-assembly rules. These restrictions limit the extent of structural diversity of $GABA_AR$ subunits and enable particular subunits, such as ρ1 and β3, to form functional homomeric cell surface ion channels when expressed alone in heterologous systems, whilst the brain-abundant subunits, such as α and γ, are retained within intracellular compartments. Why the most abundant $GABA_AR$ subunits fail to form homomeric ion channels is unknown. Normally, surface expression of α and γ subunits require co-assembly with β subunits via interactions between their N-terminal sequences in the endoplasmic reticulum. Here, we identify two critical residues in the transmembrane domains of α and γ subunits, which, when substituted for their ρ1 counterparts, permit cell surface expression as homomers.
Consistent with this, substitution of the ρ1 transmembrane residues for the α-subunit equivalents reduced surface expression and altered channel gating highlighting their importance for $GABA_AR$ trafficking and signaling. Although not ligand-gated, the formation of α and γ homomeric ion channels at the cell surface was revealed by incorporating a mutation that imparts the functional signature of spontaneous channel activity. Ligand-gating of α homomers was enabled by creating a GABA-binding β subunit equivalent interface on the α1 subunit. This permitted low efficiency GABA gating of α1 homomers. Our study identifies two single transmembrane residues, one of which is important for neurosteroid modulation, that allow homomeric $GABA_AR$ subunit cell surface trafficking. This demonstrates that α and γ subunits can form functional ion channels.
This work was supported by the MRC UK

Disclosures: S. Hannan: None. **T.G. Smart:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.24/D42

Topic: B.02. Ligand-Gated Ion Channels

Title: SAGE-516, a synthetic neuroactive steroid $GABA_A$ receptor positive allosteric modulator, reduces tremor activity in a mouse model of essential tremor

Authors: *S. GEE, C. MARCIAG, T. KAZBODA, S. MCTIGHE, B. FARLEY, M. QUIRK, F. SALITURO, J. DOHERTY, A. ROBICHAUD, R. HAMMOND
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Abstract: Essential tremor (ET) is a movement disorder characterized by kinetic tremor, typically of the hands, arms and head. While its precise pathophysiology is not fully understood,

ET has been associated with dysregulated type-A, gamma-aminobutyric acid ($GABA_A$)-mediated inhibition in the brain, resulting in cerebellar hyperactivity (Bucher 1997; Louis 2007 & 2008). Medications that activate $GABA_A$ receptors are associated with improvements in ET (Ondo et al., 2016). Some benzodiazepines are efficacious for tremor, but their utility is limited by sedation. Moreover, ethanol can potently reduce tremor without sedation (Koller and Biary, 1984; Zeuner et al., 2006). Although alcohol has actions at other central targets (e.g. *N*-methyl-D-aspartate (NMDA) receptors, voltage-gated potassium channels, and glycine receptors), the ability of alcohol to suppress tremor is thought to be mediated by activity at extrasynaptic $GABA_A$ receptors (Santhakumar et al., 2007). Consistent with this, alcohol does not suppress a preclinical measure of tremor in mice lacking extrasynaptic, α6 $GABA_A$ receptors, but transiently suppresses preclinical tremor in mice lacking synaptic, α1 $GABA_A$ receptors. Certain classes of neuroactive steroids (NAS) are positive allosteric modulators (PAMs) of both synaptic and extrasynaptic $GABA_A$ receptors. Here, we tested whether the NAS, SGE-516 (Botella et al., 2015), suppresses tremor in a preclinical, harmaline tremor model. Administration of harmaline in rodents produces a postural and kinetic tremor that resembles ET in humans (with respect to tremor frequency), is sensitive to anti-tremor medications that are effective in humans (e.g. propranolol), and can be measured digitally via a piezoelectric metal plate. SGE-516 administration (1 mg/kg i.p.) 30 min prior to harmaline (10 mg/kg i.p.) significantly suppressed the peak harmaline power (between 10-20Hz) by 51.5 ± 13.6% (mean ± SEM, n = 15 mice, $p < 0.005$, One-way ANOVA, Holm-Sidak's multiple comparison test). Interestingly, a higher dose of SGE-516 (3 mg/kg i.p.) did not significantly reduce harmaline tremor. The beta blocker, propranolol (10 mg/kg, i.p.), was included as a positive control and significantly reduced peak harmaline power by 49 ± 20.8%. These data suggest that SGE-516 demonstrates anti-tremor activity in a mouse model of ET, and support the targeting of extrasynaptic $GABA_A$ receptors for novel treatments of ET.

Disclosures: S. Gee: A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **C. Marciag:** None. **T. Kazboda:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **S. McTighe:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **B. Farley:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **M. Quirk:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **F. Salituro:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **J. Doherty:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

funds); Sage Therapeutics. **A. Robichaud:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics. **R. Hammond:** A. Employment/Salary (full or part-time):; Sage Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sage Therapeutics.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.25/D43

Topic: B.02. Ligand-Gated Ion Channels

Support: GM118801
AA10422

Title: Modulation of both β2- and β3-containing $GABA_A$Rs is necessary for etomidate-induced suppression of LTP *in vitro*

Authors: *G. SURGES[1], A. FIGUEROA[1], C. LOR[1], N. KUNZ[2], G. E. HOMANICS[2], R. A. PEARCE[1]
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Abstract: Background: Etomidate (ETOM) modulates $GABA_A$Rs containing either β2- (β2-$GABA_A$Rs) or β3-subunits (β3-$GABA_A$Rs). In the hippocampus, this enhancement of inhibitory neurotransmission is thought to contribute to ETOM suppression of learning and memory. We reported recently that a mutation that prevents modulation of β2-$GABA_A$Rs (β2-N265M) confers resistance to ETOM-induced suppression of LTP (SfN2017 abstract number 254.14). In a previous study we had reported that mice with a similar mutation of the β3-$GABA_A$R subunit (β3-N265M) remained susceptible to ETOM-induced LTP suppression (Rodgers et al., J. Neuroscience, 2015). Since these two sets of studies were performed using mice of different background strains (β2-N265M in C57BL/6J, β3-N265M in 129X1/SvJ) and with different stimulation protocols, equipment, and ETOM concentrations , we conducted a head-to-head comparison of mice carrying the N265M mutation of either the β2- or β3-subunit in the same mixed backgrounds (50% C57BL/6J, 50% 129X1/SvJ) to test the robustness of this difference. **Methods:** Using extracellular recordings from hippocampal brain slices taken from mice carrying the N265M point mutation in either the β2- or β3-subunit of the $GABA_A$R, we measured LTP in the CA1 region of the hippocampus in 60-100 day old mice of a mixed C57BL/6J and 129X1/SvJ background. We used a stimulus intensity that produced a half-maximal EPSP response, both to assess EPSP slope and to induce LTP by a theta-burst protocol. We performed one-tailed Student's t-tests to compare LTP in groups of 8 brain slices in the

presence or absence of 1μM ETOM.
Results: The intensity needed to produce half a maximal EPSP was approximately 200μA and did not differ between genotype. As expected, ETOM suppressed LTP in WT animals from both mouse lines (β2-N265M: CTRL 130±3% vs. ETOM 115±5%, p=0.007; and β3-N265M: CTRL 134±7% vs. ETOM 115±4%, p=0.01). However, ETOM failed to suppress LTP in β2-N265M (CTRL 129±3.5% vs. ETOM 124±2%, p=0.10) and β3-N365M mutant mice (CTRL 134±5.5% vs. ETOM 128±4%, p=0.21).
Conclusions: Our results indicate that modulation of both β2- and β3-$GABA_A$Rs is necessary for ETOM to suppress LTP in mice of mixed backgrounds. The finding that ETOM modulation of β3-$GABA_A$Rs is necessary conflicts with our previous results, possibly due to methodological differences or background strains. This finding highlights the need to test the contributions of specific drug targets under varying conditions (electrophysiological methods, background strains) in order to establish robust associations with physiological effects.

Disclosures: G. Surges: None. **A. Figueroa:** None. **C. Lor:** None. **N. Kunz:** None. **G.E. Homanics:** None. **R.A. Pearce:** None.

Poster

200. GABA(A) Receptors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 200.26/D44

Topic: B.02. Ligand-Gated Ion Channels

Support: March of Dimes
Louis Stoke for Minority participation

Title: Folic acid supplementation alters Smad3, DnMT1, and DnMT3a in SH-SY5Y neuronal cells

Authors: *K. VAZQUEZ[1,2], A. EL IDRISSI[2]
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Abstract: Prenatal nutrition is a crucial factor in embryonic development and can influence phenotype through epigenetic modulation. Folic acid (FA), the synthetic form of the B vitamin folate, is a necessary nutrient for proper neural tube closure and development. Folic acid interacts with DNA methyltransferases such as DNMT1, DNMT3a, and DNMT3b to induce neuronal cell differentiation. As a water-based compound, folic acid can accumulate in the bloodstream over time and passes through the blood-placental barrier. Yet its dose toxicity for the developing embryo and for the levels of bioavailability for embryonic metabolism has not been established. In our previous study, a microarray analysis of fibroblast FA treated cells revealed that as many

as 1,000 genes were either upregulated or downregulated by folic acid supplementation, including SMAD3, a transcription modulator involved in the migration of the GABAergic neurons during embryonic development, and fragile X mental retardation 1 (FMR), the primary gene responsible for fragile X syndrome.
The effects of folic acid dose on neurodevelopment were explored by evaluating FA treated SH-SY5Y neuronal cell line expression of SMAD3 mRNA with quantitative real-time reverse transcriptase PCR (qRT-PCR) and protein with immunofluorescence microscopy, and DnMT1 and DnMT3a protein expression. We also tested the levels of GABA indirectly by testing Glutamic acid decarboxylase 65/67 mRNA in (qRT-PCR) and protein either through western blot or confocal microscopy and quantified with Imaris; $GABA_A$ beta 3 (GABRβ3) levels were also quantified with similar methods.
Results showed that folic acid dose affected SMAD3 gene and protein, and it was found to be co-localized with DnMT1, while FMRP co-localized with DNMT3a. DnMT1 and DnMT3a increased with folic acid treatment. $GABA_A$ beta 3 (GABRβ3) slightly decreased with FA concentration 16-125ng/ml but increased with 250ng/ml. 250ng/ml is possibly toxic to the cells. Glutamic acid decarboxylase 65/67 mRNA and protein decreased with FA concentration.
Taken together, these results indicate that increasing FA of differentiating neuronal cell alters the expression of SMAD3 and GABAergic system protein, as well as DNA methyltransferases. The mechanism by which FA alters these genes may involve DNA methyltransferases, such as DnMT1 and DnMT3a. Further research is needed to determine the neurotoxic dose of folic acid in its effects on pre-natal central nervous system development.

Disclosures: K. Vazquez: None. **A. El Idrissi:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.01/D45

Topic: B.07. Synaptic Plasticity

Title: Parvalbumin interneurons of visual primary sensory cortex in adult mice express Acan and several other genes involved in the making of the PeriNeuronal Net (PNN)

Authors: *J. P. ROSSIER[1], L. T. GRAYBUCK[2], M. J. HAWRYLYCZ[4], E. LEIN[5], B. TASIC[3], H. ZENG[6]
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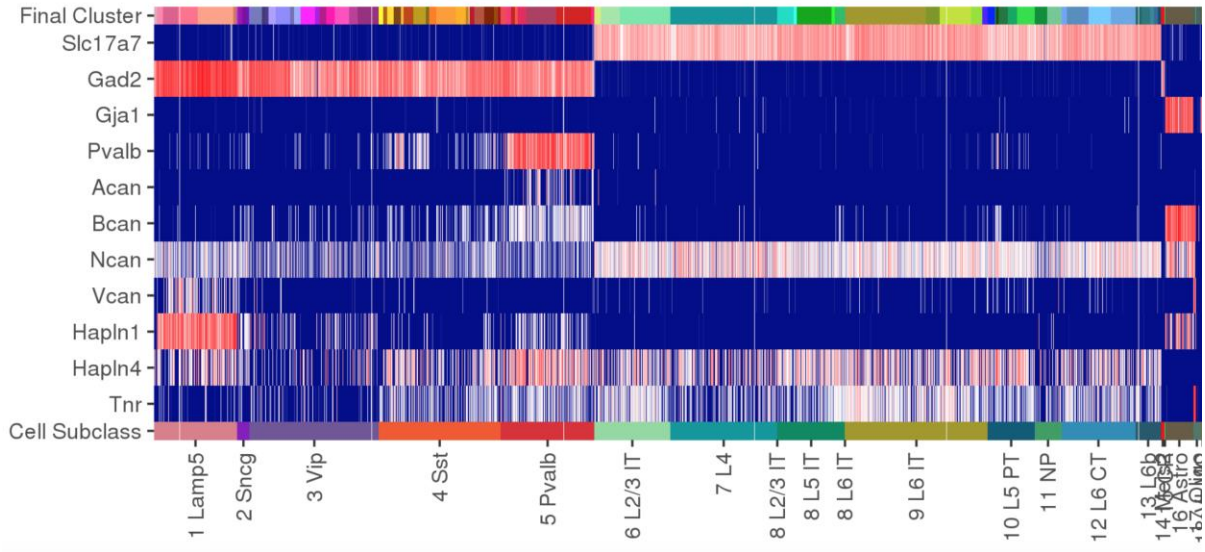
Abstract: The PeriNeuronal Net (PNN) in the brain is a specialized extracellular matrix structure forming a mesh-like lattice surrounding neuronal cell bodies It is found in most areas of

the brain. It has been shown to enwrap synaptic terminals synapsing onto cell bodies, and could function as a “fence” blocking movements of pre- and post-synaptic proteins. During brain development, the formation of PNN is associated with the end of the critical period of plasticity. Proteins of PNN are four proteoglycans: aggrecan (*Acan*), brevican (*Bcan*), neurocan (*Ncan*) and versican (*Vcan*). They include two hyaluronan and proteoglycan link proteins: (*Hapln1,4*) and one tenascin (*Tnr*). Polysaccharides of PNN are hyaluronan- and chondroitin-sulfate formed by an array of enzymes encoded by *Has1-3, Chst1-15*, *Csgalnact1-2* and*St6galnac1-6*.
The present work investigates expression of genes previously implicated in the formation of PNN around parvalbumin (PV) interneurons. We examined the Allen Institute single cell transcriptomics dataset containing14301 cells isolated from the primary visual cortex of 56-day old mice (Tasic et al., BioRxiv, 2017, doi:https://doi.org/10.1101/229542) for the expression of PNN genes. Among the 5759 GABAergic neurons, 21% were PV interneurons which could be separated by their expression profiling in 8 clusters. One of these clusters, Pvalb-Tpbg (trophoblast glycoprotein), was composed of 391 cells, all expressing Pvalb and 55% expressing *Acan*, which was restricted to Pvalb-expressing neurons. The other proteoglycans *Bcan* and *Ncan* were expressed in most of the cells including glia. *Vcan* and *Tnc* were barely detected in PV interneurons. *Hapln1* was expressed in most classes of interneurons and glia. *Hapln4* and *Tnr* were expressed in most of the cells except glia. In conclusion PNN genes, including the following polysaccharide-synthesis genes *Has1,3*; *Chst1,2,7,10-12*; *Csgalnact2*; *St6galnac2-6* are expressed in PV interneurons while *Csgalnact1 and Chst15* are not. Mice KO for these latter key enzymes in the synthesis of chondroitine-sulfate have a prolong critical period..



Disclosures: J.P. Rossier: None. **L.T. Graybuck:** None. **M.J. Hawrylycz:** None. **E. Lein:** None. **B. Tasic:** None. **H. Zeng:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.02/D46

Topic: B.07. Synaptic Plasticity

Support: NINDS intramural funds

Title: Activity-induced structural changes at the nucleus and endoplasmic reticulum of hippocampal neurons

Authors: *J.-H. TAO-CHENG
NINDS, NIH, Bethesda, MD

Abstract: Neurons exhibit activity-induced structural changes such as increase of thickness and curvature of the postsynaptic density (PSD), decrease in contact area between subsurface cistern and plasma membrane, and formation of CaMKII clusters and synaptic spinules by electron microscopy. These structural characteristics help in identifying the activity state of the neuron and should be taken into consideration when interpreting ultrastructural features of the neurons. Here in organotypic hippocampal slice cultures where experimental conditions can be easily manipulated, two additional features are documented in forebrain neurons as reliable benchmarks for activity-induced structural changes: (1) The neuronal nucleus showed conspicuous clustering of dark chromatin, and (2) the endoplasmic reticulum formed stacks with a uniform gap of 13 nm filled with dark materials. Both structural changes progressed with time and were reversible upon returning the slice cultures to control medium for a period of time. These activity-induced structural changes were also verified in other experimental systems such as dissociated hippocampal neuronal cultures as well as perfusion-fixed brains. Furthermore, the time course and recovery of the increase in thickness and curvature of the postsynaptic density upon stimulation were quantified in slice cultures. These changes in PSD as well as the neuronal nuclear chromatin clustering were detectable as early as 30 seconds of depolarization with high K^+ (90 mM) or treatment with NMDA (50 μM). In contrast, the formation of ER cisternal stacks did not become apparent for another 30 seconds, and the time course of formation and recovery is also different from that of the chromatin clustering. These structural changes were blocked by APV, an NMDA antagonist. Furthermore, when the extracellular calcium was chelated by EGTA in dissociated cultures, treatment with high K^+ medium no longer induced these changes. These results indicate that the activity-induced nuclear chromatin clustering and formation of ER stacks in neurons are calcium-dependent, and that they may bring insights to neuron's response to calcium rise upon stimulation.

Disclosures: J. Tao-Cheng: None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.03/D47

Topic: B.07. Synaptic Plasticity

Support: NSFC#81771455

Title: Physical exercise improves dendritic spine plasticity and enhances synaptic transmission in mouse frontal cortex

Authors: *L. ZHANG, K. CHEN, Y. ZHENG, J.-A. WEI, H. OU-YANG, K.-F. SO
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Abstract: Objectives: Physical exercise improves cognitive functions, but little is known about its cortical effects. The present study aims to investigate the modulation of cortical spine plasticity by chronic exercise in mouse. Methods: Transcranial in vivo two-photon imaging was used to study the spine plasticity and neuron activity of layer 5 pyramidal neurons (L5PRN) in mouse motor cortex. Pharmaceutical approaches was further used to interrogate the role of mammalian target of rapamycin (mTOR) pathway within exercise-induced effects. Results: Treadmill exercise significantly increases spine formation rate and survival of L5PRN within motor cortex. Improved spine plasticity is accompanied with enhanced excitatory postsynaptic transmission. Further mechanistic studies attributes brain derived neurotropic factor (BDNF) and downstream mTOR activation underlying exercise-related beneficial effects for enhanced learning of motor skills. Conclusion: We provide the first in vivo evidences showing improved spine plasticity and neuron activity by chronic exercise, and may guide the intervention of psychiatric disorders using physical exercise.

Disclosures: L. Zhang: None. **K. Chen:** None. **Y. Zheng:** None. **J. Wei:** None. **H. Ou-yang:** None. **K. So:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.04/D48

Topic: B.07. Synaptic Plasticity

Support: JSPS KAKENHI Grant 26250014
JSPS KAKENHI Grant 17H01387
JST CREST JPMJCR14W2

Title: Cytoplasmic structure inside dendritic spine modulates molecular mobility

Authors: *K. OBASHI[1,2], A. MATSUDA[3,2], Y. INOUE[3,2], S. OKABE[1,2]
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Abstract: The cytoplasm of dendritic spines is characterized by the enrichment of F-actin, together with other structural features, such as the postsynaptic density and the spine apparatus. These nanostructures in the spine compartment restrict the mobility of macromolecules, which conversely affect functions of spine nanostructures. To evaluate this interplay between molecular dynamics and structure, real-time monitoring of molecular mobility inside the spine cytoplasm is required. Currently available techniques for the measurement of molecular mobility, such as fluorescence recovery after photobleaching (FRAP), are useful in quantitative measurements of diffusional coupling between dendritic shafts and spines, but direct readout of molecular diffusivity inside spines cannot be achieved. We applied the technique of two-photon fluorescence correlation spectroscopy (2P-FCS) and two-photon raster image correlation spectroscopy (2P-RICS) to monitoring dynamics of fluorescent proteins within dendritic spines of cultured neurons. To exclude artifacts derived from the small volume of spines, we first took a model-based evaluation for the readout of FCS inside small compartments using Monte Carlo simulation. 2P-FCS and 2P-RICS with different probe sizes revealed the size-dependent reduction in diffusion inside spines. Measurements in spines after LTP-inducing stimuli indicated a transient increase in mobility, which was dependent on F-actin. Finally, FRAP of synaptic proteins during LTP enabled us to indirectly estimate molecular mobility inside spines, when combined with a physical model based on spine morphological parameters. The model indicated that both mobility and stable fraction of large synaptic molecules increased at the initial phase of LTP. Our data support the idea that intra-spine cytoplasmic reorganization at the initial phase of LTP increases the mobility of large molecules, which subsequently facilitates intermolecular interaction related to maintenance of LTP.

Disclosures: K. Obashi: None. **A. Matsuda:** None. **Y. Inoue:** None. **S. Okabe:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.05/D49

Topic: B.07. Synaptic Plasticity

Support: ANR-15-CE16-0010

Title: Control of perineuronal net and cortical plasticity by the activity of fast spiking-parvalbumin interneurons

Authors: *G. DEVIENNE, B. CAULI, I. COHEN, S. PICAUD, L. TRICOIRE, J. ROSSIER, B. LAMBOLEZ
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Abstract: During the post-natal development of the cerebral cortex, the closure of the highly plastic period, called critical period, is concomitant with the accumulation of a specialized extracellular matrix made of chondroitin sulfate proteoglycans, the perineuronal net (PNN), around fast-spiking inhibitory interneurons expressing parvalbumin (FS-PV). Destroying the PNN by enzymatic digestion, or decreasing the inhibitory tone reopens the critical period. We aim at identifying physiological signals that up or down-regulate the PNN.
It is known that selective inhibition of FS-PV cells for only 24 h using targeted viral transduction of a DREADD (hM4Di) in vivo restores plasticity in the adult mouse visual cortex. We found that this protocol induces a robust reduction of the PNN surrounding DREADD-expressing FS-PV neurons (decrease of Wisteria floribunda labelling) after treatment with the DREADD agonist CNO.
The DREADD hM4Di has somatodendritic effects, but also presynaptically inhibits transmitter release. Hence, in vivo activation of hM4Di in FS-PV cells may result either in decreased or in increased somatodendritic excitation of PV neurons due to disinhibition of pyramidal cells. To discriminate between these possibilities, we characterize acute electrophysiological effects of CNO treatment, as well as the effects of DREADD-induced excitation of FS-PV or pyramidal cells on the PNN. Using EEG recordings in awake mice expressing hM4Di in FS-PV cells, a decrease of cortical gamma oscillations following CNO injection is observed, consistent with a decrease of FS-PV activity. Using patch-clamp recordings in cortical slices, we found that CNO moderately decreases the somatodendritic excitability of FS-PV cells. We also probed the effect of selectively exciting FS-PV or pyramidal neurons in vivo on the PNN using the above paradigm, except that excitatory DREADD hM3Dq is used instead of hM4Di. Our results show that neither excitation of FS-PV neurons nor of pyramidal cells induced detectable decrease of PNN density.
This set of experiments suggest that hM4Di induces a moderate silencing of FS-PV cell in vivo, which may be the trigger of the observed PNN reduction. We hypothesize that FS-PV neurons act as sensors of the local network activity to regulate their PNN and cortical plasticity.

Disclosures: G. Devienne: None. **B. Cauli:** None. **I. Cohen:** None. **S. Picaud:** None. **L. Tricoire:** None. **J. Rossier:** None. **B. Lambolez:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.06/D50

Topic: B.07. Synaptic Plasticity

Support: CREST of JST (JPMJCR1652)
Gant-in-aid from JSPS (26221001)
AMED (17dm017120h0002)
International Research Center for Neurointelligence (WPI-IRCN) at The University of Tokyo Institutes for Advanced Study

Title: Potentiation of presynaptic functions by mechanical forces generated by spine enlargement

Authors: H. UCAR[1,2], S. WATANABE[3], J. NOGUCHI[3], S. YAGISHITA[1,4], Y. MORIMOTO[1], N. TAKAHASHI[5], *H. KASAI[1,2]
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Abstract: We are studying whether the mechanical force caused by the enlargement of the dendritic spines has direct effects on presynaptic functions. We used the Schaffer collateral (SC) innervating CA1 pyramidal neurons in hippocampal slice cultures. First, we measured the vesicle status of the presynaptic boutons of SC by using the trans-SNARE probe which measured Förster resonance energy transfer (FRET) between t-SNARE (Syntaxin1A) and v-SNARE (VAMP2) by utilizing fluorescence lifetime imaging (FLIM) and time-correlated single photon counting (TCSPC) method. We found rapid increases in the FRET value when we pushed single presynaptic boutons by a fluorescent-dye coated fine glass electrode, indicating that the mechanical pushing of the plasma membrane towards the vesicle membrane can induce the trans-SNARE formation. Similar increases in the trans-SNARE formation were found when we applied hypertonic sucrose solution, which exerts osmotic pressures on the plasma membrane of presynaptic boutons. Second, we measured glutamate release probability (Pr) from an identified single bouton, using a variant of iGluSnFR in SC, and its responses to single action potentials delivered at 0.07 Hz. We found the pushing augmented the Pr in a good correlation with the increases in the trans-SNARE formation. Similar augmentation was observed by hypertonic sucrose solutions. Lastly, we induced spine enlargement by spike-timing-dependent plasticity (STDP) at the dendritic spine using 2-photon glutamate uncaging to test the physiological

relevance of the mechanical effect. For this study, we found synapse candidates between SC and CA1 pyramidal neurons by overlapping optical signals of boutons (expressing trans-SNARE probe) and dendritic spines (filled by Alexa-dye by whole-cell patch-clamping). We found that spine enlargement caused an increase in the trans-SNARE formation, even though we did not stimulate presynaptic axons by action potentials. Importantly, we found that the increase in the trans-SNARE formation was not detected when spines twitched and did not push the bouton, even though spines were enlarged. Besides, prevention of enlargement by infusing actin inhibitors via patch-pipette prevented FRET increase in all trials. Thus, we have revealed that the mechanical force on the presynaptic membrane is sufficient for enhancing Pr by increasing the trans-SNARE formation, and we suggest that the spine enlargement can potentiate the synaptic transmission by direct mechanical coupling with a presynaptic terminal, in addition to its well-recognized role in postsynaptic accumulation of glutamate receptors for long-term potentiation.

Disclosures: H. Ucar: None. **S. Watanabe:** None. **J. Noguchi:** None. **S. Yagishita:** None. **Y. Morimoto:** None. **N. Takahashi:** None. **H. Kasai:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.07/D51

Topic: B.07. Synaptic Plasticity

Support: AIRAlzh Onlus-COOP Italia
Fondo di sviluppo unimi- linea B 15-06-3022001-05

Title: Cyclase-associated protein 2 role in the cytoskeletal organization of the spine

Authors: *S. C. PELUCCHI[1,2], L. VANDERMEULEN[1], S. MUSARDO[3], D. LIM[4], D. DI MARINO[5], M. PASSAFARO[6], M. MIKHAYLOVA[7], F. GARDONI[1], M. DI LUCA[1], E. MARCELLO[1]
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Abstract: ADAM10, an essential protease of the brain, is active only when it is inserted at the synaptic membrane and, therefore, its localization is linked with its activity. In fact, ADAM10 cleaves its substrates, among which the synaptic adhesion molecule N-cadherin, only when it is correctly inserted into the plasma membrane. Therefore, the correct trafficking of ADAM10 to the plasma membrane correlates directly with its capability to regulate the synaptic morphology

and neuronal connectivity.
The cyclase-associated protein 2 (CAP2) is a new ADAM10 binding partner. Here we confirmed ADAM10/CAP2 interaction and identified the domains responsible for the association through several biochemical approaches.
At first, we show that CAP2, an actin binding protein that has been poorly described in the brain, is a regulator of actin dynamics in dendritic spines. In particular, the capability of the protein to create dimers regulates its G-actin sequestering activity. Moreover, our data prove that the F-actin-binding site of CAP2 is fundamental for the regulation of the endocytosis of ADAM10 and, thereby, of its localization.
Since CAP2 is an actin-binding protein that interacts with ADAM10, we assume that CAP2 may act as a linker between dendritic spine actin dynamics and ADAM10 synaptic localization, thus affecting the enzyme activity and spine remodeling.

Disclosures: S.C. Pelucchi: None. **L. Vandermeulen:** None. **S. Musardo:** None. **D. Lim:** None. **D. Di Marino:** None. **M. Passafaro:** None. **M. Mikhaylova:** None. **F. Gardoni:** None. **M. Di Luca:** None. **E. Marcello:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.08/E1

Topic: B.07. Synaptic Plasticity

Support: NIH Grant RO1NS062736

Title: NMDA receptor signaling mechanisms driving structural plasticity of dendritic spines

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Abstract: The ability to learn and integrate new information requires the dynamic modification of brain circuits. Formation, stabilization and elimination of dendritic spine synapses are vital for this experience-dependent rearrangement of neuronal circuits. Notably, the shrinkage and elimination of spine synapses have been linked to improvements in learning, and increased rates of spine loss are associated with intellectual disability and behavioral impairment. Morphological changes in dendritic spines are closely linked to changes in synaptic function, and it is now widely accepted that the shrinkage and elimination of spines can be driven by glutamatergic activity patterns that lead to the long-term depression (LTD) of synaptic strength. Synaptic weakening and spine shrinkage requires activation of the NMDA-type glutamate receptor (NMDAR). Intriguingly, blocking Ca^{2+}-influx through the NMDAR did not prevent spine shrinkage and LTD induction. Instead, these novel findings support a model where glutamate

binding triggers conformational changes in the NMDAR signaling complex, which are sufficient to induce spine shrinkage and synaptic weakening, independent of NMDAR-mediated Ca^{2+}-influx. Using pharmacological and molecular manipulations in combination with two-photon imaging and glutamate uncaging, we have shown that activation of p38 MAPK is necessary for this non-ionotropic NMDAR signaling and activity-dependent spine shrinkage. Currently, we are further delineating the composition and function of this non-ionotropic NMDAR signaling complex in input-specific structural and functional spine plasticity. Specifically, we are focusing on how conformational changes in the NMDAR complex drive p38 MAPK activation and on how p38 MAPK activation is translated to spine structural changes. Results from these experiments will lead to a better understanding of the signaling mechanisms driving dendritic spine elimination during neuronal circuit development and plasticity and should provide new insights into how dysregulation of these plasticity mechanisms contributes to neurological disorders.

Disclosures: D.K. Park: None. **I.S. Stein:** None. **J.N. Jahncke:** None. **K.M. Zito:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.09/E2

Topic: B.07. Synaptic Plasticity

Support: Project is supported by FASIE (Foundation for Assistance to Small Innovative Enterprises) in 2017

Title: Features in the structural & functional reorganization of the screen and nuclear nerve centers of white rats after acute transient ischemic attack

Authors: *V. AKULININ, A. STEPANOV, D. AVDEEV, A. GORBUNOVA
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Abstract: In the present study the structural features of screen (neocortex, hippocampus) & nuclear (amygdala) brain formations of white rats (n = 70) in 1, 3, 7, 14, 21 & 30 days after acute transient ischemic attack caused by bilateral 20-min occlusion of the arteria carotis communis were analyzed by using light & electron microscopy, immunohistochemical methods, DAPI stain, morphometry. The experiment was perfomed adhering to the principles of animal welfare. The brain was fixed by perfusion of 4% paraformaldehyde solution in 0.1 M phosphate buffer (pH 7.2-7.4) through aorta. Primary antibodies to neuron specific enolase (NSE), glial fibrillary acidic protein (GFAP), Ki67, p53, Bcl-2, caspase-3, synaptophysin p38 и MAP-2 were used for immunofluorescence examination. Morphometric image analysis was performed using ImageJ 1.46. Statistical hypothesis testing was carried out used the program STATISTICA 8.0 with a

nonparametric methods. The mixed nature of neuronal death was found. However, the major part in the death of neurons was played by the processes of fast (1, 3 & 7 days of reperfusion) & distant (14, 21 & 30 days of reperfusion) postischemic necrosis. The basic mass of the dark neurons from acute period restored their tinctorial characteristics in the distant period. Apoptosis regulating proteins (p53, bcl-2) were detected in single neurons. Caspase-3 had high activity only in axons & synaptic terminals, that probably showed its pleiotropism, participation in the adaptation & recovery processes by postischemic activation of neuroplasticity. Damage of neocortex & hippocampus neurons had a fine-focal form. The maximum decrease in the total number density of neurons was in layer III of the neocortex (95% CI: 16-28) & CA1 hippocampus (95% CI: 33-47%). Against the background of neuronal damage, neuroglia proliferation (Ki 67) was activated, GFAP expression increased, neuroglial index increased, a large number of satellite cells & reactive microglia appeared. The peak proliferation of the astrocytes was observed after 3 days of the reperfusion in the neocortex. The increase in the neuroglia index (NGI) was due to the proliferation of neuroglia cells & reduce of the total number density of neurons. We found that as small is the number of synapses, but more NGI, the area of mitochondria & neuroglia cell fibrillar baskets in the visual field in normalcy, as less is the damage of synapses & neurons after ischemia. In our study, such brain region was the amygdala.

Disclosures: V. Akulinin: None. **A. Stepanov:** None. **D. Avdeev:** None. **A. Gorbunova:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.10/E3

Topic: B.07. Synaptic Plasticity

Support: MRC Doctoral studenship
Wellcome Trust Investigator Award

Title: Activity-dependent form and function of chandelier cells and their synapses

Authors: *A. PAN VAZQUEZ, W. WEFELMEYER, J. BURRONE
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Abstract: The axon initial segment (AIS) is a structure at the start of the axon with a high sodium and potassium channel density, defining the site of action potential generation. It is also the target of inhibitory synapses formed by a specific GABAergic interneuron, the Chandelier cell. Due to this strategic synaptic placement, Chandelier cells are thought to powerfully control network activity. Despite this, we know surprisingly little about this cell type. By visualising Chandelier cell interneurons and their boutons in somatosensory cortex at different

developmental stages, we uncovered a critical temporal window of synapse formation at the AIS, which corresponds with the electrophysiological and morphological maturation of the Chandelier cell. Using a targeted chemogenetic approach, we showed that modulating the activity of either pyramidal cells or Chandelier cells themselves, resulted in a decrease in axo-axonic synapse number along the AIS. In parallel, we also observed a decrease in the length of the AIS and, as a consequence, a reduction in intrinsic excitability. Surprisingly, the same manipulation of neuronal activity in mature mice showed the opposite effect, an increase in axo-axonic synapse number. Since axo-axonic synapses change polarity from depolarising to hyperpolarising late in development, this form of plasticity likely constitutes a homeostatic mechanism that serves to keep network activity stable. To confirm this, we studied the functional impact of this synaptic plasticity using whole-cell electrophysiology as well as voltage imaging. In conclusion, our work on the activity-dependent development of Chandelier cells has uncovered a bi-directional plasticity of axo-axonic synapses in juvenile and adult mice. We propose that the AIS and its synapses are highly plastic and form an important hub for stabilising neuronal activity.

Disclosures: A. Pan Vazquez: None. **W. Wefelmeyer:** None. **J. Burrone:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.11/E4

Topic: B.07. Synaptic Plasticity

Title: Isoflurane inhibits brain-derived neurotrophic factor release leading to reduced synaptic vesicle exocytosis and dendritic spine loss

Authors: K. W. JOHNSON[1], F. S. LEE[2], H. C. HEMMINGS, Jr.[3], *J. PLATHOLI[1]
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Abstract: General anesthetics modulate synaptic transmission by acting on multiple pre- and postsynaptic targets including neurotransmitter release, neurotransmitter receptors, and dendritic spine dynamics. Inhibition of glutamate release is one of several ways general anesthetics depress excitatory synaptic transmission, but the underlying cellular and molecular targets remain unclear. We hypothesized that isoflurane, a common general anesthetic, reduces brain-derived neurotrophic factor (BDNF) release, resulting in decreased presynaptic Ca^{2+} entry and synaptic vesicle (SV) release, and reduced postsynaptic dendritic spine size and number. Dissociated hippocampal neurons from wild-type and loss-of-function BDNF Val66Met knock-in mice with reduced BDNF secretion were used to test this hypothesis. Isoflurane-induced changes in BDNF release were measured using the genetically encoded biosensor BDNF-pHluorin. Hippocampal neurons in culture with varying levels of BDNF secretion were used to

determine the effect of reduced endogenous BDNF amounts on Ca^{2+} entry and SV exocytosis, using the fluorescent Ca^{2+} indicator MgGreen and vGlut1-pHluorin, respectively. Postsynaptic isoflurane-induced changes in dendritic spine morphology were visualized using time-lapse imaging. Our results show that isoflurane attenuated BDNF release. This identifies a new molecular signaling pathway contributing to inhibition of SV exocytosis and persistent spine changes by isoflurane.

Disclosures: K.W. Johnson: None. **F.S. Lee:** None. **H.C. Hemmings:** None. **J. Platholi:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.12/E5

Topic: B.07. Synaptic Plasticity

Support: CNPq

Title: Sexually dimorphic synaptic organization of the posterodorsal medial amygdala

Authors: F. DE SOUZA DALPIAN[1], A. A. RASIA-FILHO[2], *M. E. CALCAGNOTTO[1]
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Abstract: Introduction: The medial nucleus of the amygdala (MeA), mainly the posterodorsal medial (MePD) modulates different social behavior and displays a notable neural plasticity and sexual dimorphism. Male-female differences are found in the morphology, connectivity, and local neuropil structure of MePD. The amygdala dysfunction is associated with several human neurological disorders such as epilepsy and autism. The aim of the present study was to investigate inhibitory and excitatory synaptic organization is sexually dimorphic and lateralized in adult MePD. Material and Methods: Acute coronal brain slices were prepared from adult male (n=20) and female (n=53) Wistar rats. Spontaneous and miniature excitatory end inhibitory post-synaptic currents (EPSC and IPSC) were recorded by whole-cell patch-clamp technique in visually identified neurons from MePD, using an infrared differential interference contrast (IRDIC) video microscopy system. Cells were filled with biocytin during the patch recordings to correlate the structural and functional properties of recorded cells. EPSC and IPSC properties were analyzed using Mini Analysis 6.0.7 software. Results are presented as the mean ± SEM. To compare results between different cell types, we used a one-way ANOVA followed by Tukey test with significance level of $p < 0.05$. All the animal procedures were performed according the Ethics Committee on Animal Use - UFRGS (approval # 28885). Results: The sEPSC frequency and amplitude onto neurons from the left MePD in males (n=14 cells) and females in diestrus, (n=12 cells) were significantly higher than females in proestrus (n=14 cells) and estrous (n=16 cells). The mEPSC amplitude onto MePD neurons was significantly higher in males (n=20 cells)

than females (n=58 cells). Moreover, the sIPSC frequency onto left MePD neurons and sIPSC amplitude onto right MePD neurons, were significantly higher in males (n=10 cells) and female in diestrus (n=11 cells) and estrous (n=11 cells) when compared to females in proestrus (n=13 cells). The mIPSC properties were similar for all groups. Conclusion: Taken altogether, these findings suggested a sexual dimorphism and lateralization of synaptic function in adult MePD and these features could provide a neural substrate for social behavior and neural plasticity modulation.

Disclosures: F. de Souza Dalpian: None. **A.A. Rasia-Filho:** None. **M.E. Calcagnotto:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.13/E6

Topic: B.07. Synaptic Plasticity

Support: University of Turin
Netherlands Institute for Neuroscience
Fundacio La Marato de TV3

Title: Interfering with Semaphorin3A in perineuronal nets to enhance plasticity

Authors: D. CARULLI[1,3], R. BROERSEN[2,4], *F. DE WINTER[1], H.-J. BOELE[4], B. HOBO[1], C. CANTO[2,4], E. M. MUIR[5], C. I. DE ZEEUW[2,4], J. VERHAAGEN[1]
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Abstract: Neuronal plasticity is crucial for our brain to learn, adapt to the environment and recover from brain injury. Plasticity decreases with age, particularly after childhood/adolescence. Perineuronal nets (PNNs) play a crucial role in restricting plasticity in the adult central nervous system. However, it is not entirely known how they act. PNNs are macromolecular assemblies of extracellular matrix and are composed of hyaluronan and chondroitin sulfate proteoglycans, which are kept together by link proteins and tenascin-R. We recently identified the chemorepulsive axon guidance protein Semaphorin3A (Sema3A) as a prominent component of PNN, suggesting that it may be a prime candidate in the control of PNN-mediated plasticity. To test this hypothesis we investigated the effect of interfering with Sema3A in the PNN of the deep cerebellar nuclei (DCN) of adult mice, at both the synaptic and behavioral level. Given that the DCN have abundant PNNs and are essential for associative eyeblink conditioning, they form a

brain structure that is uniquely suited to investigate the role of PNN-associated Sema3A in learning-associated plasticity. To interfere with Sema3A signaling, we used an adeno-associated viral vector (AAV) encoding a soluble form of the Sema3A receptor component Neuropilin-1 (NP1-Y297A-Fc). NP1-Y297A-Fc retains its ability to interact with Sema3A, while binding with its other ligand, vascular endothelial growth factor (VEGF), is abolished by the mutation Y297A. With this approach, NP1-Y297A-Fc would act locally as a scavenger for Sema3A in the nets. We found that treatment with NP1-Y297A-Fc induces a significant increase in the size of axon terminals of Purkinje cells (the main inhibitory input on DCN neurons), which retain their discrete distribution along the target neuron membrane. In contrast, the digestion of the whole PNNs by the enzyme chondroitinase results in a decreased partition between neighboring Purkinje terminals. During associative motor learning, i.e. in mice subjected to eyeblink conditioning, PNNs and their Sema3A content in the DCN are reduced, suggesting that Sema3A plays an inhibitory role in the formation of this type of memory. Notably, digesting the whole PNNs in the DCN leads to faster learning in the eyeblink conditioning paradigm. These data show that PNNs are crucial for cerebellar plasticity and cerebellum-dependent learning, and support the hypothesis that the chemorepulsive axon guidance cue Sema3A is an effector protein with a key role in PNN-mediated plasticity.

Disclosures: D. Carulli: None. **R. Broersen:** None. **F. De Winter:** None. **H. Boele:** None. **B. Hobo:** None. **C. Canto:** None. **E.M. Muir:** None. **C.I. De Zeeuw:** None. **J. Verhaagen:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.14/E7

Topic: B.07. Synaptic Plasticity

Support: Korea NRF-2015R1D1A1A01059654

Title: Postsynaptic density protein 95 (PSD-95) is transported by kinesin motor to synaptic regions

Authors: *K. YOO, K. LEE, J.-Y. OH, H. KIM
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Abstract: Postsynaptic density protein 95 (PSD-95), a postsynaptic scaffolding protein, has pivotal roles in the aspects of structure and function in the excitatory postsynapses. PSD-95 has been deeply implicated in brain functions, such as learning and memory, as well as in brain disorders. Although transport of PSD-95 to synaptic regions and its regulatory mechanisms have been extensively studied, much still remains unclear. To evaluate the role of kinesin motor protein (KIF5) in dendritic transport of PSD-95 protein, we expressed a dominant-negative form

of kinesin (ΔMD), which doesn't contain N-terminal motor domain. The ΔMD expression significantly decreased PSD-95 level in the dendrites. Consistently, KIF5 was associated with PSD-95 in co-IP assays using both HEK cells and brain lysates, and an *in vivo* assay using proximity ligation assay (PLA). This interaction was mediated by the tail in C-terminal region of kinesin and the ADPDZ3 domain of PSD-95. Interestingly, the association between two proteins showed a dose-dependent pattern with Staufen protein, suggesting its role as an adaptor or regulatory function. Additionally the ADPDZ3 expression significantly reduced the number of PSD-95 particles in distal dendrites. Taken together, our data suggest a new mechanism for synaptic transport of PSD-95 and synaptic plasticity.

Disclosures: K. Yoo: None. **K. Lee:** None. **J. Oh:** None. **H. Kim:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.15/E8

Topic: B.07. Synaptic Plasticity

Support: ECAE`s Research Office

Title: Dynamic morphological and physiological remodeling of the diaphragm neuromuscular junction of mice with aging

Authors: *M. A. FAHIM[1], M. SEGHIER[1], M. HASAN[2], C. HABAK[1]
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Abstract: Background. Aging is associated with changes in muscle physiology and morphology, which are tied to activity in the neuromuscular junction (NMJ). However, it is unclear whether age-related changes depend on processes inherent to aging or on an overall decrease in physical activity. The diaphragm is a continuously-active muscle, regardless of age, while the NMJ is stable throughout the lifespan and serves as an elegant model to measure plasticity, because it exhibits high structure and function turnover. The purpose is to assess whether these two components allow for age-related changes to be dissociated from physical activity-related levels. Methods. In the present study we investigated both structural and functional age-related changes in the diaphragm muscle in a total of 20 male C57BL/6NNia mice, divided into two groups, one young group of 10 mice aged 7 months and a second group of 10 mice aged 28 months. Structurally, with a combined silver-cholinesterase method, presynaptic portions of the NMJ were assessed. Functionally, intracellular recordings of spontaneous miniature endplate potentials (MEPP) and the quantal content of endplate potentials (EPP) were recorded. Data were

analyzed statistically using two-tailed student t-tests to compare between groups.
Results. When comparing older versus younger mice groups structurally (at $p<0.001$), presynaptic portions of the NMJ displayed regions of abnormal distension, and sprouting. Dispersion of terminal branches into a series of regions was observed, consistent with increased remodeling. Functionally, intracellular recordings of MEPP and calculated quantal content of EPP yielded significant increases in older mice in MEPP amplitudes (23%) and frequency (29%), along with a pronounced increase in EPP amplitude and calculated quantal content (42%), and no change in resting membrane potentials or membrane capacitance in old compared to young mouse diaphragms.
Conclusion. Findings indicate that the mouse NMJ undergoes a process of physiological and morphological remodeling during aging. Functional changes display up-regulation in neurotransmitter release, while morphological changes exhibit increased complexity and sprouting, all of which indicate regenerative processes. These changes do not dissociate between post- or pre-synaptic sources, nor between processes inherent to aging vs general level of activity, however, they are likely compensatory in nature to maintain the integrity of the NMJ.

Disclosures: M.A. Fahim: None. **M. Seghier:** None. **M. Hasan:** None. **C. Habak:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.16/DP03/E9

Topic: B.07. Synaptic Plasticity

Support: CRG Kaust Grant "KAUST-EPFL Alliance for Integrative Modeling of Brain Energy Metabolism" to Pierre Magistretti
We acknowledge financial support from the King Abdullah University of Science and Technology (KAUST) baseline funding from Professor Andrea Falqui.

Title: Lactate derived from astrocytic glycogen is necessary for stabilization of synapses following learning

Authors: *C. CALI[1], E. VEZZOLI[3], L. PONZONI[4], E. SOGNE[1], N. GAGNON[1], M. SALA[5], M. FRANCOLINI[4], D. BRAIDA[4], A. FALQUI[1], P. J. MAGISTRETTI[2]
[2]BESE, [1]KAUST, Thuwal, Saudi Arabia; [3]Deparment of Pharmacol. and Biomolecular Sci., [4]Dept. di Biotecnologie Mediche e Medicina Traslazionale, Univ. of Milan, Milano, Italy; [5]Inst. di Neuroscienze, Prof, Milano, Italy

Abstract: Long-term memory formation is an energy-expensive process, which is accompanied by structural changes at synapses, including, but not limited to an increase in spine density, for example. To directly investigate structural changes occuring during learning, and their

dependance on brain energy metabolism, an in-depth 3D Electron Microscopy (EM) study was performed on adult mice brains subjected to a novel-object recognition (NOR) behavioral training, in presence of 1,4-Dideoxy-1,4-imino-D-arabinitol hydrochloride (DAB), a potent inhibitor of glycogenolysis. Memory consolidation and long-term potentiation impairments induced by the DAB treatment were reversed by intrahippocampal injection of lactate. The following 3D ultrastructural analysis on sparse reconstruction of spines and synaptic densities revealed that both density and size of spines increased significantly compared to naive animals, together with the appearance of glycogen clusters in astrocyte processes. The DAB treatment impaired the formation of new spines, and the application of L-Lactate together with the DAB rescued both memory formation and spine density, but failed to rescue the accumulation of glycogen clusters. Moreover, 3D analyses of dendritic mitochondria revealed an impaired fission, which was also rescued by intrahippocampal L-Lactate administration. Altogether, these evidences indicate that impairing lactate production from astrocytic glycogen results in the impairment of structural and biochemical synaptic plasticity features and memory consolidation.

Disclosures: C. Cali: None. **E. Vezzoli:** None. **L. Ponzoni:** None. **E. Sogne:** None. **N. Gagnon:** None. **M. Sala:** None. **M. Francolini:** None. **D. Braida:** None. **A. Falqui:** None. **P.J. Magistretti:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.17/E10

Topic: B.07. Synaptic Plasticity

Support: Whitehall Foundation

Title: Environmental regulation of silent synapses in the dorsolateral striatum

Authors: *A. MEYERS[1], J. A. BEELER[2]
[1]Queens Col., Flushing, NY; [2]Psychology, Queens Col. CUNY, Flushing, NY

Abstract: Silent synapses are glutamatergic synapses lacking AMPA mediated responses. As a consequence, they are 'silent' in response to glutamate release at resting membrane potentials due to Mg++ block of NMDA receptors. Prevalent during early development, silent synapses nearly disappear in adulthood, with low levels of residual expression (~5-10%), particularly in striatal projection neurons. Drugs of abuse such as cocaine, opioids, and chronic nicotine increase the prevalence of silent synapses in medium spiny neurons in adult animals. It has been proposed that increased silent synapses may provide a mechanism by which drugs of abuse reorganize circuits in the brain around drug-related stimuli, contributing to the resilience of drug-reinforced behavior to extinction and the incubation phenomenon where cravings can increase, rather than

diminish, with time following abstinence. There has been little examination of what role silent synapses may play in a normal, healthy organism, nor how environmental factors may regulate the prevalence of silent synapses. To address these questions, we examined the effect of high fat diet in the prevalence of silent synapses in the dorsolateral striatum. Using patch-clamp electrophysiology (minimal stimulation assay) and identifying direct and indirect pathway medium spiny neurons via genetic fluorescent labeling (iMSNs, GFP driven by D2 promoter; dMSNs, tdTomato driven by D1 promoter via D1-cre mouse line crossed with floxed tdTomato mice), we tested the impact of chronic high fat diet on silent synapses in both the direct and indirect pathways. Mice received ad libitum access to high fat diet (Teklad TD. 06414, 60% calories from fat) for minimally four weeks before testing. Similar to drugs of abuse, we observe a substantial increase in silent synapses in medium-spiny neurons in mice fed high fat diet. Cocaine and opioids increase silent synapses in only the direct and indirect pathways, respectively. In contrast, high fat diet increases prevalence of silent synapses in both pathways. These data suggest that high fat diet, like drugs of abuse, may alter fundamental mechanisms of circuit remodeling.

Disclosures: A. Meyers: None. **J.A. Beeler:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.18/E11

Topic: B.07. Synaptic Plasticity

Title: The novel NMDA receptor modulator NYX-2925 enhances dendritic spine-autonomous structural and functional plasticity *in vitro*

Authors: *R. M. MITCHELL[1], L. P. CACHEAUX[1], M. BOWERS[1,2], A. I. SHANKER[1], R. A. KROES[1,2], J. R. MOSKAL[1,2]
[1]Aptinyx Inc., Evanston, IL; [2]Falk Ctr. for Mol. Therapeutics, McCormick Sch. of Engineering, Northwestern Univ., Evanston, IL

Abstract: On principal excitatory neurons, structural plasticity involves both alterations in the size of existing spines (enlargement or shrinkage in response to LTP/LTD, respectively) as well as the formation and elimination of spines (spine stability/turnover or dynamics). These structural changes manifest in response to functionally relevant stimuli and are therefore believed to be the structural correlate of learning and memory. Whereas these adaptive responses are integral components of Hebbian learning, they are also altered in neurological conditions such as severe/prolonged stress and related PTSD, brain injury (TBI and stroke), epilepsies, and genetic abnormalities (Fragile X, Rett, etc.). Mechanisms governing structural plasticity appear to overlap with functional plasticity (e.g. AMPA receptor insertion), but have yet to be fully

elucidated. We have developed a library of novel NMDA receptor modulators that enhance functional plasticity in behavioral models of learning and memory and electrophysiological models such as potentiation of CA1 field potentials (classical LTP). However, whether these compounds modulate structural plasticity acutely or in models of neurological disease is unknown. To assess the role of our lead compound NYX-2925 on structural plasticity in excitatory spines, we have employed a high-frequency glutamate uncaging (HFU) protocol in cultured rat neurons that is known to induce structural LTP (sLTP) in isolated spines. We find that NYX-2925 robustly enhances NMDA receptor-dependent increases in spine volume. The enhancement of sLTP is evident both in the magnitude of change in spine volume and the number of spines that respond to sLTP induction. Furthermore, to determine if NYX-2925 enhances plasticity-related AMPA receptor insertion (a direct measure of functional plasticity), we utilized a protocol for chemically-induced LTP (chemLTP) and assessed synaptic surface GluA1 insertion. We find that NYX-2925 also significantly enhances glycine-induced GluA1 surface expression within the post-synaptic density in cultured primary neurons. Thus, NYX-2925 facilitates acute structural and functional plasticity in addition to learning and memory in naive rodents, and shows potent efficacy in preclinical models of neurological disorders. These findings inform the mechanism by which NYX-2925 may exert therapeutic effects and highlight the clinical potential of compounds that facilitate NMDA receptor-dependent structural plasticity.

Disclosures: R.M. Mitchell: 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. **L.P. Cacheaux:** A. Employment/Salary (full or part-time):; Aotinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc. **M. Bowers:** 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. **A.I. Shanker:** A. Employment/Salary (full or part-time):; Aptinyx Inc. **R.A. Kroes:** 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. **J.R. Moskal:** 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..

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.19/E12

Topic: B.07. Synaptic Plasticity

Support: NIH SBIR - 1R43AG048651-01A1

Title: A complex-selective and safe HDAC inhibitor with pro-synaptic effects - A promising therapy for neurodegenerative disorders

Authors: *A. PIRONE, N. O. FULLER, M. HEWITT, M. QUINTON, T. D. MCKEE, B. A. LYNCH, A. ROSENBERG, M. IVARSSON
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Abstract: Post-translational modifications of histone proteins, such as acetylation, play a central role in regulating neuronal gene expression and brain function. Emerging evidence implicates dysregulation of gene expression in cognitive and neurodegenerative disorders. Previous studies have shown that increase in histone acetylation enhances synaptic plasticity, learning and memory. Therefore, treatment with histone deacetylases inhibitors (HDACi) is a promising strategy for therapeutic intervention in neurological disorders with synaptic pathology. However, the combination of limited brain penetration and lack of specificity of HDACis has led to peripheral side effects and limited viability for any chronic human therapy. Here, Rodin Therapeutics describes proprietary compound **Rodin-A**, a brain penetrant, safe, and selective inhibitor of HDAC1 and HDAC2. Chronic treatment *in vivo* with **Rodin-A** significantly increased (27%) spine density in the CA1 region of the dorsal hippocampus of wild type mice and improved the impaired LTP in the 5xFAD mice, a model of Alzheimer disease (AD). Furthermore, **Rodin-A** treatment resulted in increased levels of pre- and post-synaptic proteins and phosphorylated tropomyosin-related kinase B receptor (pTrkB), a neurotrophin receptor known to promote LTP and synaptic plasticity. While previously studied HDACi, such as CI-994, showed pro-synaptic effects *in vivo*, lack of therapeutic window precluded use to treat neurological disorders. **Rodin-A** achieves equivalent pro-synaptic effects with a substantially improved safety margin. Together, our results describe a new, selective and safe HDACi which modulates structural and synaptic plasticity. **Rodin-A** represents a new potential therapeutic intervention in disorders of synaptic plasticity and cognition, including neurodegenerative disorders such as AD.

Disclosures: **A. Pirone:** A. Employment/Salary (full or part-time):; Rodin therapeutics full time. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); rodin stock options. **N.O. Fuller:** A. Employment/Salary (full or part-time):; Rodin therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rodin therapeutics. **M. Hewitt:** A. Employment/Salary (full or part-time):; Rodin Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rodin Therapeutics. **M. Quinton:** None. **T.D. McKee:** None. **B.A. Lynch:** A. Employment/Salary (full or part-time):; Rodin therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rodin therapeutics. **A. Rosenberg:** A. Employment/Salary (full or part-time):; Rodin therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rodin therapeutics. **M. Ivarsson:** A. Employment/Salary (full or part-time):; Rodin

therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rodin therapeutics.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.20/E13

Topic: B.07. Synaptic Plasticity

Support: ERC Advanced Investigator Grant 322744;LO
Swedish Research Council K2012-62X-03185-42-4; LO
Swedish Brain Power (LO, TK)
Stratneuro
Wings for Life
Karolinska Institutet Research Foundations (LO)
Karolinska DPA (LO)

Title: Nogo receptor 1 protein levels are rapidly downregulated by metabotropic N-methyl-D-aspartate receptor signalling

Authors: *A. T. BRODIN, E. BECHER, K. WELLFELT, L. OLSON, T. E. KARLSSON
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Abstract: Nogo receptor 1 (NgR1) is an important receptor for several myelin associated inhibitors of neurite growth. By binding these ligands, which despite their name are also expressed by neurons, NgR1 restricts plasticity during development, learning and injury. Some regions in the mammalian brain, including the hippocampus, remain highly plastic in adulthood despite strongly expressing NgR1 and its ligands. It is known that NgR1 mRNA is downregulated by strong neural activity but information about protein regulation is more limited. We have used murine primary hippocampal cell cultures to investigate if, how and when NgR1 protein is regulated by neural activity.
Interestingly, we found that NgR1 levels are specifically regulated by metabotropic N-methyl D-aspartate receptor (NMDAR) signalling. NgR1 levels are significantly lower already 30 minutes after NMDA treatment, while blocking the active site of the NMDAR with amino-5-phosphovaleric acid (APV) instead increases NgR1 levels over the same time scale. Blocking the ion pore with MK801 does not affect NgR1 levels, implying that metabotropic NMDAR signalling is responsible for regulating NgR1 levels.
Our results suggest that NgR1 is only sensitive to certain forms of neural activity, perhaps to ensure that plastic changes are only allowed under certain conditions. NgR1 could be a novel pathway by which NMDAR regulates structural plasticity in the mammalian brain. This has

implications for our understanding of how lasting memories are formed and how the adult nervous system's resistance to regeneration could be overcome.

Disclosures: A.T. Brodin: None. **E. Becher:** None. **K. Wellfelt:** None. **L. Olson:** None. **T.E. Karlsson:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.21/E14

Topic: B.07. Synaptic Plasticity

Support: NIH Grant 5 R01 NS058784-06

Title: Post-ischemic cortical excitability is modulated by transplanted human neural stem cells

Authors: T. N. WEERAKKODY[1], *R. AZEVEDO-PEREIRA[2], J. VU[3], F. DU[4], X. LIANG[4], T. BLISS[4], J. R. HUGUENARD[1], G. K. STEINBERG[5]
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Abstract: Introduction: Transplanted stem cells can improve behavioral recovery after stroke, however their direct actions on surviving sensorimotor circuits are not well understood. We and others have demonstrated that the transplantation of human neural stem cells (hNSCs) enhances *structural* plasticity in ischemic brain via increased neurite sprouting. Here, we performed a comprehensive *electrophysiological* assessment of the stroke-injured rat cortex after transplantation of two hNSC lines, G010 (fetal-derived) and NR1 (hES-derived). **Method:** Vehicle, G010 cells, or NR1 cells were transplanted into the ischemic cortex of Nude rats one week after distal middle cerebral artery occlusion. Neurological recovery was assessed weekly using the whisker-paw test. Acute brain slices were prepared one week post-transplantation for electrophysiological recording. A linear multichannel recording probe was placed in the peri-infarct motor cortex (M1 region) perpendicular to the pial surface. Local field potentials (LFPs) were recorded simultaneously from all cortical layers following circuit activation with a single electrical stimulus delivered to layer 2/3. We also obtained whole-cell patch clamp recordings from pyramidal neurons in superficial lamina of the peri-infarct to examine the balance of excitatory and inhibitory synaptic inputs. **Results**: Both hNSC lines enhanced behavioral recovery after stroke but with different time course. G010 cells improved performance on the whisker-paw test as early as one week post-transplantation whereas NR1 cells induced comparable effects at three weeks. To ascertain corresponding changes in cortical circuitry, we performed current source density (CSD) analysis of evoked LFPs, a method used to more

accurately localize synaptic currents. After stroke, CSD analysis revealed that inhibition in superficial lamina is elevated bilaterally (i.e. net loss of excitability). G010 and NR1 cells increased circuit excitability within layer 2/3, altering inhibitory/excitatory balance. Whereas G010 transplantation reduced network inhibition, NR1 enhanced excitation within superficial lamina. Whole-cell patch clamp recordings in pyramidal neurons suggested that NR1-induced gain in excitability is due to reduced synaptic inhibition, while G010 transplants revealed an increase in synaptic inhibition, which is contradictory to the reduced inhibition seen in the G010 extracellular recordings. **Conclusions:**Stem cell transplantation modulates motor circuit activity caused by stroke injury and this is associated with overall increases in circuit excitability, and presumably motor-sensory function.

Disclosures: T.N. Weerakkody: None. **R. Azevedo-Pereira:** None. **J. Vu:** None. **F. Du:** None. **X. Liang:** None. **T. Bliss:** None. **J.R. Huguenard:** None. **G.K. Steinberg:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.22/E15

Topic: B.07. Synaptic Plasticity

Support: NIH grant AG054719
NIH grant AG043552-05
Alzheimer's Association NIRG-339422
NIH INRSA 5T32NS061788-10

Title: RhoA-associated kinases ROCK1 and ROCK2 mediate amyloid-β induced synaptic degeneration in Alzheimer's disease

Authors: *B. W. HENDERSON[1], S. V. BACH[2], J. J. DAY[2], J. H. HERSKOWITZ[3]
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Abstract: Current estimates project that there are approximately 5.4 million Americans affected by Alzheimer's disease (AD). Cognitive decline is a clinical hallmark of AD, while accumulation of amyloid-β (Aβ) is a pathological hallmark. Aβ accumulation induces cellular mechanisms that drive synapse loss in AD, resulting in abnormal neuronal firing and network de-synchronicity. Yet, there are few therapeutic strategies that target synapse loss to delay or prevent cognitive decline and detrimental network alterations in AD. RhoA, a Rho GTPase family member, and its primary downstream effectors, the Rho-associated coiled-coil containing protein kinases (ROCK) 1 and ROCK2, are potent regulators of actin dynamics and influence neuronal morphology and synaptic plasticity. Our previous work demonstrated that ROCK1 and

ROCK2 protein levels are increased in mild cognitive impairment due to AD (MCI) and AD cases and that Aβ activates the RhoA/ROCK pathway. We hypothesize that Aβ-induced ROCK1 and ROCK2 activity promotes dendritic spine degeneration, reducing neuronal firing in primary hippocampal cultures. By coupling genetic or pharmacologic manipulation of ROCK signaling pathways with highly innovative three-dimensional modeling of dendritic structure and microelectrode array (MEA) analyses, we highlight key roles for ROCKs in synaptic degeneration that may contribute to cognitive decline in AD progression.

Disclosures: B.W. Henderson: None. **S.V. Bach:** None. **J.J. Day:** None. **J.H. Herskowitz:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.23/E16

Topic: B.07. Synaptic Plasticity

Support: NIH R01 NS40296

Title: ADAR-dependent RNA editing of complexin regulates activity-mediated structural and functional plasticity at the *Drosophila* neuromuscular junction

Authors: *E. BRIJA, R. W. CHO[1,2], J. T. LITTLETON[1,2]
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Abstract: Chemical synaptic transmission is a critical step in neuronal communication that is extensively modulated during neural plasticity. Across systems, activity-dependent regulation is required for chemical synapses to undergo structural and functional plasticity. The *Drosophila* neuromuscular junction (NMJ) has historically been a powerful model system to study synaptic transmission and undergoes robust activity-dependent structural and functional plasticity (Cho et al., 2010; Huntwork and Littleton, 2007). Previously, our lab has shown that structural growth at the NMJ is regulated by increased spontaneous neurotransmitter release, and that phosphorylation of the SNARE-binding protein Complexin (Cpx) is required for activity-dependent structural and functional plasticity at the NMJ (Cho et al., 2015). Our recent electrophysiology and imaging studies of the larval NMJ demonstrate that Cpx-dependent functional and structural plasticity can further be regulated by RNA editing. Cpx undergoes RNA editing via ADAR (adenosine deaminase acting on RNAs), the enzyme responsible for all known RNA editing in *Drosophila.* Cpx transcript editing produces Cpx protein products with varying C-terminals, including a phospho-competent, a phospho-mimetic, and a phospho-incompetent version. Our studies suggest that Cpx phosphorylation is edit-dependent and that editing of Cpx alters the regulation of mini frequency and its ability to regulate synaptic growth. Furthermore,

we find that ADAR is required to express activity-dependent structural and functional plasticity at the NMJ. Our results suggest that RNA editing of Cpx regulates Cpx-mediated activity-dependent functional and structural plasticity in *Drosophila*, providing a novel mechanism by which presynaptic plasticity can be regulated.

Disclosures: R.W. Cho: None. **J.T. Littleton:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.24/E17

Topic: B.07. Synaptic Plasticity

Support: NIH R01 NS085167
NIH R01 NS094384
DARPA N66001-17-2-4011

Title: Directed cortical plasticity as a function of vagus nerve stimulation rate, train duration, and pulses

Authors: *E. BUELL, K. LOERWALD, M. BORLAND, J. BUELL, C. KELLY, C. CHANDLER, M. KILGARD
Univ. of Texas at Dallas, Richardson, TX

Abstract: *Background*
Pairing a brief train of vagus nerve stimulation (VNS) with an external event can reorganize the sensory or motor cortex. Repeatedly pairing a tone with sixteen VNS pulses presented at a frequency of 30 Hz significantly increases the number of neurons in primary auditory cortex (A1) that respond to tones near the paired tone frequency. It is not known if changing VNS pulse rate or duration would increase or decrease the degree of cortical map plasticity.
Objective/Hypothesis
This project investigates the effects of VNS rate, train duration, and number of pulses on cortical plasticity. We hypothesize that changing these parameters will affect the degree of driven plasticity.
Methods
Rats were assigned to groups that received tone-paired VNS at a specific rate, train duration, and number of pulses (Table 1). Animals received stimulation 300 times per day over a 20 day period, regardless of group. Experimental animals were compared with naïve control animals.

Rate Group	Number of Animals	VNS Pulses	VNS Rate (Hz)	VNS Train Duration (ms)

Low	10	16	7.5	2000
Standard	10	16	30	500
High	10	16	120	125
Train Duration Group				
Short	10	4	30	125
Standard	10	16	30	500
Long	10	64	30	2000
Pulses Group				
Short	10	4	7.5	500
Standard	10	16	30	500
Long	10	64	120	500

Results

The VNS moderate rate group exhibited significantly more A1 neurons that respond to the paired tone. These changes were not observed in rats that received high or low rate VNS. Preliminary data shows 4 pulses of VNS drives plasticity when delivered at 30 Hz,
but not at 7.5 Hz. Sixty-four pulses of VNS does not drive plasticity whether it is delivered in 500 ms or 2000 ms trains.

Conclusion

These results suggest that the magnitude of plasticity driven by VNS is sensitive to changes in multiple stimulation parameters. The high temporal precision of VNS-tone pairing protocols may help to explain the cellular mechanisms responsible for the beneficial effects of precisely timed VNS during restoration of sensory or motor function.

Disclosures: E. Buell: None. **K. Loerwald:** None. **M. Borland:** None. **J. Buell:** None. **C. Kelly:** None. **C. Chandler:** None. **M. Kilgard:** F. Consulting Fees (e.g., advisory boards); MicroTransponder.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.25/E18

Topic: B.07. Synaptic Plasticity

Support: DP2 OD008425 (HZ)
R21 NS084315 (HZ)
R21 NS097856 (HZ)

R01 NS081071(TM)

Title: Chronic *in vivo* imaging of excitatory synapses on cortical interneurons

Authors: *J. B. MELANDER[1], B. C. JONGBLOETS[2], M. QIN[2], E. AARTS[3], T. MAO[2], H. ZHONG[2]
[1]Stanford Univ., Stanford, CA; [2]Vollum Inst., Oregon Hlth. & Sci. Univ., Portland, OR; [3]Utrecht Univ., Utrecht, Netherlands

Abstract: Neocortical inhibitory interneurons exert powerful control over brain function by influencing the timing and computation of the circuits formed by excitatory pyramidal neurons. Consequently, excitatory inputs onto cortical interneurons drive the activity of these neurons and thereby play a major role in the excitation/inhibition (E/I) balance of the brain. Despite their importance, little is known about the dynamics of these excitatory synapses residing on cortical interneurons. This is because unlike the synapses onto excitatory neurons in cortex, which are characterized by distinct morphological proxies known as dendritic spines, most excitatory synapses onto interneurons reside directly on the smooth dendritic shafts, and cannot be readily identified under light microscopy. Here, we took advantage of a recently-developed fluorescence labeling strategy for endogenous proteins called endogenous labeling via exon duplication (ENABLED) (Fortin et al., 2014). We used this strategy to generate a *PSD-95-ENABLED* mouse line, in which the postsynaptic marker PSD-95 could be visualized in a Cre-dependent manner for live imaging without overexpression. By utilizing various Cre delivery methods, we examined the chronic dynamics of the synaptic contents, as presence of PSD-95 fluorescent puncta, within dendritic spines of cortical pyramidal neurons, as well as within the shaft synapses of parvalbumin-positive (PV+) and vasoactive intestinal peptide-positive (VIP+) neurons via transcranial *in vivo* two-photon imaging under an "open-window" configuration. The activity-dependent dynamics of these synapses were also examined. We found that excitatory synapses onto different neuronal types exhibit distinct dynamic properties.

Disclosures: J.B. Melander: None. **B.C. Jongbloets:** None. **M. Qin:** None. **E. Aarts:** None. **T. Mao:** None. **H. Zhong:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.26/E19

Topic: B.07. Synaptic Plasticity

Support: MRC Programme grant G0901299

Title: Spine dynamics and experience dependent structural plasticity in the barrel cortex of layer 2/3 neurons

Authors: *G. SEATON, A. M. DE HAAN, G. HODGES, K. D. FOX
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Abstract: Functional plasticity studies in cortical layer 2/3 (L2/3) have demonstrated both experience dependent potentiation (EDP) and depression (EDD) in response to whisker deprivation, whilst structural plasticity in these layers remain largely uncharacterized. We investigated the relationship between functional plasticity and structural plasticity on the basal dendrites of L2/3 barrel cortex neurons. We have previously shown the CaMKII-t286a mouse model, which lacks EDP and LTP, to have higher baseline spine turnover rates compared to wild type controls, but deficits in new spine formation and new spine persistence in response to whisker deprivation. Here we investigate structural correlates of EDP and EDD in Chessboard whisker deprivation (CWD) and Whole whisker pad deprivation (WWD) in adult and adolescent wild type animals. In addition to baseline turnover, formation and elimination in response to whisker deprivation, newly formed spine stability and spine size fluctuations were analysed.In vivo 2-photon microscopy was used to image dendritic spines both before and after whisker deprivation. Baseline condition imaging (before deprivation), revealed similar spine turnover rates in adult and adolescent animals. CWD is known to cause potentiation of spared whisker responses in layer 2/3 (Hardingham N. Neuron 10;60(5):861-74 (2008). We found that CWD, also increased spine formation over a four-day period post-deprivation and a high percentage of new spines persisted for 14 days. Conversely, spine elimination was only increased transiently for 24 hours.WWD in adult animals does not cause potentiation or depression of whisker responses. Following WWD in adult animals, spine formation and elimination rates were maintained at baseline levels, reflecting the absence of potentiation in spared whisker responses using this deprivation paradigm.WWD in adolescent animals does cause depression of L2/3 whisker responses followed by a homeostatic rebound (Glazewski S. Philos Trans R Soc Lond B Biol Sci. 372(1715) (2017). Following WWD in adolescent animals, we found an increase in spine elimination, that was maintained for 11 days post deprivation, compared to undeprived controls. Formation rates however were only elevated transiently 24 hours after deprivation and were unrelated to the homeostatic rebound in principal whisker responses. These results suggest that potentiation and depression of whisker responses are related to changes in spine formation and elimination rate respectively, but that homeostatic changes are dependent on other factors.

Disclosures: G. Seaton: None. **A.M. de Haan:** None. **G. Hodges:** None. **K.D. Fox:** None.

Poster

201. Structural Plasticity I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 201.27/E20

Topic: B.07. Synaptic Plasticity

Support: Helmholtz Association

Title: Neuronal and synaptic organization of layer 1 in the human temporal lobe neocortex

Authors: *J. M. STÖHR[1], A. ROLLENHAGEN[2], K. SÄTZLER[3], M. VON LEHE[4], J. H. R. LÜBKE[2,5,6]
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Abstract: Synapses are the structural key element involved in the execution, modulation and termination of signal transduction between neurons in any given brain network. However, our knowledge about the structural composition, in particular the synaptic organization of the human brain, is still comparably small. Rather nothing is known about synapses and their target structures in cortical layer 1 (L1). However, L1 is of importance because terminal tuft dendrites of pyramidal neurons are the Ca^{2+} spike initiation zone that interacts with the Na^{+} action potential initiation zone in the axon and may be responsible for regenerative potentials critical for the integration and amplification of sensory and modulatory inputs.
Using non-affected neocortical access tissue from biopsy samples from pharmaco-resistant epileptic patients a quantitative analysis of synaptic boutons in L1 of the human temporal lobe (TL) neocortex was performed. Serial ultrathin sections provided the basis for a fine-scale electron microscopic analysis and subsequent 3D volume reconstruction of synaptic structures and finally, the generation of quantitative 3D models of synapses in L1 of the TL neocortex.
In contrast to the underlying cortical layers, L1 in the adult human TL is comparably cell sparse, but contained putative Cajal-Retzius cells and GABAergic interneurons, as well as dendrites and synaptic boutons of various shape and size and non-neuronal astrocytes and oligodendrocytes. Upon structural criteria L1 can be subdivided into sublamina L1a (astrocytic and cellular domain) and sublamina L1b as the more ‘synaptic and dendritic domain’.
The majority of synaptic contacts was excitatory and had a single, but comparably large active zone. They were established on dendritic shafts but preferentially on different types of dendritic spines. Synaptic boutons varied substantially in surface area (~6.1µm²) and volume (~0.42µm³), in their content of mitochondria, shape and size of active zones and the total pool of synaptic vesicle per bouton (~923). The total pool of synaptic vesicles suggests relatively large readily releasable, recycling and resting pools.
Freeze fracture replica preparations combined with single- and double postimmunogold labeling suggest a co-localization of presynaptic Ca^{2+} domains and postsynaptic glutamate receptors of the AMPA- and NMDA-type, that will be quantified leading to the generation of Ca^{2+}/receptor distribution maps.
In summary, our results demonstrate similarities but also differences not only with synapses in

other layers of the human TL neocortex but also with their counterparts in various animal species.

Disclosures: J.M. Stöhr: None. **A. Rollenhagen:** None. **K. Sätzler:** None. **M. von Lehe:** None. **J.H.R. Lübke:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.01/E21

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01MH107182

Title: Regulation of dendritic spine morphology by small form of ankyring and homer1

Authors: *S. YOON[1], L. E. DIONISIO[2], P. PENZES[4,5,3]
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Abstract: Genome-wide association studies have shown that *ANK3* variants (encoding Ankyrin-G, AnkG) are associated with multiple neuropsychiatric disorders, such as bipolar disorder, intellectual disability and autism spectrum disorder. However, the molecular mechanisms of AnkG that modulate synaptic organization or plasticity and contribute to neuropsychiatric pathogenesis remain unclear. Here, we identified a PPXXF domain, which is recognized by Homer1, in a small form of AnkG (AnkG 190) and confirmed the interaction between AnkG and Homer1 by immunoprecipitation and *In situ* Proximity Ligation Assay (PLA). Homer1 is associated with autism and epilepsy in humans, and homer1 protein is known to interact with Shank and mGluR1/5 and regulate dendritic spine morphogenesis positively. PLA combined with structured illumination microscopy (SIM) revealed interaction of AnkG and Homer1 closely localized at membrane and this interaction was reduced by the mutation of a PPXXF domain. We have shown that AnkG and Homer1, both neuropsychiatric disorder genes, interact in a complex to regulate spine morphology. In addition, these data implicate a potential role for AnkG and Homer1 in psychiatric disorder pathogenesis.

Disclosures: S. Yoon: None. **L.E. Dionisio:** None. **P. Penzes:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.02/E22

Topic: B.07. Synaptic Plasticity

Support: NIH R01NS100785

Title: Neuronal sheddome analysis uncovers a novel mechanism for CNTNAP2 ectodomain in the regulation of calcium dynamics

Authors: *M. D. MARTIN-DE-SAAVEDRA[1], M. DOS SANTOS, 60611[3], O. VAREA[4], B. SPIELMAN[2], R. GAO[2], M. FORREST[2], K. MYCZEK[2], A. SANZ-CLEMENTE[5], D. COMOLETTI[6], J. N. SAVAS[7], P. PENZES[8]
[1]Physiol., [2]Northwestern Univ., Chicago, IL; [3]Northwestern, Chicago, IL; [4]Inst. for Res. in Biomedicine, Barcelona, Spain; [5]Pharmacol., Northwestern Univ. - Chicago, Chicago, IL; [6]Neurosci. and Cell Biol., CHINJ Rutgers, New Brunswick, NJ; [7]Northwestern University, Feinberg Sch. of Medici, Chicago, IL; [8]Dept Physio, Nothwestern Univ. Feinberg Sch. Med., Chicago, IL

Abstract: Numerous transmembrane proteins undergo proteolytic processing resulting in the release of a soluble extracellular fragment ("ectodomain shedding"). The role of ectodomain shedding has not been globally explored in development and disease, in particular at synapses. The physiological functions of ectodomain shedding are only beginning to be uncovered, particularly because the function of most shed ectodomains are not known. Nevertheless, several general functions for ectodomain shedding have been proposed. In the particular case of synaptic adhesion molecules, ectodomain shedding is generally thought to terminate adhesion, causing loss of cell-cell contacts and synapse weakening. By combining bioinformatics analysis with mass spectrometry, we show that the neuronal sheddome is mirrored by the human cerebrospinal fluid (CSF) and is enriched in adhesion molecules, as well as neurodevelopmental disorder risk factors. We performed a global bioinformatics analysis of the synaptic sheddome and its relationship with the CSF proteome. We show that the ectodomain of CNTNAP2, a risk factor for multiple neurodevelopmental disorders including autism spectrum disorder, is present in human CSF, and undergoes synaptic activity-dependent ectodomain shedding. Using biochemistry, confocal and structured-illumination superresolution microscopy (SIM), we map the spatial localization of synaptic ectodomain. Using ectodomain-affinity pull-down coupled with mass spectrometry, we identify multiple previously unknown binding partners of CNTNAP2 ectodomain. Bioinformatics analysis reveals that calcium signaling is major target for CNTNAP2 ectodomain binding, revealing a novel mechanism for calcium channel regulation by shed ectodomains.

Disclosures: M.D. Martin-de-Saavedra: None. **M. Dos Santos:** None. **O. Varea:** None. **B. Spielman:** None. **R. Gao:** None. **M. Forrest:** None. **K. Myczek:** None. **A. Sanz-Clemente:** None. **D. Comoletti:** None. **J.N. Savas:** None. **P. Penzes:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.03/E23

Topic: B.07. Synaptic Plasticity

Support: NIH Grant 2R01MH097216-06
SNSF Fellowship P2SKP3_161675

Title: Proteomic profiling of the 16p11.2 microduplication mouse model: Implications for neuropsychiatric disease

Authors: *M. FORREST[1], Y.-Z. WANG[2], N. H. PIGUEL[1], L. E. DIONISIO[1], N. A. HAWKINS[3], C. P. PRATT[1], V. BAGCHI[1], J. A. KEARNEY[3], J. N. SAVAS[2], P. PENZES[1,4]
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Abstract: The 16p11.2 microduplication is a rare form of chromosomal rearrangement that confers risk of multiple neuropsychiatric conditions including, schizophrenia, autism spectrum disorder, bipolar disorder and Rolandic epilepsy. The 16p11.2 chromosomal region contains 27 protein -coding genes however, the mechanism by which altered gene dosage in this region increases disease risk is still incompletely understood. To uncover novel disease-relevant pathways, we undertook a quantitative proteomic profiling of cortical membrane fractions from the 16p11.2 microduplication mouse model (dp/+). We discovered a large set of both upregulated and downregulated proteins, including proteins within and outside the duplicated 16p11.2 region, suggesting a widespread proteomic dysregulation. Bioinformatic analysis identified that upregulated and downregulated proteins clustered into distinct biological processes and were enriched for unique sets of neuropsychiatric risk factors. Candidate proteins from this screen were studied in cultured neurons with the 16p11.2 duplication using live imaging, immunocytochemistry and biochemical techniques. Finally, we show that the dp/+ mouse model has behavioral phenotypes consistent with its neuropsychiatric and proteomic profile, indicating that systems biology approaches may be able to predict mechanisms and phenotypes in other disease models. Our work demonstrates that the 16p11.2 microduplication leads to proteomic and behavioural alterations, which improves our understanding of neuropsychiatric disease mechanisms, and our ability to design rational therapeutics for affected patients.

Disclosures: M. Forrest: None. **Y. Wang:** None. **N.H. Piguel:** None. **L.E. Dionisio:** None. **N.A. Hawkins:** None. **C.P. Pratt:** None. **V. Bagchi:** None. **J.A. Kearney:** None. **J.N. Savas:** None. **P. Penzes:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.04/E24

Topic: B.07. Synaptic Plasticity

Title: Synaptic plasticity revealed by spatial light interference microscopy(slim) coupled with fluorescence imaging

Authors: *Y. LEE[1], M. KANDEL[2], C. BEST[3]
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Abstract: Advances in quantitative phase imaging (QPI) techniques allow unlabeled biological specimens to be imaged with sub-nanometer sensitivity and diffraction limited resolution. The recently developed technique, called Spatial Light Interference Microscopy (SLIM), has been useful in discovering emergent behavior in human neuronal networks and intercellular dynamics. This technique allows for a wide-field imaging of live neuronal activities, and is used for measurement of dynamic structural changes over long-time scales. We use SLIM combined with standard fluorescence microscopy to measure receptor trafficking in living cortical neurons over time. In addition, we show receptor distribution profiles in 4, 50 and 100-micron coronal sections of fixed murine cortex, hippocampus and cerebellum. For this we used Clarity in the 50 and 100-micron sections prior to imaging, with dual labeled receptor pools, to reduce light absorption and scattering in the thicker tissue samples. The developed technique will be important in quantifying the modulators of synaptic receptor dynamics during development, in higher brain functions such as learning and memory and in disease.

Disclosures: Y. Lee: None. **M. Kandel:** None. **C. Best:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.05/E25

Topic: B.07. Synaptic Plasticity

Support: HHMI Gilliam Fellowship
NIH Grant EY02858
Mathers Charitable Foundation

Title: Increased M1 structural plasticity and enhanced motor learning in mice lacking PirB

Authors: *E. ALBARRAN[1], J. B. DING[2], C. J. SHATZ[3]
[1]Neurosciences Program, Stanford Univ. - Neurosciences Program, Stanford, CA; [2]Neurosurg., Stanford Univ. Dept. of Neurosurg., Palo Alto, CA; [3]Prof Biol & Neurobiol, Dir. Bio-X, James H. Clark Ctr., Stanford, CA

Abstract: Dendritic spine dynamics of Layer 5 Pyramidal neurons (L5PNs) are thought to be physical substrates for motor learning and memory of motor skills. Here we explore this idea by studying mice lacking Paired immunoglobulin receptor B (PirBKO). PirB is expressed in pyramidal neurons throughout the forebrain, and regulates activity dependent synaptic plasticity in hippocampus and visual system (Djurisic et al, Mol Psychiatry 2018). In motor cortex of PirBKO mice, there is an increase in spine density on apical dendritic tufts of L5PNs, as well as an increase in mEPSC frequency in whole cell recordings from neurons in acute slice, compared to WT littermate controls. To investigate the elevated spine density further, chronic 2-photon imaging of PirBKO;Thy1-YFP mice was conducted. PirBKO mice have elevated rates of spine formation and to a lesser degree, spine elimination, yielding a net increase in spine density compared to WT. Given these changes in spine dynamics, we hypothesized that PirBKO mice would exhibit aberrant motor learning behavior. Surprisingly, adult PirBKO mice learned a single-pellet reaching task significantly faster than littermate controls. Chronic imaging of L5PN dendrites throughout the learning period revealed that PirBKO mice exhibit significantly elevated spine formation rates during the early learning stage but spine elimination rates remain unchanged throughout. Moreover, newly formed spines in PirBKO survive for longer periods compared to controls. These results suggest that increased structural plasticity in motor cortex may be advantageous and can translate into enhanced acquisition and maintenance of motor skills.

Disclosures: E. Albarran: None. **J.B. Ding:** None. **C.J. Shatz:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.06/E26

Topic: B.07. Synaptic Plasticity

Support: NIH MH104319 and NS074644 to KMH
NIH MH100510, NS094330, NS094362, DC016169 to BVZ
NSF NeuroNex 1707356
Brain Research Foundation to KMH

Title: Specificity of optically-evoked LTP at area CA1 pyramidal neuron synapses

Authors: *O. I. OSTROVSKAYA, M. KUWAJIMA, K. M. HARRIS, B. V. ZEMELMAN
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Abstract: The hippocampal slice model of long-term potentiation (LTP) is a useful platform for investigating synaptic plasticity, but an ultrastructural marker for synapses that have undergone plasticity is lacking. Consequently, we have devised a single AAV construct that expresses ChR2-sfGFP and mAPEX2 under the control of a human synapsin promoter. This construct allows optically-stimulated axons to be identified and reconstructed using 3D electron microscopy. Our goal has been to confirm that this approach can reliably induce LTP at hippocampal area CA3 to area CA1 pyramidal neuron synapses. Adult C57/Bl6 male mice were injected with the AAV vector unilaterally into hippocampal area CA3. Slice preparation and LTP induction experiments commenced 4-8 weeks post-injection. Different sets of CA3 axons expressed ChR2 in ipsilateral and contralateral slices. First, we recorded field EPSP (fEPSP) responses from optical stimulation in slices from each hemisphere. Optically-evoked fEPSPs from ipsilateral and contralateral CA1 *stratum radiatum* did not differ in slope or amplitude but were significantly smaller than electrically-evoked responses recorded in age-matched non-injected controls. Likewise, LTP induced using 50 Hz trains of light pulses produced a similar increase in the slope in the ipsilateral and contralateral slices and lasted at least 3 hrs. However, optical stimulation of labeled commissural fibers terminating on the contralateral CA3 neurons might inadvertently recruit unlabeled Schaffer collaterals. To prevent unlabeled axon recruitment, we severed area CA3 in slices contralateral to the virus injection site. Although CA3 removal reduced the magnitude of optically-evoked LTP during the first hour post-induction, the potentiation was just as great as in the intact slices at the 2-3 hr time points. These results suggest that optically-evoked LTP is supported entirely by the ChR2-expressing axons. We expect ongoing examinations of mAPEX2 labeling to reveal ultrastructural changes at potentiated synapses.

Disclosures: O.I. Ostrovskaya: None. **M. Kuwajima:** None. **K.M. Harris:** None. **B.V. Zemelman:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.07/E27

Topic: B.07. Synaptic Plasticity

Support: NSERC

Title: Effects of testosterone and surgical stress on hippocampal dendritic morphology in adult male rats

Authors: *L. K. ISAACS, E. M. LAWTON, A. L. MENDELL, N. J. MACLUSKY
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Abstract: Gonadal and stress-related steroid hormones induce profound changes in hippocampal dendritic morphology that may contribute to normal cognitive function and the development of neurological disorders. Previous work in our laboratory has shown that apical dendritic branching of pyramidal neurons in the cornu ammonis 3 (CA3) subfield of the hippocampus is increased following orchidectomy (ORCH) in male rats, with an accompanying decrease in dendritic spine density (Mendell et al., Brain Struct Funct 222:587-601, 2017). However, the mechanisms and timing underlying these effects remain unknown. Because severe stress leads to truncation of CA3 apical dendrites, we hypothesized that the effects of ORCH in pyramidal neuronal morphology might reflect a combination of loss of testosterone (T) with those of surgical stress. To test this hypothesis, young adult male Sprague-Dawley rats (age 60-70 days) were either left intact, underwent ORCH followed by subcutaneous implantation of cholesterol-filled (ORCH+C) or T-filled (ORCH+T) Silastic capsules, or underwent sham ORCH (n=3-6 animals/group). Cholesterol was used to control for any effects of the capsule implantation, while the sham-operated and surgically naïve rats served as controls for the surgical procedure. Animals were sacrificed at either 10-days or 1-month post-surgery, and their brains were Golgi impregnated for analysis of neuronal structure. Dendritic branching and dendritic spine density were analyzed in the CA1 and CA3 hippocampal subfields. At 10-days post-surgery, CA3 apical dendrites of ORCH+C rats displayed significant expansion in dendritic branching compared to sham-operated controls. In ORCH+T rats, CA3 branching was restored to levels similar to those in surgically naïve males. At 1-month post-surgery, ORCH+C rats displayed CA3 apical dendritic branching resembling that observed at 10-days, but ORCH+T rats had similar CA3 dendritic branching patterns to ORCH+C rats. No treatment-dependent differences were seen in apical branching of CA1 neurons, or in dendritic spine density in either CA1 or CA3 10-days or 1-month post-surgery. These findings indicate that the effects of ORCH on hippocampal CA3 dendritic structure are apparent as early as 10-days post-surgery and persist for at least one month. These effects reflect an interaction between stress-induced dendritic atrophy and neuromodulatory effects of T on hippocampal dendritic morphology.

Disclosures: L.K. Isaacs: None. **E.M. Lawton:** None. **A.L. Mendell:** None. **N.J. MacLusky:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.08/E28

Topic: B.07. Synaptic Plasticity

Support: CNPq

Title: Biological Roles of Microglial cells in Spinal Cord synaptic plasticity after peripheral nerve injury

Authors: *R. P. CAMPOS[1], M. B. DA SILVA[2], V. RIBEIRO-RESENDE[2]
[1]Univ. Federal Do Rio De Janeiro, Rio De Janeiro, Brazil; [2]Inst. de Biofísica Carlos Chagas Filho, UFRJ, Brazil, Brazil

Abstract: One of the key features of PNS is their regenerative potential, allowing axons to regrow, depending on the severity of the injury. Many cell events are triggered in the spinal cord to support motoneurons to survive and axonal regeneration after nerve injury. Changes in the synaptic plasticity around motoneurons are often observed, where old connections are removed, and new ones are created. Microglial cells are primitive macrophages that invade Central Nervous System (CNS) in early states and are responsible to eliminate synapses during the development. In this study, we investigate the synaptic plasticity after different kind of injuries in PNS as well as the role of microglial cells in this process. Adult male C57Bl6 mice were employed as the experimental model where the uninjured group had no surgery (control) and other groups had an incision made in the right mid-thigh level followed by sciatic nerve isolation. The crush group had, after isolation, the sciatic crushed for 15s and the transection group had 5 mm of the nerve cut off at the same region. To evaluate microglial influence, animals received minocycline 45mg/Kg intraperitonially daily. All experimental conditions were evaluated by walking track test to study their motor function. Lesioned groups had deficient performance compared to Control group, although Crush animals demonstrate significant improvements through the time points evaluated (1,4,7 and 14 days after lesion, DAL). There was no difference between animals which received minocycline or not. Quantitative analysis of Sinaptophysin staining in motoneurons reveled significant decrease of synapses in lesioned groups when compared to Controls. After the same period, both lesioned groups showed increased number of reactive microglial cell (Iba-1positive) followed by often observation of amoeboid morphology. The use of minocycline retarded this increase up to 4 DAL. There was no significant difference between transection and crush lesion in synaptophysin and Iba1 quantifications. Taken together, we correlated here synapse plasticity with the recruitment of microglial cells in the spinal cord tissue after sciatic nerve crush or transection lesion

Disclosures: R.P. Campos: None. **M.B. da Silva:** None. **V. Ribeiro-Resende:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.09/E29

Topic: B.07. Synaptic Plasticity

Support: PSL Nanopaint (Aux frontiers des labex)

Title: NanoPaint: Tracking of the cannabinoid type 1 receptor with biofunctional quantum dot nanoconstructs reveals fast nanoscopic structural plasticity of the neuronal cell membrane

Authors: *D. ZALA[1], T. PONS[2], N. LEQUEUX[2], Z. LENKEI[1], M. TASSO[3]
[1]Ctr. of Psychiatry and Neurosci., Paris, France; [2]ESPCI, Paris, France; [3]INIFTA, La Plata, Argentina

Abstract: Single-particle tracking with quantum dots constitutes a powerful tool to follow the dynamics of cell membrane receptors unveiling their intricate mechanisms of membrane diffusion, velocity, endocytic uptake and fate. Super-resolution microscopy and live imaging in three dimensions (3D) of cell membrane-bound quantum dots (QDs) also provide a wealth of single-particle trajectories that can be exploited as a source of spatial information to effectively reconstruct the cell membrane in 3D with high spatio-temporal resolution. Single QD nanoparticles tracking cell receptor dynamics can accurately and rapidly (seconds) ‘paint’ the cell membrane with a level of 3D detail that not only sets the ground to analyze cell membrane deformation under pertinent biological stimuli, but also sheds light on the membrane topography and membrane plasticity. In this work, very bright, small and stable biofunctional QD nanoconstructs were employed to demonstrate the "nanoPaint" concept in conjunction with live 3D super-resolution microscopy. QDs recognizing the neuronal cannabinoid type 1 receptor (CB1R) were used to ‘paint’ the cell membrane and to follow membrane deformations of mature cultured rat hippocampal neurons. We show that the high axonal expression of CB1R and its rapid membrane diffusion are interesting characteristics to fully reconstruct pre-synaptic terminals including the plasma-membrane juxtaposing the synaptic cleft. Typically, less than one minute acquisition is sufficient to obtain enough information for a 3D reconstruction with a resolution in the tens of nanometers range. Time-lapse reconstructions at 30s to 1min temporal resolution of filopodia and axons highlights the high nanoscale dynamics of the cell membrane shape. Insights of QD penetration in the neuronal synaptic cleft highlight the potential of nanoPaint method as a precision tool for neuronal structural plasticity studies.

Disclosures: D. Zala: None. **T. Pons:** None. **N. Lequeux:** None. **Z. Lenkei:** None. **M. Tasso:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.10/E30

Topic: B.07. Synaptic Plasticity

Support: NIH grant EY007023
NIH grant NS090473
HFSP long-term fellowship

Title: Enrichment of plasticity-related synaptic proteins at functionally identified V1 synapses during ocular dominance plasticity *in vivo*

Authors: *P. IP[1], T. KU[2], S. EL-BOUSTANI[3], K. CHUNG[2], M. SUR[2]
[1]Picower Inst. for Learning and Memory, [2]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [3]Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Abstract: In mice, the primary visual cortex (V1) in one hemisphere receives dominant input from the contralateral eye and relatively weaker input from the ipsilateral eye. Monocular deprivation (MD) induced by brief eyelid closure of one eye results in unbalanced input to V1 neurons. MD applied during the critical period results in ocular dominance plasticity, due to weakening of neuronal responses to the deprived (closed) eye followed by strengthening of responses to the non-deprived (open) eye. Previous studies suggested that persistent spine remodeling can be induced by MD, resulting in a robust effect on functional plasticity of responses in V1 neurons. However, the mechanisms by which MD remodels dendritic spines are unknown. For example, the eye-specific and other functional properties of spines eliminated during short term MD are unclear, as are the molecular mechanisms that lead to dendritic spine elimination and homeostatic spine strengthening or formation. We have previously described a prominent re-distribution of the immediate early gene Arc and surface AMPARs in individual identified neurons following MD and eye re-opening using fluorescently tagged probes together with two-photon imaging of dendritic spines. However, visualization of fluorescent probes under two-photon microscopy is still restricted by the optical diffraction limit and the availability of individual probes. Here, we employed the magnified analysis of the proteome (MAP) to linearly expand the cortex by fourfold to examine, at super-resolution scale, the enrichment of plasticity proteins at the postsynaptic density to correlate to structural changes of the same dendritic spines observed with two-photon microscopy. To achieve this, plasmids expressing GCaMP6s and the structural filler mRuby2 were delivered into individual mouse V1 neurons during the critical period by two-photon guided electroporation. Electroporated neurons were imaged before and after MD to assess how the decrease in synaptic drive remodels spines. By measuring eye-specific drive in neurons and spines in which we expressed GCaMP6s, we found that spines with

input from the closed eye rapidly reduced in size, whereas increasing numbers of spines responded to the open eye. Following functional imaging *in vivo*, the cortices were subjected to MAP processing for identifying the enrichment of plasticity-related synaptic proteins. Various antibodies targeting pre- and post-synaptic terminals were used to verify the enrichment of plasticity-related proteins. Ongoing studies suggest that active redistribution of synaptic proteins underlies functional experience-dependent plasticity of V1 neurons.

Disclosures: P. Ip: None. **T. Ku:** None. **S. El-Boustani:** None. **K. Chung:** None. **M. Sur:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.11/E31

Topic: B.07. Synaptic Plasticity

Support: NIH Grant 1R01MH104319-01A1,02,03,04
NSF Grant 1707356

Title: Presynaptic ultrastructure changes in response to LTP stimulation in stratum radiatum of hippocampal CA1 neuropil

Authors: *L. M. KIRK[1], K. ZATYKO[1], C. BROMER[2], T. M. BARTOL, JR[3], T. J. SEJNOWSKI[3], K. HARRIS[1]
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Abstract: Long term potentiation (LTP) is the sustained increase in evoked response following the delivery of high frequency stimulation. In the hippocampus, LTP is the cellular correlate of learning and memory. There are many ultra-structural changes that occur at hippocampal synapses several hours after LTP. Most of this work has previously focused on changes of postsynaptic structures. For example, it is well documented that post synaptic densities (PSDs) and dendritic spines (the site of most excitatory synapses) are enlarged several hours following LTP induction (Bourne and Harris, 2011). However, less is known about presynaptic structure changes in the same paradigm. Previously we showed that two hours following LTP there is a significant drop in the reserve pool of synaptic vesicles, with a larger drop occurring at boutons that contain mitochondria (Smith et al., 2016). While it is tempting to speculate that the vesicles become more mobile between boutons, we also see a decrease in transport packets (groups of less than 10 vesicles in inter-bouton regions) two hours following LTP (Bourne et al., 2013). Here we have used serial section electron microscopy combined with Cell Blender tools to measure the presynaptic bouton surface area in *stratum radiatum* of CA1 in hippocampal slices

that have received either control or LTP stimulation in order to test the hypothesis that the reserve pool of vesicles contributes to presynaptic bouton growth after LTP.

Disclosures: L.M. Kirk: None. **K. Zatyko:** None. **C. Bromer:** None. **T.M. Bartol:** None. **T.J. Sejnowski:** None. **K. Harris:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.12/E32

Topic: B.07. Synaptic Plasticity

Support: NIH Grant 1R01MH103848

Title: Increased Fkbp5 expression slows GR activity and neurogenesis, impacting learning and memory

Authors: *I. OZSAN[1], X. WANG[2], J. J. SABBAGH[1], E. J. WEEBER[2], L. J. BLAIR[1]
[1]Mol. Med., [2]Mol. Pharmacol. and Physiol., Univ. of South Florida, Tampa, FL

Abstract: *FK506-binding protein 5* (*FKBP5*) contains single nucleotide polymorphisms (SNPs) that combine with environmental factors to increase risk of psychiatric disorders including post-traumatic stress disorder (PTSD), major depression (MDD) and bipolar disorder. Importantly, some of these SNPs increase *FKBP5* expression through reduced *FKBP5* DNA methylation. *FKBP5* is also upregulated with aging through a similar mechanism. *FKBP5* encodes for FKBP51, a protein known to regulate glucocorticoid receptor (GR) trafficking together with the 90 kDa heat shock protein (Hsp90). This heterocomplex slows GR transactivation altering stress response in a short, negative feedback loop. However, the downstream effects of increased FKBP51 are still unclear. To evaluate the consequences of enhanced *FKBP5* expression, we generated a novel FKBP51 overexpressing mouse using site-directed insertion of the human *FKBP5* gene. Using this model, we have found that high *FKBP5* expression did not contribute to increased depression-like behavior, as we hypothesized. Instead, mice overexpressing *FKBP5* showed increased anxiety, reduced pleasure-seeking behavior, and altered learning and memory. Through histochemical analysis, we found that GR nuclear translocation and neurogenesis were reduced in mice overexpressing *FKBP5*. Therefore, increased *FKBP5* expression slows GR transactivation and the production of new neurons, which could contribute to altered learning and memory.

Disclosures: I. Ozsan: A. Employment/Salary (full or part-time):; University of South Florida. **X. Wang:** A. Employment/Salary (full or part-time):; University of South Florida. **J.J. Sabbagh:** A. Employment/Salary (full or part-time):; University of South Florida. **E.J. Weeber:**

A. Employment/Salary (full or part-time):; University of South Florida. **L.J. Blair:** A. Employment/Salary (full or part-time):; University of South Florida.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.13/E33

Topic: B.07. Synaptic Plasticity

Support: ERC Grant RG83283

Title: Reliable learning with unreliable synapses

Authors: *D. V. RAMAN, T. S. O'LEARY
Engin. Dept., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Synaptic plasticity allows neuronal networks to change their behaviour in targeted ways. Does this mean all synaptic changes are useful or relevant to a specific task being learned? Recent experiments suggest not. Individual synapses can constantly and spontaneously reconfigure, even when network spiking activity is suppressed [1]. Moreover the magnitudes of activity-dependent and independent reconfiguration are often comparable. How can a precise memory/behaviour be encoded if some synaptic plasticity is unrelated to these tasks? We derive a simple, biologically consistent synaptic plasticity rule that can both learn and maintain a learned state in spite of constant, task-irrelevant weight changes. The rule requires no communication between synapses. The only necessity is a globally shared, scalar indicator of behavioural performance, as could be provided by a bulk neuromodulator. The rule can coexist with other learning and synaptic regulation processes, improving the nervous system's robustness to reconfiguring synapses.
Several experimentally important observations and hypotheses arise out of implementing our learning rule in a network model. Firstly, the rule works even as large synaptic changes can occur in directions uncorrelated with task learning. This could allow for homeostasis and training multiple tasks. Secondly, bulk properties of synaptic dynamics remain constant, independently of whether learning is ongoing or completed. These properties include the distribution of synaptic speeds, directions, and strengths. The implication is that experimental validation of task learning through observation of these properties may not always be possible. Thirdly, neural representations of task features experience a consistent rate of change, even after the learning phase has finished. This complements recent experimental studies based on long term calcium imaging of neural activity in mice as they perform learned tasks [2]. Task-related neural representations changed consistently over time.
[1] Driscoll, L. N. et al. (2017). Dynamic reorganization of neuronal activity patterns in parietal cortex. Cell, 170(5), 986-999.

[2] Ziv, N. E., & Brenner, N. (2017). Synaptic Tenacity or Lack Thereof: Spontaneous Remodeling of Synapses. Trends in neurosciences.

Disclosures: D.V. Raman: None. **T.S. O'Leary:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.14/E34

Topic: B.07. Synaptic Plasticity

Title: Fragile X mental retardation protein regulates dendritic branching and spine morphology in the dorsal striatum following repeated cocaine administration

Authors: *J. HUEBSCHMAN, L. SMITH
Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Cocaine, and other drugs of abuse, are known to cause synaptic changes in the brain, altering the connectivity between cells to produce potentially long lasting effects after drug exposure. In particular, previous studies have shown that drug exposure in rodents causes an increase in dendritic spine density and synaptic strength of medium spiny neurons (MSNs) in the nucleus accumbens (NAc) and dorsal striatum – brain regions which are key players in goal-oriented and habitual behaviors likely involved in the development of addiction. In this study, we identify a role for the fragile X mental retardation protein (FMRP), a neuronal RNA binding protein, in regulating these dendritic changes. FMRP regulates the translation of hundreds of brain mRNAs, many of which are involved in synaptic function. Loss of this protein, as seen in fragile X syndrome (FXS), results in an increase in dendritic spines in cortical and hippocampal brain regions, particularly immature spine types, suggesting that FMRP is involved in regulating spine maturation and elimination. Previously, we showed that lack of FMRP in *Fmr1* knockout (KO) mice allows cocaine-induced increases in dendritic branching and spine density in NAc shell at a time point when it is not yet observed in wild type animals, suggesting FMRP limits this process. More specifically, the observed increase primarily involved thin spine types, typically considered more immature and labile (Smith et al., Neuron, 2014). Here we show significant interactions between genotype and cocaine treatment when we looked at dendritic branching and spine density in the dorsal lateral striatum (DLS), suggesting that FMRP has a role in regulating drug-induced synaptic plasticity in this region as well. Specifically, we observe a similar cocaine-induced increase in overall spine density in *Fmr1* KO animals that is not observed at this time point in wild type animals, but in DLS the increase does not appear to be spine type specific. Ongoing work in our lab is examining FMRP's regulation of dendritic branching and spine density in the dorsal medial striatum, a region known to be involved in reward-related goal-oriented behaviors, following cocaine exposure. We are also investigating

FMRP's role in regulating synaptic morphology and function in an embryonic mouse cortical-striatal co-culture model.

Disclosures: J. Huebschman: None. **L. Smith:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.15/E35

Topic: B.07. Synaptic Plasticity

Support: NIH Grant DA022727-11
NIH Grant NS106906-01
NIH Grant MH100093-05
Farber grant

Title: Synaptic nanomodules underlie the organization and plasticity of spine synapses

Authors: *M. HRUSKA[1], N. HENDERSON[1], S. J. LE MARCHAND[2], M. B. DALVA[1]
[1]Dept. of Neurosci., Thomas Jefferson Univ., Philadelphia, PA; [2]Bio-Imaging Ctr., Univ. of Delaware, Newark, DE

Abstract: Experience results in long-lasting changes in dendritic spine size, yet how the molecular architecture of the synapse responds to plasticity remains poorly understood. Here, a combined approach of multi-color stimulated emission depletion microscopy (STED) and confocal imaging demonstrates that structural plasticity is linked to the addition of unitary synaptic nanomodules to spines. Spine synapses *in vivo* and *in vitro* contain discrete and aligned sub-diffraction modules of pre- and post-synaptic proteins whose number scales linearly with spine volume. Live-cell time-lapse super-resolution imaging reveals that N-methyl-D-aspartate receptor (NMDAR)-dependent increases in spine size are accompanied both by enhanced mobility of pre- and post-synaptic modules that remain aligned with each other and by the coordinated addition of new nanomodules. These findings suggest a simplified model for experience-dependent structural plasticity relying on an unexpectedly modular nano-molecular architecture of synaptic proteins.

Disclosures: M. Hruska: None. **N. Henderson:** None. **S.J. Le Marchand:** None. **M.B. Dalva:** None.

Poster

202. Structural Plasticity II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 202.16/E36

Topic: B.07. Synaptic Plasticity

Support: R21NS105070 (NINDS)
F32MH115441 (NINDS/NIMH)
R01EY025437 (NEI)
U01NS090438 (NINDS)

Title: *In vivo* imaging of synapse assembly/disassembly across a full dendritic arbor on a minute time scale

Authors: *J. BOIVIN, K. P. BERRY, Y. XUE, P. T. C. SO, E. NEDIVI
MIT, Cambridge, MA

Abstract: The recent development of parallelized imaging approaches has enabled large-scale imaging of network activity at soma-level resolution, but it remains challenging to visualize small structures such as individual synapses while maintaining a broader view of a large tissue volume. To tackle this challenge, we are developing high-resolution, high-throughput multiline-scan temporal focusing (TF) for fast structural imaging of large tissue volumes at synaptic resolution *in vivo*. Using our multiline-scan TF system, we perform 2-color imaging of the full dendritic arbor of a layer 2/3 pyramidal neuron with its resident spines and inhibitory synapses in less than 2 minutes, more than an order of magnitude faster than traditional point-scan microscopy. In our first application of this technique to a biological question, we visualize the structural dynamics of inhibitory synapses across the full dendritic arbor over timescales that were infeasible with point-scan microscopy. Inhibitory synapses show strikingly high rates of turnover when imaged once per day, but it is unknown how frequently these synapses are assembled and disassembled on the scale of hours or minutes, or whether their dynamics are coordinated or distributed asynchronously throughout the dendritic arbor. By imaging the full arbor rather than short dendritic segments, we can assay not only the turnover of individual inhibitory synapses, but also the distribution of these dynamic synapses in terms of their proximity to the soma, dendritic branch order, basal or apical identity, and potential spatial clustering and temporal synchrony of dynamic events. The utility of our system extends beyond the structural dynamics of inhibitory synapses. This parallelized approach for multicolor, high-resolution imaging is compatible with genetic labeling of other structures and opens the door to exploring a myriad of dynamic cellular and subcellular events that happen faster than can be monitored using conventional point-scan microscopy.

Disclosures: J. Boivin: None. **K.P. Berry:** None. **Y. Xue:** None. **P.T.C. So:** None. **E. Nedivi:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.01/E37

Topic: B.08. Intrinsic Membrane Properties

Title: Theta frequency selectivity in signal gain in stellate cells of the medial entorhinal cortex under mimicked *in vivo* conditions

Authors: *N. KATYARE, S. SIKDAR
Indian Inst. of Sci., Bangalore North, India

Abstract: In-vivo intracellular recordings from stellate cells have confirmed the presence of intracellular theta oscillations which influence spike timings, and ramps of synaptic inputs which generate the actual grid-like firing fields.
To understand how these mechanisms interact, we analysed signal gain of these cells in presence of in-vivo like fluctuating conductance based synaptic inputs injected through the Dynamic clamp (based on Destexhe et. al., Neuroscience, 2001), in rat brain slices.
We analysed the collective voltage response when the cells were firing in theta frequency and measured the signal gain both inclusive and exclusive of the subthreshold responses.
We observed that the signal gain amplitude correlated with the average firing frequency of the neurons, implying a linear relationship of signal gain with the neuronal excitability. Interestingly, however, the signal gain consistently showed a peak in theta frequency which was insensitive to the firing rate.
The theta frequency peak was also relatively unaffected by the actual levels of excitatory and inhibitory synaptic conductances, and a range of their standard deviations. However, we observed that this peak frequency changed when the synaptic time constants were changed beyond a certain range, indicating that the kinetics of the underlying stochastic synapses influenced the frequency selectivity.
Next, in order to determine if the mechanisms imparting intrinsic frequency selectivity to these cells also do contribute, we measured the signal gain in the absence of HCN current. And indeed, we observed that on blocking HCN channels, the theta peak shifted to a lower frequency range ($p < 0.001$).
A computational model with HCN and persistent sodium channels with similar simulated in-vivo conditions could reproduce these results, suggesting a role of amplified resonance. The model also suggested selective sensitivity of firing rate to the fluctuations rather than mean of the excitatory currents in presence of HCN, indicating a role of high pass filtering imparted by HCN

channels.
These findings suggest that under in-vivo like level of activity, the voltage responses of stellate cells are governed by the dynamics of the underlying subthreshold process, determined mainly by an interplay between the intrinsic frequency selectivity and synaptic kinetics.
This kind of gain modulation can underlie the error correction mechanisms necessary for spatially periodic firing and can justify the steeper slope of phase precession observed in these cells.
This is the first report of such signal gain measurements in stellate cells and also the first report of signal gain measurements using conductance based inputs.

Disclosures: N. Katyare: None. **S. Sikdar:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.02/E38

Topic: B.08. Intrinsic Membrane Properties

Support: Senior Research fellowship from University Grants commission, India
DBT-IISc partnership fund

Title: Nicotine modulates electrophysiological properties of hippocampal subicular neurons through block of HCN channels

Authors: *S. VASNIK[1], S. K. SIKDAR[2]
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Abstract: Different behavioral states in animals are associated with different brain oscillation. These oscillations are consequences of synchronous activity of neurons in a network. Subiculum is a region of the hippocampus which generate theta wave during arousal and REM sleep that is important in memory formation. The subiculum receives cholinergic inputs during cognitive functions which contribute to theta wave generation. Also, I_h mediated by HCN channels has a robust role in the generation of theta oscillation at the cellular level. To understand the significance of cholinergic input at the cellular level, we investigated, if nicotine, an agonist of nicotinic acetylcholine receptor (nAChR) modulates the activity of subicular burst firing neurons known to express HCN channels. Using biocytin staining and patch clamp technique on hippocampal rat brain slices, we characterized the morphology and intrinsic properties of the neurons. On bath application of nicotine, we observed a decrease in sag amplitude, resonance frequency and strength of these neurons. These effects were persistent even in the presence of non-specific nAChR blocker i.e. DHβE which suggests that the changes are not mediated via nAChR but directly by channels responsible for resonance property. Nicotine treatment also

modulated the input resistance of the cell. Perfusion of acetylcholine in the presence of atropine (muscarinic acetylcholine receptor antagonist) also demonstrated similar effects in a reversible manner. In voltage-clamp mode, isolated I_h showed a significant decrease in the amplitude in presence of nicotine. Our study suggests a modulatory role of ACh on burst firing neurons by changing its intrinsic properties including the shift in resonance frequency to lower theta range. Future experiments will be directed towards confirming if endogenous ACh release shows a similar effect on burst firing subicular neuron

Disclosures: S. Vasnik: None. **S.K. Sikdar:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.03/E39

Topic: B.08. Intrinsic Membrane Properties

Title: Single-cell RNA and electrophysiological profiling of D1+ and D2+ principal neurons of the prefrontal cortex

Authors: *R. DE SA[1], A. DIJKE[2], J. WINTERER[3], K. LE CORF[1], C. FOLDY[3], A. FRICK[1]
[1]Neurocentre Magendie U1215, Bordeaux Cedex, France; [2]Technische Univ. München in Munich, Munich, Germany; [3]Brain Res. Inst., Univ. of Zurich, Zurich, Switzerland

Abstract: Dopaminergic modulation of the prefrontal cortex (PFC) circuits is crucial for cognitive processes such as working memory, planning, and attention, and dysfunction in this system has been linked to cognitive deficits associated with schizophrenia and autism spectrum disorders. Despite its physiological and physiopathological importance, we are still lacking a clear understanding of the basic principles of DA actions in the PFC.
We set out to provide a detailed classification of layer 5 pyramidal neurons mediating the two main streams of DA signaling — DA receptor group 1 (D1) and DA receptor group 2 (D2). To achieve this, we combined electrophysiological whole-cell recordings in acute slices of the prelimbic part (PL) of the medial PFC with single-cell RNA sequencing, morphological and immunohistochemical analysis.
Our results demonstrate that layer 5 pyramidal neurons fall into two distinct groups based on their integrative properties. These physiological measures strongly correlate with differences in genes coding for voltage-gated ion channels. In addition, analysis of the full transcriptome (~14073 genes detected) reveals significant differences in 534 gene products, including those coding for ligand-gated ion channels, cell adhesion molecules, and intracellular signaling cascades.
Overall, our results suggest that there are two main types of layer 5 pyramidal neurons (D1- vs D2-types) that can be clearly distinguished by their electrophysiological and molecular

properties. These findings may not only shed light on the identity of PFC neurons, but may also have important implications for our understanding of dopamine signaling in the prefrontal cortex during cognitive tasks.

Disclosures: R. De sa: None. **A. Dijke:** None. **J. Winterer:** None. **K. Le Corf:** None. **C. Foldy:** None. **A. Frick:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.04/E40

Topic: B.08. Intrinsic Membrane Properties

Title: TRPC3 and NALCN channels are essential for pacemaking of nigral dopamine neurons

Authors: *K. UM[1], L. BIRNBAUMER[2], H. KIM[1], M. PARK[1]
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Abstract: Dopamine neurons in the substantia nigra pars compacta (SNc) are slow pacemakers that generate spontaneous action potentials, regularly. Although this pacemaking activity is very important in maintenance of background dopamine levels and proper functioning of basal ganglia, it is not clear what channels play a major role in driving of pacemaking in SNc dopamine neurons. Here we report that two nonselective cation channels, TRPC3 and NALCN channels are essential for pacemaking in SNc dopamine neurons. In both midbrain slices and acutely dissociated SNc dopamine neurons, we found that pyr10, a specific blocker for TRPC3 channels, completely abolished pacemaking and hyperpolarized membrane potentials. In this condition, somatic current injection like leak currents revived pacemaker activity again, suggesting that TRPC3 channels drive pacemaking as a part of leak channels, that have been regarded as major inward currents in midbrain dopamine neurons during the initial phase of pacemaking cycle. However, spontaneous firing survived in dopamine neurons of TRPC3 knockout (KO) mice and the spontaneous firing rate did not differ between TRPC3 KO and wild type mice. Nevertheless, in the TRPC3 KO mice, pyr10 did not affect spontaneous firing rates at all, indicating that pyr10, in wild type mice, inhibited pacemaking by specifically blocking only TRPC3 channels. In TRPC3 KO mice, blockade of NALCN channels stopped spontaneous firing and hyperpolarized membrane potential, which was greater than the changes in wild type mice, indicating that NALCN channels completely compensate TRPC3 channel currents in TRPC3 KO mice. In wild type mice, blockade of NALCN channels completely abolished spontaneous firing, indicating that NALCN is also essential for pacemaking. Taken together, we could conclude that TRPC3 and NALCN channels are two major channels that drive pacemaking in nigral dopamine neurons.

Disclosures: K. Um: None. **L. Birnbaumer:** None. **H. Kim:** None. **M. Park:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.05/E41

Topic: B.08. Intrinsic Membrane Properties

Support: ERC-ADG - Advanced Grant

Title: Investigating the analog modulation of action-potential waveforms in axonal arbors of cortical neurons using whole-cell patch-clamp recordings and high-density microelectrode arrays

Authors: *V. EMMENEGGER, J. BARTRAM, S. SITNIKOV, A. HIERLEMANN
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Abstract: Analog-digital facilitation (ADF) is a type of short-term plasticity, where the subthreshold membrane potential in the presynaptic element enhances the spike-evoked synaptic response. Most cases of ADF have been induced by long (0.3-10 s) subthreshold depolarization of the soma, while in few cases, transient (15-200 ms) hyperpolarization has been evoked immediately before the action potential (AP). In both cases, somatic membrane fluctuations modulate the biophysical properties of voltage-gated ion channels causing changes in the AP waveform, which result in larger release of neurotransmitters. However, it is still unknown, whether the modulation of the AP waveform changes with increasing distance from the soma and differs in different axonal arbors, and whether such modulation affects the velocity of AP propagation.

Here, we used CMOS-based high-density microelectrode arrays (HD-MEA) with 26,400 microelectrodes, which enabled unprecedented high-resolution access to investigating axonal signaling at multiple sites simultaneously, thus providing in-depth information on the propagation of AP. The subthreshold depolarization and hyperpolarization of the presynaptic cell was performed using whole-cell patch-clamp recordings from cells in low-density cortical cultures, plated on a HD-MEA that allowed to trace the effects of such manipulations on AP propagation characteristics. Array-wide spike-triggered average signals were computed, and their spatiotemporal distribution was reconstructed.

In order to study the changes in extracellular AP waveforms, we first induced pharmacological modulations using dendrotoxin and carbamazepine, which increased AP width and amplitude. As a next step, we evoked AP broadening and amplitude changes by subthreshold depolarization and hyperpolarization. We detected the extracellular AP waveforms directly under the soma and traced them throughout the axon during various time spans and for different holding potentials. We found that changes in AP propagation velocity were correlated to the detected AP broadening. Our preliminary data evidenced changes in AP waveforms with increasing distance

from the soma along the axon, but further experiments on synaptically coupled neurons using paired recordings will be performed to better understand the influence of AP modulation on ADF.
Information encoding in neuronal circuits is probably contingent on both, temporal spike patterns and spike waveforms. In the light of the latter being typically disregarded in computational models, the study of the analog modulation of AP waveforms will contribute to a better understanding of neuronal information processing.

Disclosures: V. Emmenegger: None. **J. Bartram:** None. **S. Sitnikov:** None. **A. Hierlemann:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.06/E42

Topic: B.08. Intrinsic Membrane Properties

Support: Ministry of Science and Technology, Taiwan
Chang Gung Medical Foundation, Taiwan

Title: Characterization of intrinsic and network-dependent discharges in different types of basolateral amygdala neurons

Authors: *G.-H. WANG[1,2], Y.-C. YANG[1,3]
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Abstract: The amygdala is considered as the center of emotion and emotional memory, and is widely implicated in many diseases such as anxiety, autism and epilepsy. Since amygdala circuitry comprises interconnected pyramidal neurons and interneurons, we sought to characterize different types of basolateral amygdala (BLA) neurons, and investigate the intrinsic membrane properties and synaptic transmission that govern their network-dependent activities by pharmacological manipulations, step-current injection, and electrical stimulation with current-clamp recordings of BLA neurons in acute BLA slices from C57BL/6 mice (aged p17-25). Solutions mimicking physiological conditions were used (K^+-based internal solution: in mM, 116 $KMeSO_4$, 6 KCl, 2 NaCl, 20 HEPES, 0.5 EGTA, 4 MgATP, 0.3 NaGTP, 10 $NaPO_4$ creatine, and pH 7.25 adjusted with KOH; saline for external solution: in mM, 125 NaCl, 26 $NaHCO_3$, 25 glucose, 2.5 KCl, 1.25 NaH_2PO_4, 1 $MgCl_2$, and 2 $CaCl_2$). The pyramidal neurons can be identified morphologically with a soma diameter of >5 μm and electrophysiologically with relatively low-frequency firing activity in response to injection of supra-threshold depolarizing currents. In contrast, the interneurons are of smaller size (soma diameter <5 μm) and mostly fire

high-frequency spikes during depolarizing currents. Delivery of high-frequency stimulus (e.g. 1-s train of 0.4-ms monophasic rectangular pulse at frequency of 60 Hz and an intensity of 400 μA) in BLA resulted in target cell-dependent oscillation of both pyramidal neurons and interneurons. Responses to high-frequency stimulation mimicking neural activities were examined with and without inhibition of fast synaptic transmission, suggesting distinct contribution of GABAergic and glutamatergic transmission. We also applied the electrical stimulation at different distance from different recording neurons, and discovered that stimulus-induced oscillation was also distance-dependent. We conclude that BLA neurons have distinct membrane properties and synaptic response that differentially contribute to their physiological activities and network-dependent oscillations.

Disclosures: G. Wang: None. **Y. Yang:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.07/E43

Topic: B.08. Intrinsic Membrane Properties

Support: Grant-in-Aid for Scientific Research on Innovative Areas15H05880
Grant-in-Aid for Scientific Research on Innovative Areas 15H05872

Title: The effect of static magnetic fields on the membrane excitability of pyramidal neurons in mice

Authors: *Y. TAKAMATSU[1], A. S. SINHA[3], T. AKITA[3], A. FUKUDA[3], T. MIMA[2]
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Abstract: It has been reported that static magnetic fields (SMFs) by a compact magnet can suppress the corticospinal excitability in human studies. However, the exact neurophysiological basis of this phenomenon has not been well known yet. We investigated the effect of SMFs on the activity of pyramidal neurons in cerebral cortices of mice by the whole-cell current clamp technique to further understand the physiological mechanism of SMFs at the cellular levels. Brain slices were prepared from C57BL/6J mice (3 weeks, 8-13 g, n = 6) and incubated in the artificial cerebrospinal solution for 1 hour. After the recovery, brain slices were exposed to NdFeB magnet for 30 min (284 mT). The whole-cell current clamp was performed at 10 and 20 min after the exposure to SMFs, which was compared to the control condition without SMFs exposure. We recorded the action potential, from total 57 cells (control; n = 20, 10 min after the SMFs; n = 16, 20 min after the SMFs; n = 21) in layer II/III pyramidal cells in the mice motor cortex brain slice. We found that the rheobase current was higher and the input resistance was

lower significantly at 10 min compared to control condition. On the other hand, these effects were recovered at 20 min after the exposure to SMFs. Our findings successfully replicated the short-term plastic change of human brain function after SMFs at the cellular level. The finding showed that SMFs temporarily increased the minimum threshold current required for action potential firings at 10 min after the exposure, indicating increased membrane permeability of the neurons.

Disclosures: Y. Takamatsu: None. **A.S. Sinha:** None. **T. Akita:** None. **A. Fukuda:** None. **T. Mima:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.08/E44

Topic: B.08. Intrinsic Membrane Properties

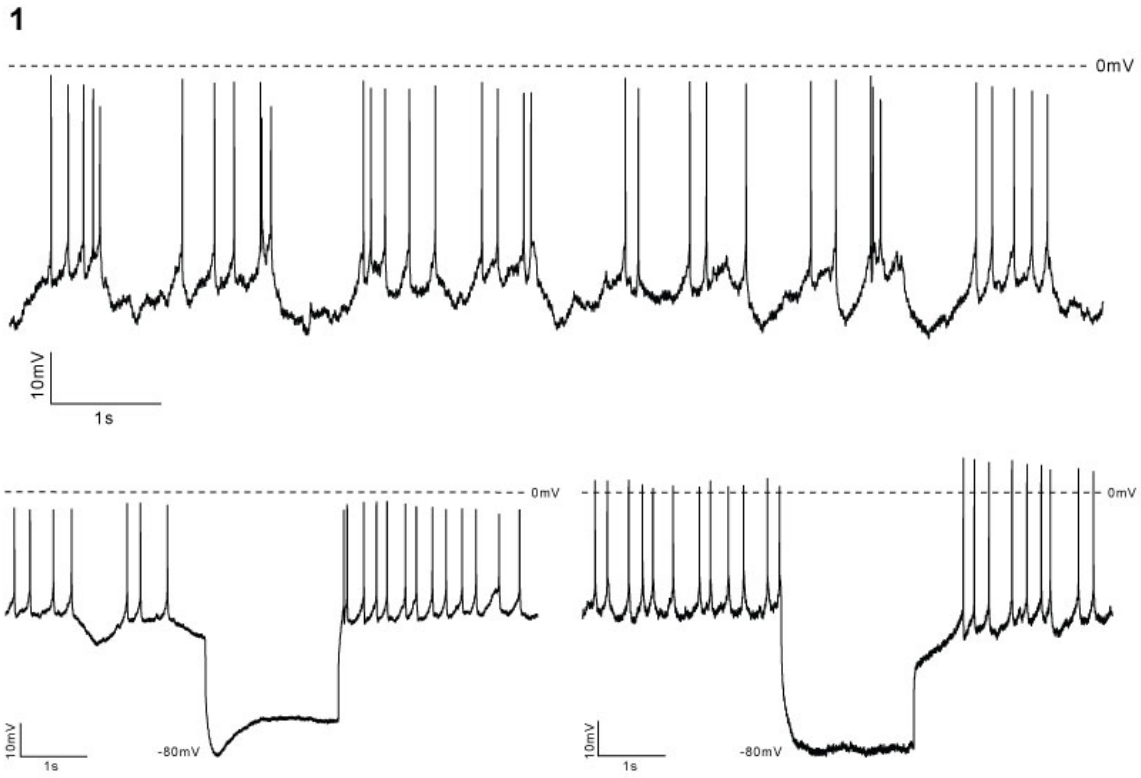
Support: DFG Grant CRC1193

Title: Projection specificity of *in vivo* electrophysiological properties of ventral tegmental area dopamine neurons

Authors: *K. OTOMO[1,2], N. FARASSAT[1], K. M. COSTA[1], C. A. PALADINI[3], J. ROEPER[1]
[1]Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt Am Main, Germany; [2]Intl. Max Planck Res. Sch. for Neural Circuits, Max Planck Inst. for Brain Res., Frankfurt, Germany; [3]UTSA Neurosciences Inst., Univ. of Texas at San Antonio, San Antonio, TX

Abstract: We have previously described that the significant *in vitro* diversity of intrinsic electrophysiological properties of dopamine (DA) neurons in the ventral tegmental area (VTA) was associated with their distinct axonal projections (Lammel et al. 2008). However, it remained unclear to what degree these intrinsic biophysical differences might shape the electrical activity in the intact brain, where VTA DA neurons are embedded in functional circuits. To address this question, we recorded extracellularly *in vivo* and labeled individual VTA DA neurons, with fluorogold retrograde tracing for axonal projection identification. We focused on two prominent projection sites: the medial and lateral shell of the nucleus accumbens (m-NAcc & l-NAcc, respectively). As m-NAcc-projecting VTA DA neurons displayed about 2-fold longer rebound pauses *in vitro* after a hyperpolarizing current injection compared to those projecting to the l-NAcc, we studied spontaneous pauses in firing in these two populations in anesthetized C57Bl/6N mice. In accordance with the intrinsic differences in rebound delays, identified m-NAcc-projecting VTA DA neurons also displayed significantly longer pauses (2.2 ± 0.4 s, n=21) *in vivo* compared to those occurring in VTA DA neurons projecting to the l-NAcc (1.2 ± 0.2 s, n=24, p = 0.02). To directly explore the subthreshold activity of these neurons in intact brains,

we applied our recently-developed *in vivo* patch methods to this population. VTA DA neurons were recorded *in vivo* in the whole-cell configuration and filled with neurobiotin for morphological reconstruction and neurochemical identification. Similar to *in vitro*, *in vivo* DA neurons display large differences in sag-amplitudes and rebound behavior after terminating a hyperpolarizing current injection, which ranges from transient rebound bursting to long pausing and slow return to firing threshold (Fig. 1). We are now combining *in vivo* patching with axonal tracing to study whether differences in subthreshold integration among VTA DA neurons *in vivo* are also associated with distinct axonal projection targets.



Disclosures: K. Otomo: None. **N. Farassat:** None. **K.M. Costa:** None. **C.A. Paladini:** None. **J. Roeper:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.09/E45

Topic: B.08. Intrinsic Membrane Properties

Support: NIH R01 DA041705

Title: Morphologically realistic computational models of bursting and rebound properties of medial and lateral substantia nigra dopamine nuerons

Authors: *C. J. KNOWLTON[1], K. OTOMO[2], S. STOJANOVICH[2], J. ROEPER[3], C. C. CANAVIER[4]
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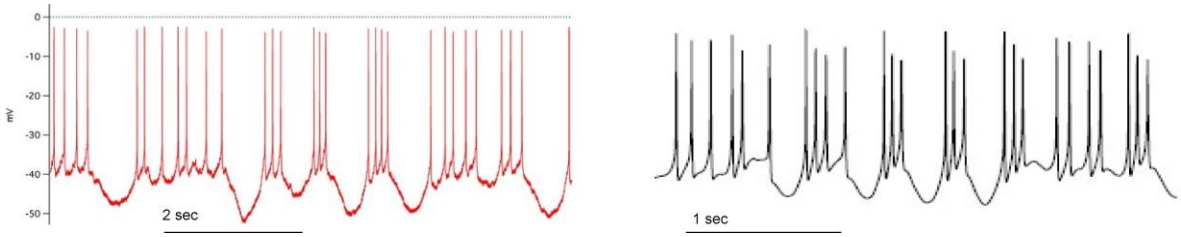
Abstract: In our morphologically realistic NEURON models of substantia nigra (SN) dopamine (DA) neurons, in vivo synaptic stimulation is modeled by a random train of EPSPs activating distributed NMDA receptors combined with variable tonic GABAA receptor activation. The model includes a K-ATP channel that facilitates, and an SK channel that inhibits, bursting. Our recent in vivo patch clamp recordings in anesthetized mice from medial SN DA neurons confirmed that these cells exhibit episodes of regular burst firing that are separated by hyperpolarized intervals (red trace). The model (black trace) replicates sequences of regular, three to four-spike bursts driven by a rhythmic oscillation in ADP in local domain of the K-ATP channel; ATP consumption by the calcium pump drives the activation of the K-ATP channel by ADP. The model predicts that the level of Ca2+ buffering can control the regularity of bursting- the simulation shown has 0.5% free Ca2+. In addition, recent in vitro experiments on identified medial and lateral SN DA mouse neurons projecting to the dorsal striatum revealed two distinct responses following a 2 s hyperpolarizing current: 1) a rebound burst with shorter interspike intervals (ISI) and less pronounced spike afterhyperpolarization (AHP) or 2) an afterdepolarizing potential (ADP) with spike failure prior to the resumption of pacemaking. Our morphologically realistic model of an SN DA neuron in vitro (without synaptic drive) reproduces the first type of response with a strong contribution of the T-type calcium channel to the activation of the SK channel, and the second with a weak contribution. In the model, the burst is caused by a transient decrease in outward SK currents following the hyperpolarizing current step due to deactivation of high threshold calcium channels and the transient increase in inward T-type and HCN currents. On the other hand, removal of inactivation followed by activation of the T-type channel accounts for the ADP. Spike failure is attributable to increased recruitment of SK current by the T-type channels in this population.



Disclosures: C.J. Knowlton: None. **K. Otomo:** None. **S. Stojanovich:** None. **J. Roeper:** None. **C.C. Canavier:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.10/E46

Topic: B.08. Intrinsic Membrane Properties

Support: University of Wisconsin-Milwaukee Research Growth Initiative

Title: Intrinsic excitability of retrosplenial cortical neurons varies as a function of age and sex

Authors: *H. YOUSUF, J. R. MOYER, Jr.
Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: The granular retrosplenial cortex (gRSC) forms reciprocal connections with the hippocampus (Van Groen & Wyss, 2003). In rats, the gRSC is well-positioned to contribute to spatial learning and associative fear memories (Vann et al., 2009; Kwapis et al., 2015). Furthermore, previous studies have demonstrated sex differences in associative fear learning (Dalla et al., 2009), however, the extent to which sex differences in the electrophysiological properties of gRSC neurons contributes to these differences remains unknown. Despite its role in complex forms of memory, little is known about the intrinsic membrane properties of gRSC neurons, and nothing is known about how they vary as a function of sex. Using visually-guided, patch-clamp recordings in brain slices, we studied the intrinsic excitability of gRSC neurons as a function of developmental age and sex. We characterized a distinctive population of pyramidal neurons in L5 from both adult females and adult males. The majority of pyramidal neurons in L5 of the gRSC in both sexes have a prominent afterdepolarization (ADP) following a single spike and these neurons are characterized as regular-spiking ADP neurons (RS_{ADP}). Interestingly, RS_{ADP} neurons in L5 of gRSC from male rats exhibited an enhanced intrinsic excitability compared with those from female rats. For example, RS_{ADP} neurons from adult males had a lower action potential threshold and a reduced fast afterhyperpolarization (fAHP) compared to those from the adult female. Stark differences in the electrophysiological properties of gRSC neurons were also observed during development. For example, unlike adult neurons, the majority of recordings from male rats between postnatal days 14-29 indicate that those L5 pyramidal neurons do not have a prominent ADP, and are thus characterized as regular spiking (RS) neurons. In addition, their properties differ from those of adult male RS neurons, which have significantly higher neuronal excitability, a more depolarized resting membrane potential, a reduced action potential half-width, and a reduced fAHP. Exactly when during development, gRSC neurons in L5 shift from the classic RS property to the RS_{ADP} firing property observed in adults, and whether this varies with sex is currently unknown. These results demonstrate that the granular retrosplenial cortex is a sexually dimorphic region that may contribute to observed sex differences in fear memories. Our studies also suggest that neurons within gRSC are

physiologically dynamic during development and thus may play a critical role in emotional development.

Disclosures: H. Yousuf: None. **J.R. Moyer:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.11/E47

Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant F32 DC016775
NSF Award 1622977

Title: Combined biophysical and statistical modeling of central projection neurons reveals roles of ion channels in stimulus encoding

Authors: *N. G. GLASGOW[1], Y. CHEN[2], R. E. KASS[3], A. KORNGREEN[4], N. N. URBAN[1]
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Abstract: The relationship between functional ion channel expression and how a given cell performs a computation - such as how that cell encodes specific features of a stimulus - is not understood. Yet, this link is essential to comprehend how the collection of ion channels in a cell create emergent single neuron computation and is critical for understanding how channel modulation affects stimulus encoding. Here we use a combined computational approach to link the variability of functional ion channel expression across cells to how a given cell encodes specific features of a stimulus. Specifically, we combine simulations from detailed biophysical models containing explicit specification of morphology and ion channel densities, with statistical generalized linear models (GLMs), which parameterize neuronal input-output relations. To probe the specific roles of ion channel variability in stimulus encoding, we use previously published biophysical models of two morphologically and functionally distinct projection neuron cell types: mitral cells (MCs) of the mammalian olfactory bulb, and layer V cortical pyramidal cells (PCs). We simulated MC and PC responses to gaussian white noise while varying individual ion channel densities. We found that varying some ion channel densities changed stimulus encoding more strongly than others. In our MC model, spike triggered averages (STAs) and GLM parameters were most affected by varying A-type K^+ channels, Ca^{2+}-activated K^+ channels, and L-type Ca^{2+} channels. Importantly, GLM fitting revealed sensitivity to channel variation that the STA did not capture. Initial simulations with the PC model generally support our STA findings, but also include effects of varying I_h channels, a channel type not present in the current MC model. Further GLM analysis will allow stimulus reconstruction and a more precise

determination of how variability of functional ion channel expression relates to variability of encoding specific stimulus features across cells. Overall, our computational platform offers a robust approach for exploring the relationship between functional ion channel expression and single neuron computation.

Disclosures: N.G. Glasgow: None. **Y. Chen:** None. **R.E. Kass:** None. **A. Korngreen:** None. **N.N. Urban:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.12/E48

Topic: B.08. Intrinsic Membrane Properties

Support: Ministry of Science and Technology, Taiwan
Chang Gung Medical Foundation, Taiwan

Title: The contribution of intrinsic K^+current to subthalamic burst discharges and locomotor behavior

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Abstract: The subthalamic nucleus (STN) is an important structure involved in modulation of the basal ganglia activity. The STN fires in two major types of spontaneous activities, the spike mode and the burst mode. Excessive burst discharges in the STN is a distinctive feature in patients or animal models of Parkinson's disease (PD), a state of dopamine deprivation. Fast switches between different modes of discharges by dopamine-dependent membrane potential changes were observed in the STN. Consistently, deep brain stimulation of the STN that depolarizes the subthalamic neuron would decrease the chances of burst discharges and ameliorate locomotor deficits of PD. The make of repetitive burst discharges is basically a collaborative work by membrane potential-dependent activities of different ion channels. We have previously demonstrated that hyperpolarization of STN neurons could speed up the recovery of low-voltage-activated T-type Ca^{2+} channels from inactivation, and consequently promote pathogenic burst discharges. In addition to the Na^+ and T-type Ca^{2+} channels, K^+ channels may play an important role in defining the height, duration, and superimposing spiking frequencies of burst discharges. Indeed, we have found that ERG K^+ channels effectively shape the pattern of burst discharges and thus locomotor activities. We therefore continued an in-depth

investigation on the possible roles of the other voltage-gated K^+ conductances that have been relatively neglected in physiological and pathogenic subthalamic discharges. We combined electrophysiological, pharmacological, optogenetic and behavioral methods in vitro (using C57BL/6 mice or Wistar rats aged p17-40) and in vivo (using adult male Wistar rats weighing 260 to 380 g) to show that specific voltage-dependent K^+ channels have a prominent effect on subthalamic burst discharges and consequently shape locomotor behaviors particularly in the state of PD

Disclosures: C. Huang: None. **G. Wang:** None. **Y. Yang:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.13/E49

Topic: B.08. Intrinsic Membrane Properties

Title: Trim69 E3 ubiquitin ligase regulates neuronal excitability in the mouse hippocampus

Authors: *S.-Y. LEE[1,2], H.-J. JEONG[3,4], H.-K. SO[3,4], Y.-B. KIM[2,4], J.-R. LEE[3], M.-J. HAHN[3], J.-S. KANG[3,4], H. CHO[2,4]
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Abstract: Protein modification by ubiquitin has emerged as a key regulator of neuronal activity. However, many of the ion channels targeted and the underlying molecular mechanisms involved in this process have not yet been determined. Trim69, an E3 ubiquitin ligase, is structurally and evolutionarily conserved in zebrafish, mouse, rat, and human. Although Trim69 is implicated in zebrafish neurogenesis, its role in *mammalian brain* is unclear. In this study, we investigated its function in mouse hippocampal neurons by using mice lacking Trim69 function. The expression study revealed that Trim69 is highly enriched in the hippocampus. In addition, Trim69 deficient-dentate gyrus granule cells (GCs) exhibit neuronal hyperexcitability. Based on the electrophysiological analysis, Trim69 seems to regulate neuronal activity via modulation of SK channels. The mechanistic study suggests that Trim69 is required for the modulation of SK channel activity without altering their expression levels.

Disclosures: S. Lee: None. **H. Jeong:** None. **H. So:** None. **Y. Kim:** None. **J. Lee:** None. **M. Hahn:** None. **J. Kang:** None. **H. Cho:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.14/E50

Topic: B.08. Intrinsic Membrane Properties

Support: Wellcome Trust-DBT India Alliance Senior fellowship, IA/S/16/2/502727
Ministry of Human Resource Development, India
DBT-IISc partnership program

Title: Activity-dependent long-term intrinsic plasticity in dentate gyrus granule cells

Authors: *P. MISHRA, R. NARAYANAN
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Abstract: The concomitant roles of synaptic plasticity and neuron-specific intrinsic plasticity as cellular substrates of learning and memory are well established. The dentate gyrus (DG) has been implicated in spatial navigation, learning and memory. The mechanisms behind and implications for synaptic plasticity in the DG have been thoroughly investigated. In contrast, the assessment of the protocols, mechanisms and implications associated with DG intrinsic plasticity has been surprisingly limited. In this study, motivated by theta-modulated burst firing in DG granule cells, we investigated the ability of theta burst firing (TBF) in inducing activity-dependent intrinsic plasticity. We performed somatic whole-cell current-clamp recordings from DG granule cells in 6–8 weeks old male Sprague-Dawley rats. We assessed changes in several intrinsic properties by recording associated physiological measurements before and 40 minutes after the induction of TBF in DG granule cells (n=28). In response to TBF, we observed a significant 16% reduction in input resistance (R_{in}) accompanied by a contrasting increase in firing rate, measured as a significant leftward shift in the f–I curve (~7 Hz increase in response to a 250 pA current). Among other significant TBF-induced changes, we noted a depolarizing shift (~4 mV) in the resting membrane potential, a reduction in the maximal impedance amplitude (~15%), a reduction in temporal summation measured in response to alpha excitatory current injections (~5%), a hyperpolarizing shift in the action potential threshold (~3 mV) and the emergence of spike doublets (~38% reduction in the first inter-spike interval). Importantly, although opposing changes in sub- and supra-threshold excitability measurements point to changes in multiple channel properties, we found significant correlations across changes observed in these measurements. For instance, we found significant and strong correlation between the reduction in R_{in} and the hyperpolarizing shift in action potential threshold, indicating correlated changes in putatively distinct mechanisms that resulted in opposing effects on neuronal excitability. We are currently performing experiments to delineate ion channels that mediate this form of plasticity, apart from exploring potential correlations among molecular mechanisms that underlie the

concurrent, yet contrasting, TBF-induced changes in sub- and supra-threshold intrinsic excitability. Finally, we are also addressing the question on whether heterogeneities in baseline neuronal excitability could play a dominant role in the recruitment of neurons as engram cells through induction of intrinsic plasticity.

Disclosures: P. Mishra: None. **R. Narayanan:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.15/E51

Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant NS065761 to JMN

Title: Voltage gated sodium channel accessory proteins in the cell-type and circuit-specific regulation of neuronal excitability

Authors: *J. L. RANSDELL[1], J. M. NERBONNE[2]
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Abstract: The suite of voltage-gated ion channels determines the intrinsic firing properties of a neuron. It has become increasingly clear that these channels function in macromolecular complexes and interact with accessory proteins that regulate ion channel properties and function. There are cell-type specific differences in the expression patterns and the functional roles of these accessory proteins. Genetic deletion of iFGF14, a voltage-gated sodium (Nav) channel accessory protein, results in a hyperpolarizing shift in the voltage-dependence of Nav current steady-state inactivation in cerebellar Purkinje neurons, and this causes a severe reduction in Purkinje neuron firing. Conversely, in CA1 pyramidal neurons, genetic deletion of iFGF14 affects the voltage-dependence of Nav channel activation (and steady-state inactivation is unchanged), which results in an increase in repetitive firing. Another example concerns the Nav channel β4 accessory subunit (Navβ4), which is thought to function as a Nav channel blocking particle whose block and unblock is responsible for the resurgent component of the Nav current (I_{NaR}). I_{NaR} has been identified in over 20 types of neurons, however, not all of these cell-types express Navβ4. Additionally, expression of Navβ1 in cerebellar granule neurons, and iFGF12 and iFGF14b in Purkinje neurons regulate I_{NaR} amplitudes, even though the residue structure of these accessory proteins make them unlikely to participate as Nav channel open-blockers. These results paint a clear picture that Nav channel accessory proteins drive the expression and functioning of ion channels differently (across cell types) and have divergent effects on ionic currents, cellular firing and ultimately, circuit function.

Disclosures: J.L. Ransdell: None. **J.M. Nerbonne:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.16/F1

Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant 5 F31 MH111224-02
Yerkes National Primate Research Center base grant #RR-00165, Animal Resource Program at NIH
NIH Grant R01 0000057537

Title: The role of ampk in regulating basolateral amygdala principal neuron excitability

Authors: *B. O'FLAHERTY[1], J. GUO[2], P. A. WENNER[3], D. G. RAINNIE[2]
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Abstract: The prevalence of major depressive disorder (MDD), one of the most common emotional disorders in the United States, is doubled in patients with type 2 diabetes mellitus (T2DM). Traditionally thought of as two interacting, though fundamentally independent disorders, emerging evidence suggests that MDD and T2DM may share a common etiology: dysregulated metabolism. Dysregulated metabolism could disrupt neuronal activity in key limbic areas, contributing to MDD. However, before we can understand how neuronal activity becomes dysregulated under metabolic stress, we must uncover the metabolic mechanisms regulating neuronal activity in control states. The key metabolic regulator AMP-activated protein kinase (AMPK) has been shown to alter neuronal activity in response to metabolic state in the hypothalamus. However, AMPK's role in other key limbic regions such as the basolateral amygdala (BLA) remains largely unknown. Previous work in our lab has shown inhibiting PDE4, which indirectly decreases AMPK activity by inhibiting AMP synthesis, increases BLA principal neuron activity. Intracellular administration of PDE4 inhibitor rolipram (5 nM) in BLA principal neurons increased membrane resistance, decreased spike threshold, and decreased threshold for LTP induction. We hypothesize that direct inhibition of AMPK would mimic the effects of rolipram, while activating AMPK would have the opposite effects. To test this, we examined the properties of BLA principal neurons using patch-clamp electrophysiological recordings, in conjunction with intracellular and extracellular (bath) administration of Compound C (an AMPK inactivator) and AICAR (an AMPK activator). Because previous research suggests that hyperglycemic conditions can blunt AMPK's response to activators and inactivators, we performed Compound C / AICAR administration in aCSF containing 10 mM glucose (the standard concentration) or 2.5 mM Glucose (the physiological glucose concentration in the

brain). Understanding how metabolic processes affect neuronal activity in the normally funcitioning BLA will lay the groundwork for understanding how metabolic stress can dysregulate neuronal activity, potentially contributing to the development of mood disorders.

Disclosures: B. O'Flaherty: None. **J. Guo:** None. **P.A. Wenner:** None. **D.G. Rainnie:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.17/F2

Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant NS090644

Title: Characteristics of the action potential waveform at mammalian and amphibian neuromuscular junctions

Authors: *S. P. GINEBAUGH[1], K. OJALA[1], A. HOMAN[1], E. MILLER[2], S. D. MERINEY[1]
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Abstract: Action potential (AP) invasion of the presynaptic terminal causes calcium channels to open, which allows the calcium ion flux that triggers neurotransmitter release. Investigation of the AP waveform at the synapse is necessary to understand the AP-evoked activation of voltage-gated ion channels responsible for neurotransmitter release, but the small size of the axon terminal has limited investigation of the AP waveform at the level of the synapse. Our lab has developed several computational models that aid in our study of the structure and function of amphibian and mammalian neuromuscular junction (NMJ) presynaptic transmitter release sites. These models currently utilize AP waveforms electrophysiologically derived from motoneurons somas to drive the behavior of voltage-gated calcium channels in these simulations. However, measurements from other neurons have provided evidence that the AP can vary significantly between the soma and the synapse. Thus, obtaining an accurate measurement of the AP waveform at the NMJ will help to better understand the behavior of synaptic transmission and improve computational models. Here we use the Berkeley Red Sensor of Transmembrane Potential (BeRST) voltage-sensitive dye to characterize the AP waveform at the mammalian and amphibian NMJs. To collect data, we stimulated an ex vivo motor axon at 0.2 Hz and recorded the fluorescence over time with an EMCCD camera coupled to a laser that illuminates only during our brief data collection window. We sampled the entire AP through a moving bin acquisition scheme, collecting 75 bins during a single AP: the BeRST dye was illuminated and emitted light was collected over a 100 µs period, 20 µs - 1.5 ms after stimulation (subsequent bins started 20 µs after the start of the preceding bin). 20 such data sets were collected per NMJ, and the average change in fluorescence was used to calculate the AP waveform. Our data

suggests that the AP at the NMJ is very brief, with a duration at half-amplitude of 200-300 µs. In addition, we have evaluated how several pharmacologic agents influence the NMJ AP waveform. These agents include GV-58, a use-dependent calcium channel agonist, and voltage-gated and calcium-activated potassium channel antagonists (DAP & IBTX, respectively).

Disclosures: S.P. Ginebaugh: None. **K. Ojala:** None. **A. Homan:** None. **E. Miller:** None. **S.D. Meriney:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.18/F3

Topic: B.08. Intrinsic Membrane Properties

Title: Opposing effects of AdipoR1 and AdipoR2 on hippocampal neuronal excitability

Authors: W. WANG, B. LIU, C. LI, *X.-Y. LU
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Abstract: Adiponectin is a metabolic hormone produced by adipocytes. Its biological effects are mediated mainly through two receptor subtypes, AdipoR1 and AdipoR2. Both AdipoR1 and AdipoR2 are highly expressed in the dentate gyrus (DG) of the hippocampus. The goal of this study was to investigate the effects of AdipoR1 and AdipoR2 signaling on neuronal excitability of DG neurons. We generated AdipoR1-ires-Cre and AdipoR2-ires-Cre transgenic mice, which enable us to identify AdipoR1- and AdipoR2-expressing neurons and perform patch-clamp electrophysiological recordings on these cells. We found that bath application of the AdipoR1/2 agonist AdipoRon increases the neuronal excitability of AdipoR1-expressing granule neurons, but decreases the neuronal excitability of AdipoR2-expressing neurons in the DG. Furthermore, we demonstrated that disruption of AdipoR1 and AdipoR2 produced opposite effects on the excitability of DG granule neurons.These observations support that both AdipoR1 and AdipoR2 are necessary and sufficient in modulating neuronal excitability but in opposite directions**.**

Disclosures: W. Wang: None. **B. Liu:** None. **C. Li:** None. **X. Lu:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.19/F4

Topic: B.08. Intrinsic Membrane Properties

Support: NIMH MH11176802
Harold and Leila Y. Mathers Charitable Foundation

Title: Mechanisms of EPSP-Spike potentiation in memory circuits of the hippocampus

Authors: *J. K. CLARK, D. V. MADISON
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Abstract: EPSP-Spike (E-S) coupling is the relationship between synaptic activity in dendrites and the generation of the somatic action potential. The earliest reports of the form of synaptic plasticity known as long-term potentiation (LTP) showed that this type of synaptic potentiation can be accompanied by a change in EPSP-Spike coupling, resulting in E-S Potentiation. E-S potentiation represents the change in spike probability that is not accounted for by changes in synaptic activity. Previous reports have stated that E-S potentiation is blocked by the GABA-A channel blocker Picrotoxin, suggesting that E-S potentiation is mediated by a modulation inhibitory synaptic transmission. However, the long-term maintenance mechanism by which E-S potentiation occurs remains unclear. We seek to study these mechanisms by recording simultaneous input/output (I/O) relationships of dendritic field EPSPs and Population Spikes before and after the induction of LTP in area CA1 of hippocampal slices. Our data confirm the earlier findings that E-S potentiation does not occur in the presence of Picrotoxin. However, we show that the time of Picrotoxin application relative to LTP induction, influences the development, or blockage, of E-S potentiation. If applied before induction, E-S potentiation is suppressed. If applied after induction however, E-S potentiation is not suppressed. This suggests that Picrotoxin does not “block” E-S potentiation in the conventional sense, but occludes it by manipulating GABAergic signaling prior to the neuron’s intrinsic response to the induction of LTP and subsequent expression of E-S potentiation. We also show that the underlying mechanism for E-S potentiation remains functional, despite exposure to Picrotoxin, as removal of Picrotoxin after induction allows for the emergence of E-S potentiation expression. These results suggest that E-S potentiation is maintained by a persistent reduction in inhibitory transmission, but direct intracellular recordings of IPSPs do not support this mechanism.

Disclosures: J.K. Clark: None. **D.V. Madison:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.20/F5

Topic: B.08. Intrinsic Membrane Properties

Support: NIH grant NS027881
NYMC/Touro Intramural Bridge funds

Title: Regulation of the orexin-enhanced slow afterhyperpolarization (oeAHP) and the orexin-mediated inward current by intra- and extracellular Ca^{2+} in serotonergic dorsal raphe neurons

Authors: M. ISHIBASHI, N. E. MOLINA, E. A. BERRY, *C. S. LEONARD
Dept Physiol, New York Med. Coll, Valhalla, NY

Abstract: Serotonergic (5-HT) dorsal raphe (DR) neurons regulate numerous brain functions including sleep-wake states, circadian phase, reward and mood. Moreover, orexin receptor signaling at 5-HT DR neurons appears critical in the sleep disorder narcolepsy, which emerges following the loss of orexin signaling. We recently reported that in addition to producing a slow depolarization, orexin-A enhances the post-spike afterhyperpolarization (oeAHP), which alters spike encoding by increasing spike frequency adaptation. This oeAHP has two distinct components and requires Ca^{2+}influx. The first, is an enhanced apamin-sensitive SK Ca^{2+}-activated K^{+}current (tau ~ 0.5s). The second is a longer duration novel current (tau ~ 5s) that is apamin-insensitive (termed the ai-oeAHP). Several lines of evidence suggest the ai-oeAHP results from the transient closure of orexin-activated cation channels that produce the slow orexin-mediated depolarization. Here we've investigated the Ca^{2+}-dependence of this ai-oeAHP using whole-cell patch clamp recordings in mouse brain slices. We found that both the orexin-activated cation current and the ai-oeAHP were modulated by extracellular [Ca^{2+}], but not by extracellular [Mg^{2+}]. Both currents were nearly blocked by 10 mM $[Ca^{2+}]_o$ and were near-maximal at 1 mM $[Ca^{2+}]_o$. This extracellular Ca^{2+}-dependence was well fit well by a Hill equation having an IC_{50} of 1.7 and 1.9 mM and Hill coefficients near 2 for the inward cation current and ai-oeAHP, respectively. At less than 1 mM $[Ca^{2+}]_o$, the orexin-activated cation current was augmented while the ai-oeAHP was attenuated. This attenuation appeared due to reduced voltage-dependent Ca^{2+} influx since it was not altered by depleting intracellular stores with CPA, and the ai-oeAHP produced by intracellular Ca^{2+} uncaging with DMNP was not attenuated at 0.5 mM $[Ca^{2+}]_o$. The maximal ai-oeAHP current was about half the magnitude of the inward current and this ratio was preserved at >1 mM $[Ca^{2+}]_o$. Together these data suggest that the ai-oeAHP current and about half of the orexin-mediated inward current results from a population of cation channels that are inhibited by both extracellular and intracellular Ca^{2+}. Interestingly, this extracellular calcium sensitivity may be physiologically relevant since the normal increase in extracellular Ca^{2+} that is reported to promote sleep would attenuate the arousal promoting orexin actions. Moreover, these findings are relevant to the pathophysiology of hypercalcemia which would more drastically attenuate these orexin actions and could contribute to the clinical signs of drowsiness and depression.

Disclosures: M. Ishibashi: None. **N.E. Molina:** None. **E.A. Berry:** None. **C.S. Leonard:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.21/F6

Topic: B.08. Intrinsic Membrane Properties

Support: National Science Centre (Poland): 2015/17/N/NZ4/02889
Medical University of Warsaw: FW5/PM1/17
Innovative Economy Operational Programme: POIG.02.02.00-14-024/08-00

Title: Rebound depolarization in medial prefrontal cortex pyramidal neurons

Authors: *P. KUROWSKI, P. SZULCZYK
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Abstract: Rebound depolarization (RD) occurs after membrane hyperpolarization and converts an arriving inhibitory signal into cell excitation. The purpose of our study was to clarify the ionic mechanism of RD in synaptically isolated layer V medial prefrontal cortex pyramidal neurons in slices obtained from 58- to 62-day-old male rats. The RD was evoked after a step hyperpolarization below -80 mV, longer than 150 ms in 192 of 211 (91%) tested neurons. The amplitude of RD was 30.6±1.2 mV above the resting membrane potential (-67.9±0.95 mV), and it lasted a few hundred ms (n=192). RD could be observed only after preventing BK channel activation, which was attained either by using paxilline, by removal of Ca^{++} from the extra- or intracellular solution, by blockade of Ca^{++} channels or during protein kinase C (PKC) activation. RD was resistant to TTX and was abolished after the removal of Na^{+} from the extracellular solution or application of an anti-Nav1.9 antibody to the cell interior. We conclude that two membrane currents are concomitantly activated after the step hyperpolarization in the tested neurons: a. a low-threshold, TTX-resistant, Na^{+} current that evokes RD; and b. an outward K^{+} current through BK channels that opposes Na^{+}-dependent depolarization. The obtained results also suggest that a. low-level Ca^{++} in the external medium attained upon intense neuronal activity may facilitate the formation of RD and seizures; and b. RD can be evoked during the activation of PKC, which is an effector of a number of transduction pathways.

Disclosures: P. Kurowski: None. **P. Szulczyk:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.22/F7

Topic: E.09. Motor Neurons and Muscle

Support: Grant-in-Aid for Scientific Research (Japan), 18K16648

Title: Mechanisms of noradrenergic modulation of synaptic transmission and neuronal excitability in ventral horn neurons of the rat spinal cord

Authors: H. SHOJI[1], M. OHASHI[1], T. HIRANO[1], K. WATANABE[1], N. ENDO[1], *T. KOHNO[2]
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Abstract: Noradrenaline (NA) modulates the spinal motor networks for locomotion and facilitates neuroplasticity, both of which are important for neural recovery in the subacute and chronic phases of spinal cord injury. However, neither the effects of NA on synaptic transmission and neuronal excitability in spinal ventral horn (VH) neurons nor their mechanisms are well characterized. To gain insight into NA regulation of VH neuronal activity, we used a whole-cell patch-clamp approach in neonatal rats (7-15 day old). NA facilitated both excitatory and inhibitory synaptic transmissions through the activation of somatic adrenoceptors in the excitatory and inhibitory interneurons, respectively. In current-clamp recordings, NA depolarized resting membrane potentials in VH neurons, indicating that NA enhanced excitability of these neurons. In voltage-clamp recordings at -70 mV, the enhancement of excitatory synaptic transmission was induced by the activation of α_1- and β-adrenoceptors. NA induced an inward current, also mediated by the activation of α_1- and β-adrenoceptors. Activation of α_1-adrenoceptors after spinal cord injury has been reported to be associated with muscle spasm or spasticity, which interrupt fluid motion in the extremities. Therefore, our findings indicate that the activation of β-adrenoceptors may instead be used as the foundation of one of the therapeutic targets to activate neural networks in the spinal VH without causing muscle spasm or spasticity and ultimately, improve motor function after spinal cord injury.

Disclosures: H. Shoji: None. **M. Ohashi:** None. **T. Hirano:** None. **K. Watanabe:** None. **N. Endo:** None. **T. Kohno:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.23/F8

Topic: B.08. Intrinsic Membrane Properties

Title: HCN channel and type III action potential

Authors: M. TROJAN[1,2], D. KANIGOWSKI[3], &. BIJOCH[3], M. PęKAłA[3], D. LEGUTKO[3], A. BEROUN[3], M. BEKISZ[3], L. COLOM[1], E. KNAPSKA[3], *S. KODIROV[3]
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Abstract: There is a robust correlation of firing patterns of neurons and the presence of hyperpolarization-activated cyclic nucleotide gated non-selective cation (HCN-I_h or I_f-funny). HCN produces recurrent rhythmic activities and is referred to as 'pacemaker channel'. The entire septum and amygdala possess HCN, but only neurons in the medial part of the septum display pacemaker activity. This indicates that either the septum and amygdala express distinct subunits, or they express two identical subunits that possess different electrophysiological, biophysical and pharmacological properties. During whole-cell current-clamp experiments in lateral septum - LS of adult rats we have observed a new type of action potential (AP). Similar APs were present also in mice. We aimed to elucidate the cell type specificity, mechanisms and correlation with the presence of HCN. We used either coronal or modified sagittal brain slices of mice expressing fluorophore td-Tomato targeted to cholin- (vasoactive intestinal polypeptide - VIP expressing), GABA- (either GAD67 or somatostatin) and glutamate-ergic (VGluT2) types of neurons. Type III APs were triggered mostly upon strong step depolarization. In fewer instances they were triggered spontaneously at RMP. As opposed to adaptation and regular firing patterns, we term it type III AP that never occurred in isolation but rather were followed after initial 2-4 Na+ spikes. TTX blocked only the latter indicating that under pathological conditions type III could also be generated and may have purpose. As expected from MP, at which the LS neurons were vulnerable to type III APs, the L-type Ca2+ channels were suspect. Subsequently, this hypothesis was proven by using antagonist nimodipine (involved in modulation of memory) that blocked type III APs. Under these conditions, neuron was able to transit into regular spiking mode. At present time we can not conclude about the condition that is prerequisite for generation of type III APs or certain behavior in which they could play a role. Next milestone would be revealing these "Ca2+ spikes" by patch-clamp experiments in vivo, i.e. whether or not they take place under true physiological conditions.

Disclosures: M. Trojan: None. **D. Kanigowski:** None. **&. Bijoch:** None. **M. Pękała:** None. **D. Legutko:** None. **A. Beroun:** None. **M. Bekisz:** None. **L. Colom:** None. **E. Knapska:** None. **S. Kodirov:** None.

Poster

203. Control of Neuronal Firing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 203.24/F9

Topic: B.11. Glial Mechanisms

Support: Welcome Trust 095064 and 200893
British Heart Foundation RG/15/15/31742

Title: Mechanisms of CO_2-induced inhibition of cortical neuronal activity

Authors: *P. S. HOSFORD[1], A. HADJIHAMBI[1], J. MILLAR[2], A. V. GOURINE[1]
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Abstract: Eighty years ago J S Haldane reported the narcotic effect of hypercapnia in divers. Suppression of neuronal activity by CO_2 has been well documented but a precise mechanism remains unknown. We investigated the effect of hypercapnia and acidosis on cortical neuronal activity evoked by somatosensory stimulation.
Adult male rats (~250g) were anesthetized with α-chloralose (75mg kg^{-1}). Parenchymal pH and evoked neuronal activity in the somatosensory cortex were monitored using carbon fiber microelectrodes (CFM; ⌀7μm). 1 min trains of electrical stimulation (3Hz, 1.5mA, 150μs pulse duration) were applied to the forepaw to recruit somatosensory pathways. Cortical connexin hemichannnel opening in response to systemic hypercapnia was assessed by carboxyfluorescein (CBxF) dye loading.
Forepaw simulation evoked robust multiphasic extracellular potentials 10-30 ms after the stimulus onset. Integration of evoked potentials showed an increase of 1.07 ± 0.26 mV*S (n=8). This was reduced to 59±6% and 49±5% of control response in conditions of 5 and 10 % inspired CO_2, respectively. Accompanying decreases in pH were recorded: -0.12±0.05 with 5% and -0.17±0.09 pH units with 10% inspired CO_2. A similar decrease in parenchymal pH (-0.12± 0.02 pH unit) induced by systemic administration of acetazolamide (10 mg kg^{-1}, I.V), had no effect on the evoked potentials (n=8). To determine the effect of decreased pH, metabolic (isocapnic) acidosis was induced by lactic acid infusion (0.2M, I.V). Infusion rate was adjusted to achieve brain tissue pH reduction similar to that recorded in response to 10% CO_2 (~-0.2units). Isocapnic acidosis was found to have no effect on the evoked activity; 92± 2% of control (n=3).
Adenosine acting at A_1 receptors is known to strongly inhibit neuronal activity. However, DPCPX (A_1 antagonist; 1mg kg^{-1}, I.V) had no effect on the inhibitory effect of 10% CO_2; spike activity decreased to 53±13% (n=8) of control in the presence and 42±4% (n=4) in the absence of DPCPX. However, P2Y1 receptor antagonist MRS-2500 (5μM), prevented the inhibitory effect of CO_2 on cortical neuronal activity (102±6% and 81±10% of baseline (n=5) at 5 and 10%

CO_2, respectively.
Systemic hypercapnia caused a significant increase in cortical CBxF dye loading (as measured by florescence change from a baseline of 21±0.7 AU to 43±2.6AU, n=9) indicative of connexin hemichannel opening. This was significantly inhibited by NPPB (200μM) (n=4).
These data suggest that the inhibition of cortical neuronal activity caused by CO_2 is independent of pH changes and likely to be mediated by connexin hemichannel mediated ATP release and its actions on $P2Y_1$ receptors expressed by inhibitory interneurons.

Disclosures: P.S. Hosford: None. **A. Hadjihambi:** None. **J. Millar:** None. **A.V. Gourine:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.01/F10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: RO1 NS080655
RO1 NS36524
RO1 MH074368
U54 EB020403

Title: White matter microstructural abnormalities are linked to cerebral metabolite disturbances and neurocognitive impairment in treated HIV+ individuals

Authors: *T. M. NIR[1], C. CORBIN[1], C. R. K. CHING[1], N. JAHANSHAD[1], H. Y. LAM[1], J. HAREZLAK[2], G. SCHIFITTO[3], T. ZHU[4], R. A. COHEN[5], B. A. NAVIA[6], P. M. THOMPSON[1]
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Abstract: White matter (WM) and neurocognitive impairment (NCI) may persist in treated HIV+ individuals. Diffusion tensor imaging (DTI) can be used to map HIV associated microstructural differences along WM tracts, but offers limited understanding of their biochemical basis. Metabolite disturbances, reflecting neuronal health, inflammation, and demyelination, have been identified using MR spectroscopy (MRS) in treated HIV+ individuals with NCI, but the relationship with WM microstructure is unclear. We hypothesized that WM abnormalities would be associated with metabolite disturbances and NCI in 50 treated HIV+ adults (age: 48.1±7.6 yrs; 32M/18F).

1.5 T MRS and DTI brain scans (1 b0, 21 b=1000 volumes) were acquired. Metabolite concentrations of N-acetylaspartate (NAA), myo-inositol (MI), choline (Cho), glutamate/glutamine (Glx), and creatine (Cr) were measured in the frontal gray matter (FGM), frontal WM (FWM), and basal ganglia (BG). Fractional anisotropy (FA) and mean diffusivity (MD) maps and tractograms were calculated from corrected DTI. Each subject's tractogram was segmented into 25 WM bundles. DTI indices were projected point-wise along bundles. After template creation, fiber registration and correspondence, linear regressions, covarying for sex and age, tested point-wise associations between DTI indices and metabolite concentrations or NCI (ADC stage ≥1; N=8).

FA was not significantly associated with metabolite levels or NCI. Higher MD throughout the WM was associated with lower FWM NAA (FDR corrected $p<0.021$) and Cr ($p<0.007$). Sparser associations were found between lower FGM NAA and higher MD ($p<0.002$). Compared to asymptomatic individuals, those with NCI showed lower FWM NAA ($p=0.013$) and higher MD ($p<0.002$).

MD is a sensitive but non-specific biomarker of neuropathology and WM microstructure. Combining DTI and MRS improves interpretability; lower frontal NAA suggests reduced neuronal integrity; lower Cr may reflect bioenergetic system failure. Measuring neurochemical signals offers insights into the biochemical correlates of HIV WM dysfunction and NCI.

A

		FWM NAA	FWM Cr	MFC NAA	NCI
FDR critical P		0.021	0.007	0.002	0.002
Frontal Corpus Callosum	fCC	34.5%	7.2%	9.2%	--
Temporal Corpus Callosum	tCC	6.5%	--	6.2%	--
Parietal Corpus Callosum	pCC	60.9%	30.3%	6.1%	--
Occipital Corpus Callosum	oCC	40.9%	28.4%	--	--
Thalamic Occipital Projections	O_THALp L	--	--	--	--
	O_THALp R	14.1%	11.5%	--	--
Thalamic Parietal Projections	P_THALp L	28.3%	11.1%	5.2%	--
	P_THALp R	48.5%	21.8%	--	--
Thalamic Frontal Projections	F_THALp L	38.0%	--	5.4%	8.3%
	F_THALp R	47.3%	14.8%	--	7.6%
Corticospinal Tract	CST L	27.0%	--	--	5.0%
	CST R	34.5%	13.9%	--	--
Inferior Longitudinal Fasciculus	ILF L	52.4%	18.7%	5.5%	--
	ILF R	48.6%	22.2%	--	--
Inferior Fronto-Occipital Fasciculus	IFO L	50.1%	18.8%	7.4%	5.1%
	IFO R	65.2%	23.2%	--	5.4%
Cingulate Gyrus Cingulum	CGC L	39.4%	--	7.7%	--
	CGC R	49.1%	19.4%	5.3%	8.5%
Hippocampal Cingulum	CGH L	--	--	--	--
	CGH R	5.1%	--	--	--
Uncinate Fasciculus	UNC L	37.5%	--	6.9%	--
	UNC R	51.3%	--	5.5%	--
Superior Longitudinal Fasciculus	SLF L	57.3%	27.0%	--	--
	SLF R	45.1%	13.6%	--	--
Fornix	FX	15.5%	--	8.8%	--

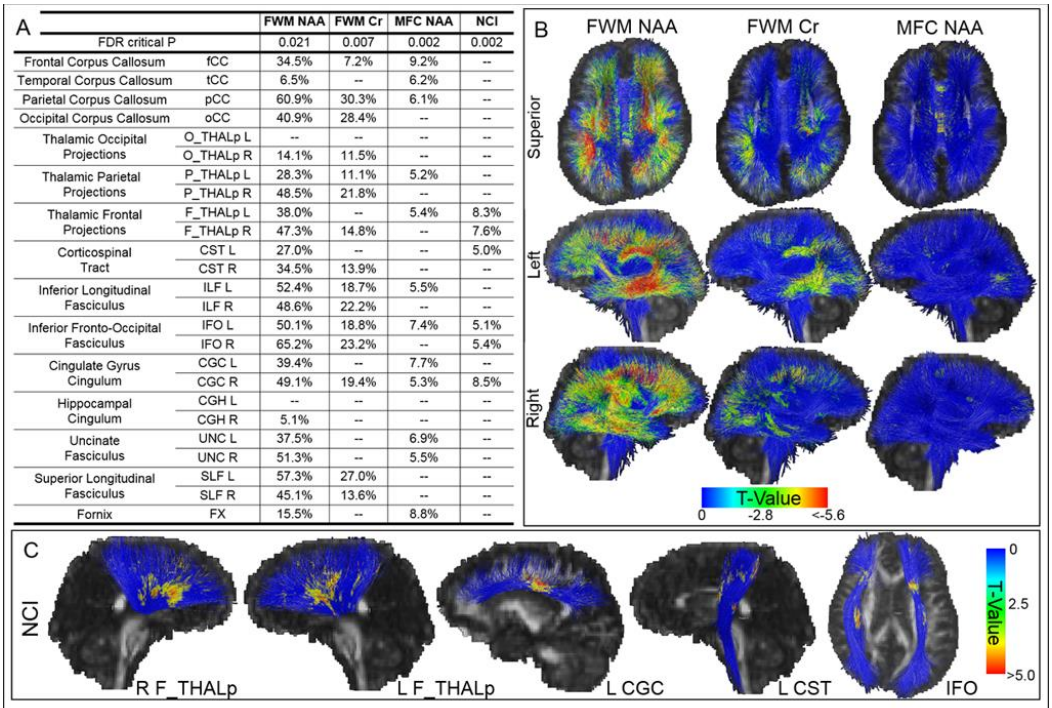

Figure 1. (A) For each tract bundle, we report the percentage of points with a significant association (P < FDR critical threshold) between MD and either metabolite levels or neurocognitive impairment (NCI defined as AIDS Dementia Complex (ADC) stage ≥ 1). **(B)** Point-wise associations between higher MD and lower frontal lobe metabolite concentrations are mapped across tracts. **(C)** NCI (higher ADC stage) is associated with higher MD.

Disclosures: T.M. Nir: None. **C. Corbin:** None. **C.R.K. Ching:** None. **N. Jahanshad:** None. **H.Y. Lam:** None. **J. Harezlak:** None. **G. Schifitto:** None. **T. Zhu:** None. **R.A. Cohen:** None. **B.A. Navia:** None. **P.M. Thompson:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.02/F11

Topic: B.12. Demyelinating Disorders

Support: MARCU STAR NIH T32
NINDS R01
NMSS PILOT STUDY GRANT

Title: Hippocampal neuropathology in patients with seizures secondary to multiple sclerosis

Authors: *K. PARRA[1], A. S. LAPATO[2], S. K. TIWARI-WOODRUFF[3]
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Abstract: BACKGROUND Multiple sclerosis (MS) is a progressive demyelinating disease of the central nervous system affecting roughly 2.3 million people worldwide. These patients are six times more likely to develop seizures than the population at large. MS patients with seizures (MS+S) require mobility devices sooner and expire earlier than MS patients without seizures. However, despite the greater morbidity and mortality in this group, there is a narrow understanding regarding how MS leads to seizure pathology. Murine models of MS+S demonstrate hippocampal glial fibrillary acidic protein (GFAP)+ astrogliosis, altered expression of aquaporin-4 (AQP4) and loss of parvalbumin (PV)+ interneurons. However, the translational relevance of these findings has not been established. **OBJECTIVE** To determine the relevance of possible translational biomarkers, myelination, leukocyte infiltration, GABAergic interneurons, and astrocytes in neurological normal, MS, and MS+S donor hippocampi. **METHODS** Myelin oligodendrocytes glycoprotein (MOG), CD45, CD6, GAD67, PV, GFAP,AQP4 and glutamate transporter-1 (GLT-1) by immunohistochemistry. **RESULTS** Preliminary data shows loss of GAD67+ somata, a trend towards decreased number of PV+ somata, and proliferation of GFAP+ astrocytes, which parallels with the astrogliosis seen in previous mouse model studies, and an altered expression of GLT-1 and AQP4. **CONCLUSIONS** MS+S hippocampi exhibit evidence of loss of inhibitory innervation and impaired astrocyte glutamate/K+ buffering that may facilitate seizure onset during MS. These results indicate that the cuprizone model is a translationally relevant model of myelination-induced seizures.

Disclosures: K. Parra: None. **A.S. Lapato:** None. **S.K. Tiwari-Woodruff:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.03/F12

Topic: B.12. Demyelinating Disorders

Support: NMSS Grant P65725

Title: Activation of the necroptosis machinery in cortical neurons in progressive MS

Authors: *C. PICON, R. JAMES, R. REYNOLDS
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Abstract: The progressive phase of multiple sclerosis (SPMS) is associated with the presence of extensive subpial grey matter lesions (GMLs) with significant neuronal loss and the presence of inflammatory infiltrates in the subarachnoid space. Here, we investigated the hypothesis that molecules produced in the meninges diffuse to the underlying GM leading to pathological hallmarks of the molecular mechanisms. We focused on the role of tumour necrosis factor (TNF), which was previously shown to be increased in the cerebrospinal fluid (CSF) and is suggested to play a role in CNS inflammation. TNF has pleotropic functions, ranging from cell survival to cell death via apoptosis or necroptosis. We studied changes in the balance of the TNF signaling pathways in the cortical grey matter of 40 SPMS cases and 10 controls. TNF-receptor 1 (TNFR-1) was significantly up-regulated in SPMS compared to controls, while no differences were found in the expression levels of TNFR2. Furthermore, SPMS cases showed a dramatic down-regulation of two key proteins involved in the apoptosis signaling pathway, CYLD and the cleaved active from of caspase 8. In contrast, MS cases showed a significant increase in the key proteins of the necroptotic pathway, phospho-RIPK3 and phospho-MLKL. Hence, we investigated the formation of the necrosome, including oligomerization of MLKL a sign of activated necroptosis. MLKL trimers were only found in the GM of SPMS cases. We then studied the localization of necroptotic proteins by IF and IHC. RIPK3 and MLKL and their phosphorylated forms were mainly localized in neurons in the grey matter. Phospho-MLKL could be localised primarily to the nucleus, which was verified by nuclear protein extraction. Finally, we investigated whether the presence of p-MLKL was associated with the activation of other markers of cell death and found that only MS cases expressing high levels p-MLKL also expressed the cleaved form of PARP-1, a marker of cell death. To reproduce the chronic elevation of pro-inflammatory cytokines in the meningeal space seen in MS, we injected lentiviral vectors carrying the TNF and interferon-gamma genes into the subarachnoid space of DA rats. Persistent cytokine production over 2 months produced chronic inflammation in the meninges and increased levels of the necroptosis markers p-MLKL and p-RIPK3 in underlying cortical neurons. Our data show that in SPMS there is a shift in the balance of TNF dependent

signaling pathways towards TNFR1-mediated necroptosis in cortical neurons, which could be responsible for the neurodegeneration observed in the grey matter of MS patients

Disclosures: C. Picon: None. **R. James:** None. **R. Reynolds:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.04/F13

Topic: B.12. Demyelinating Disorders

Support: CIHR

Title: Lipid biochemistry probed with Nile Red spectral microscopy reveals myelin lipids alterations in MS

Authors: *W. TEO[1], A. LUCHICCHI[2], A. V. CAPRARIELLO[4], G. SCHENK[3], M. MORGAN[5], J. GEURTS[3], P. K. STYS[6]
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Abstract: A hallmark feature of multiple sclerosis (MS) is the loss of myelin, a lipid-rich spiral wrapping of axons that facilitates rapid saltatory conduction. Although myelin is predominantly lipid (70-85% w/w), MS pathology is largely studied using protein reporters. We hypothesized that existing protein-based methods under-report the full extent of myelin histopathology in autopsied samples of MS. To test this hypothesis, we utilized spectral confocal microscopy of the lipophilic fluorescent dye Nile Red (NR), whose fluorescence spectral profiles change with biochemical alterations in the local tissue environment (the solvatochromic effect), paired with customized, non-linear scatter analysis. We report a number of novel tissue defects in MS. In cases of normal appearing white matter (NAWM), accumulation of lipids in NAWM was observed. These lipid-plaques exhibited distinct biochemical changes, 70% of the population displayed fibril-like structure. others without fibril-like phenotypes distributed around blood vessels. In long-standing MS case, we found biochemical changed in intact myelinated axons and their myelin sheath. In these axons, their biochemical polarity shifted to more polar. In the myelin, the lipid alteration displayed multifocal patches of lipids alteration and heterogeneity along the myelin. One of the abnormalities was the robust of Node-like gaps. The length of these gaps can be less than 10 μm. Furthermore, accumulation in ependymal layers of lipid droplets with various distinct biochemical features was observed in all MS cases (6/6), providing further evidence of lipid pathology in MS. In addition, focal lipid-plaques were identified with no correlates by standard immunohistochemistry (MBP, IBA-1), suggesting that NR lipid

histochemistry was more sensitive to early pathological changes than conventional protein immunohistochemistry. The chemical polarity changes in axons also supports the notion of conduction failure even these myelinated axons remained intact. CONCLUSION: solvatochromic properties of NR coupled with spectral microscopy represent a powerful new tool for detecting very early and subtle myelin damage, likely reflecting lipid biochemical changes. This method is more sensitive than conventional techniques such as myelin stains and immunohistochemistry.

Disclosures: W. Teo: None. **A. Luchicchi:** None. **A.V. Caprariello:** None. **G. Schenk:** None. **M. Morgan:** None. **J. Geurts:** None. **P.K. Stys:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.05/F14

Topic: B.12. Demyelinating Disorders

Support: NMSS grant RG 1501-02876
NIH K08 EY018609
Core Grant for Vision Research P30 EY016665
University of Wisconsin-Madison Office of the Vice Chancellor for Research and Graduate Education with funding from the Wisconsin Alumni Research Foundation
K08 EY018609 and an unrestricted award to the UW-Madison Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness

Title: Remyelination in the optic nerve detected by visual evoked potentials in a large animal model of demyelination

Authors: *M. HEIDARI[1], K. C. SNYDER[2], S. L. DEJANOVICH[1], A. RADCLIFF[1], J. N. VERHOEVE[3], G. J. MCLELLAN[2,3], I. D. DUNCAN[1]
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Abstract: Remyelination is a major treatment goal in multiple sclerosis (MS), but the evaluation of myelin repair in MS patients remains challenging. Optic nerve (ON) function has been monitored in MS patients with or without optic neuritis, using pattern visual evoked potentials (VEP), which undergo prolonged latency and reduced amplitude indicating slowed conduction and loss of ON fibers, respectively. While VEP abnormalities have been shown to correlate with demyelination of the ON in animal models, there is no direct evidence from these models or from MS, that remyelination leads to improvement of VEP parameters. We have explored this question in feline irradiated diet-induced demyelination (FIDID) (Duncan et. al., PNAS 2009

106, 6832) in which there is extensive demyelination of the entire CNS and profound neurologic disease. Discontinuation of the irradiated diet leads to neurologic recovery in association with global remyelination. Flash VEPs were recorded prior to the onset of clinical signs of neurological disease in 10 FIDID cats and at variable time points thereafter. Electroretinography and optical coherence tomography were used to evaluate retinal function and structure. During acute clinical
disease there was a variable and often pronounced increase in the latency of the VEP (normal mean VEP 54 msec, 95%CI, range 49-60 msec; diseased mean VEP 109 msec, 95%CI, range 90-129 msec) in the absence of retinal functional or structural abnormalities. As FIDID cats recovered neurologic function after return to a normal diet, VEP latencies improved, though not to normal. Only 2/10 cats showed vision loss. Following perfusion fixation of FIDID cats during active disease or recovery, ONs were dissected, divided into five segments and each block processed for light and electron microscopy. Though variable in the extent and distribution along the nerve, all ONs showed extensive demyelination during active disease, or remyelination on clinical recovery. There was a clear association between demyelination and prolonged VEP latency in all cats during acute disease, with subsequent partial normalization of latency in nerves which showed extensive microscopic evidence of remyelination. Measurement of the g ratio of over 3000 myelinated axons in remyelinated nerve confirmed this with a mean g ratio of 0.84. These data unequivocally demonstrate that VEPs reflect both demyelination and remyelination of the ON. Importantly, direct evidence is provided that remyelination restores ON function *in vivo*, thus validating the use of VEPs as a surrogate marker for remyelination in MS clinical trials.

Disclosures: M. Heidari: None. **K.C. Snyder:** None. **S.L. Dejanovich:** None. **A. Radcliff:** None. **J.N. Verhoeve:** None. **G.J. Mclellan:** None. **I.D. Duncan:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.06/F15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS104692
NIH Grant AI129479
UC Davis Murray B. Gardner Junior Faculty Fellowship in Infectious Disease

Title: LGN abnormalities in a macaque model of ZIKV infections

Authors: *A. M. SEELKE[1], P. DOUGHERTY[2], J. H. MORRISON[2], E. BLISS-MOREAU[2]
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Abstract: Infection with the Zika virus during gestation can have significant negative effects on neural development. While much attention has been paid to impacts on cortical development, the retina is also significantly negatively impacted. Humans infected with ZIKV show visual impairment, and retinal imaging of macaques infected with ZIKV show large retinal lesions. The neural pathway for processing visual information begins at the retina and then proceeds through the lateral geniculate nucleus (LGN) and into the primary visual cortex. Here we describe gross anatomical abnormalities in the LGN of macaque fetuses that were infected with ZIKV. Subjects were 6 full term macaque fetuses, three of which had been infected with ZIKV during mid-gestation. Brains were removed and divided in half along the midline. One half of each brain was used for pathology analysis, and the other half was coronally blocked into 4 segments, flash frozen, and stored at -80C until sectioning on a freezing microtome. Each brain block was sliced into 8 series, and one series was reserved for anatomical Nissl staining. In each brain the LGN was identified and examined for alterations in lamination and cellular organization. The examiner was blind to the condition of the brain. Qualitative analysis revealed several instances of abnormal LGN organization in animals that had been infected with ZIKV, In one instance, the koniocellular layer between layers 3 and 4 disappeared in the lateral aspect of the LGN, leaving us unable to distinguish between those parvocellular layers. In another instance, we saw a large koniocellular inclusion that engulfed the ventrolateral quarter of the LGN, resulting in an ablation of the magno- and parvocellular layers in that region. These features were not observed in control tissue. We believe that it is likely that these abnormalities within the LGN of ZIKV infected fetuses are the result of retinal lesions. Given the role that the LGN plays in visual processing, we hypothesize that any abnormalities within the LGN will be magnified within the primary visual cortex. We will examine this in the next phase of this study.

Disclosures: A.M. Seelke: None. **P. Dougherty:** None. **J.H. Morrison:** None. **E. Bliss-Moreau:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.07/F16

Topic: B.12. Demyelinating Disorders

Support: Emerald Foundation

Title: Intrathecal delivery of primary progressive multiple sclerosis-derived antibodies induces motor deficits and CNS pathology in mice

Authors: A. L. TSE, A. FINNEY-STABLE, S. J. E. SHIMSHAK, J. K. WONG, *J. LIN, S. A. SADIQ
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Abstract: B-cells likely play an important pathogenic role in multiple sclerosis (MS). This is because 90% of patients with MS have oligoclonal IgG antibodies in their cerebrospinal fluid (CSF) and anti-B cell therapies are highly efficacious in the treatment of the disease. We have previously shown that mice injected with primary progressive multiple sclerosis (PPMS) CSF display greater motor deficits, astrogliosis, and axonal damage compared to control animals. Here, we investigate whether intrathecal delivery of CSF recombinant antibodies obtained from PPMS and relapsing-remitting multiple sclerosis (RRMS) patients would elicit similar motor deficits and CNS pathology in mice.

MS CSF samples were obtained by standard lumbar puncture and immediately analyzed by fluorescence-activated cell sorting (FACS) for $CD19^+$ and/or $CD138^+$ B-cells. Through standard reverse transcription, PCR amplification, and DNA sequencing techniques, immunoglobulin variable regions were analyzed. Full IgG1 recombinant antibodies were produced. Mice underwent laminectomies at cervical levels 4 and 5 to expose the underlying spinal cord and CSF recombinant antibodies were injected under the dura mater into the subarachnoid space. Controls were injected with saline and CSF recombinant antibodies from an HTLV-1 patient and an ALS patient. In total, 4 PPMS, 1 RRMS, 1 HTLV-1, and 1 ALS antibodies were injected into 3 mice per antibody. Motor deficits were assessed by evaluating forelimb reaching, gripping and tail rigidity after one-day following intrathecal recombinant antibody delivery.

Seven of the 12 mice injected with PPMS recombinant antibodies displayed forelimb and tail deficits compared to controls and RRMS injected mice. Luxol fast blue staining showed demyelination in 2 of the 7 mice that displayed motor impairments. Spinal cord from 1 of the mice injected with PPMS recombinant antibodies showed evidence of reactive astrogliosis, as seen by an up-regulated trend in GFAP immunostaining. Similarly, a positive trend in SMI-32 intensity was observed in mice injected with PPMS recombinant antibodies, supporting a presence of axonal damage. However, immunostaining intensity for Iba-1, a marker for microglia, was similar in all groups, suggesting that microglia may not play a role in eliciting motor deficits and CNS pathology in recombinant antibody injected mice.

PPMS derived antibodies likely play a role in contributing to motor deficits and CNS pathology in mice. However, further investigation is needed to elucidate the pathogenic role of CSF antibodies in MS.

Disclosures: A.L. Tse: None. **A. Finney-Stable:** None. **S.J.E. Shimshak:** None. **J.K. Wong:** None. **J. Lin:** None. **S.A. Sadiq:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.08/F17

Topic: B.12. Demyelinating Disorders

Support: DFG grants SCHL 21021-1
INST 410/45-1 FUGG
DFG GRK2162/1
IZKF Erlangen, TP E24

Title: Early and regional-specific myeloid immune response in multiple system atrophy

Authors: *A. HOFFMANN[1], S. REIPRICH[3], E. MASLIAH[4], M. WEGNER[3], A. REIS[2], M. J. RIEMENSCHNEIDER[5], T. KUHLMANN[6], J. WINKLER[1]
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Abstract: Multiple system atrophy (MSA) is a fast progressing atypical parkinsonian disorder. Neuropathologically, MSA is characterized by intraoligodendroglial α-synuclein inclusions leading to myelination failure of oligodendrocytes. This observation supports the current hypothesis for MSA as a primary oligodendrogliopathy driving neurodegeneration. Notably, a severe neuroinflammation with thus far unknown etiology is observed in MSA and its corresponding mouse models. Here, we analyze the myeloid immune response in the context of α-synuclein$^+$ oligodendrocytes in order to understand the myeloid-oligodendroglial crosstalk in MSA. Human putaminal *post-mortem* brain tissue of MSA-P patients and healthy controls were examined. In contrast to putaminal gray matter, we detected a 4.5-fold increased number of myeloid cells in putaminal white matter striae in MSA accompanied by elevated α-synuclein inclusions and increased putaminal cell proliferation. Moreover, we analyzed a prodromal and symptomatic disease stage of a MSA mouse model (MBP29-hα-syn mice) to further examine the temporal and regional myeloid phenotype. Mirroring our findings in human *post-mortem* tissue, we detected a profoundly increased number of IBA1$^+$ cells in the corpus callosum and the striatum of MBP29-hα-syn mice already present pre-symptomatically. Additionally, IBA1$^+$ cells of MBP29-hα-syn mice showed an early and sustained elevated expression of CD68 in intracellular lysosomal structures indicating an enhanced phagocytic activity of microglial cells. More importantly, an increased proliferation by up to 80% of IBA1$^+$ cells was detected in the corpus callosum and the striatum in the prodromal disease stage. RNA sequencing of α-synuclein overexpressing primary oligodendrocytes isolated from neonatal rats revealed an upregulation of pro-inflammatory cytokines important for chemotactic attraction and proliferation of myeloid cells such as Ccl2, Cxcl10, Cx3cl1, and Csf1. Corresponding to the *in vitro* findings, an increased Ccl2 and Cxcl10 expression was identified in the corpus callosum and the striatum of MBP29-hα-syn mice compared to controls. In conclusion, our results indicate a regionally restricted and early interaction of myeloid immune cells and α-synuclein bearing oligodendrocytes leading to a severe inflammatory response. Interfering with this inflammatory crosstalk may provide a promising novel therapeutic target urgently needed for MSA.

Disclosures: A. Hoffmann: None. **S. Reiprich:** None. **E. Masliah:** None. **M. Wegner:** None. **A. Reis:** None. **M.J. Riemenschneider:** None. **T. Kuhlmann:** None. **J. Winkler:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.09/F18

Topic: B.12. Demyelinating Disorders

Support: Tisch MS Research Center (private funds)

Title: Primary progressive MS cerebrospinal fluid delays remyelination after lysolecithin-induced demyelination

Authors: S. J. E. SHIMSHAK[1], N. J. KUNG[1], *J. K. WONG[1], S. A. SADIQ[2]
[1]Tisch MS Res. Ctr. of New York, New York, NY; [2]Tisch MS Res. Ctr., New York, NY

Abstract: Multiple sclerosis (MS) is characterized by inflammatory demyelination, astrogliosis and axonal loss in the CNS. Most patients present with relapsing-remitting MS (RRMS) then eventually enter a phase of disease progression termed secondary progressive MS (SPMS). However, approximately 10-15% of patients have primary progressive multiple sclerosis (PPMS), which is characterized by unremitting disease progression from disease onset. This progressive clinical course of PPMS suggests that remyelination is impaired in contrast to relapsing-remitting (RRMS) forms of the disease. We investigated whether PPMS cerebrospinal fluid (CSF) impacts remyelination after lysolecithin-induced demyelination. In this model, remyelination spontaneously commences usually 7 days post lysolecithin administration. We studied whether factors present in CSF from PPMS patients would inhibit this remyelination. Mice underwent a laminectomy at cervical level 5 (C5) and 1µl of 1% lysolecithin was injected into the dorsal column. At 5 days post lysolecithin injection, 3µl CSF from untreated PPMS or RRMS patients was injected into the subarachnoid space, also at C5. Control mice were injected with saline or CSF obtained from healthy individuals. Motor deficits were assessed by evaluating forelimb reaching, gripping and tail rigidity at multiple time points following CSF administration. Mice were perfused 12 days after lysolecithin injection. Spinal cords were post-fixed overnight in 4% paraformaldehyde, cryoprotected in 30% sucrose, then cryosectioned for histological analyses. PPMS CSF-injected mice exhibited significantly impaired forelimb function and increased tail flaccidity compared to controls and RRMS CSF-injected mice. Luxol fast blue staining revealed a significantly larger volume of demyelination in PPMS CSF-injected mice than mice injected with saline, healthy control or RRMS CSF. Mice injected with PPMS CSF also showed a significant increase in microglial activation, evaluated by Iba1 immunostaining, compared to other groups. GFAP expression was also increased in PPMS CSF-injected mice. No significant change in the number of proliferating oligodendrocyte progenitor cells, as assessed by NG2 and Ki67, or mature oligodendrocytes, assessed by APC and Olig2, was observed. Ultimately, intrathecal delivery of PPMS CSF, but not RRMS CSF, at the site of a

lysolecithin-induced lesion yielded larger lesions, greater microglial activation and reactive astrogliosis in the cervical spinal cord, indicating that remyelination is delayed by PPMS CSF. Identification of the CSF factors responsible for this delay in remyelination is an important next step.

Disclosures: S.J.E. Shimshak: None. **N.J. Kung:** None. **J.K. Wong:** None. **S.A. Sadiq:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.10/F19

Topic: B.12. Demyelinating Disorders

Support: MS Society

Title: Persistent TNF and IFNg production induced in the cerebral meninges in a rat model of MS gives rise to chronic cortical pathology

Authors: *R. JAMES, N. D. MAZARAKIS, R. REYNOLDS
Imperial Col. London, London, United Kingdom

Abstract: The progressive phase of multiple sclerosis (MS) is characterised by accumulating grey matter (GM) pathology. The presence of immune cell infiltrates in the meninges is associated with lymphoid tissue development, greater cortical demyelination, shorter disease duration and significant neuronal loss. Analysis of isolated meninges of MS cases has shown increased gene expression for the pro-inflammatory cytokines: tumour necrosis factor (TNF) and interferon-γ (IFNγ). We aimed to test the hypothesis that chronic production of these cytokines in the meningeal compartment and diffusion into underlying GM can drive MS GM pathology. To do this we stereotactically injected HIV-1 based VSV-g pseudotyped lentiviral transfer vectors into the sagittal sulcus (SS) of DA rats to deliver continuous transgene expression (TNF + IFNγ) in the meninges. Rats were either immunised with MOG peptide or IFA as a control. A neuropathological analysis was conducted at chronic time points up to 2 months. Injection of these vectors induced the formation of lymphoid follicle-like structures in the meninges by 28 dpi, which remained at 2 months, containing CD4+ and CD8+ T-cells, CD79a+ B-cells, plasma and dendritic cells and Iba1+ macrophages, and MadCAM+ channels These aggregates extended the length of the SS and across the surface of the cortex for many hundreds of microns from the injection site. Subpial demyelination underlying these aggregates was accompanied by widespread microglial activation and was dependant on MOG immunisation. Quantification of NeuN/HuCD co-staining showed a 23-48% decrease in neuronal numbers in cortical layers II-IV at 2 months post injection. Neuronal loss occurred in both MOG and IFA immunised animals and in the absence of demyelination. TNF/TNFR1 interactions can initiate cell death by

activating pathways involved in necroptosis. Immunostaining showed TNFR1 expression by neurons. RT-PCR on cortical RNA at 28 dpi and 2 months showed an increase in expression of TNFR1 and downstream necroptotic genes, RIP3, MLKL, cIAP2 and Nox2 compared to eGFP vector control animals. RIP3+ and MLKL+ immunopositive cells with the morphology of neurons were present in TNF + IFNγ vector injected animals. Membrane staining for phosphorylated MLKL in neurons was suggestive of the final stages of necroptosis. Our results suggest that TNF in the presence of IFNγ is a potent inducer of meningeal inflammation and can activate TNF signalling pathways in cortical cells leading to neuronal death and subpial demyelination and thus may contribute to clinical progression in MS.

Disclosures: R. James: None. **N.D. Mazarakis:** None. **R. Reynolds:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.11/F20

Topic: B.12. Demyelinating Disorders

Title: Neonatal hyperthyroidism induced developmental myelination model for multiple sclerosis

Authors: *L. TOLPPANEN[1], K. LARIOSA-WILLINGHAMA[2], D. LEONOUDAKIS[2], D. MISZCZUK[1], K. LEHTIMÄKI[1], M. FLANAGAN[3], J. GIBSON[3], A. J. NURMI[1]
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Abstract: Multiple sclerosis (MS) is a chronic disabling disease in young adults, estimated to affect about 2.5 million people worldwide (Ernstsson, 2016). The mechanisms in the pathogenesis of MS include aberrant autoimmune response, progressive failure of remyelination, and neurodegeneration. Current therapies have mainly anti-inflammatory effects, whereas disease modifying therapies able to increase remyelination are still missing. Previous data has suggested that sustained neonatal hyperthyroidism modifies the myelination process in young rats. Systemic administration of thyroxine initially accelerates myelination, but is followed by myelin deficits and premature ageing if hyperthyroidism is maintained for a longer time (Pasquini, 1998).
The objective of this study was to validate an animal model of changes in developmental myelination process. This model would be used to test therapeutic compounds for enhancing myelination.
Developmental myelination model was induced by daily s.c. injections of L-Thyroxine sodium salt pentahydrate (T4) in CD rat pups from P2 to P11. Pups were monitored daily for juvenile development; postnatal day of eruption of upper teeth, full teeth, and body weight. At P10

changes in white matter (WM) between T4 and vehicle treated rats (n=6/group) were assessed using DTI-MRI. Pups were sacrificed at different ages (daily from P3 to P11) in order to assess the changes in the myelin basic protein (MBP) levels using ELISA (n=5-6 pups/group/timepoint).
Daily treatment with T4 starting at P2 resulted in accelerated maturation of the T4 treated animals. Upper teeth eruption started for T4 treated rats already at 7 days of age, 2 days earlier than in vehicle rats. All rats in T4 group reached full teeth eruption at P8 age that was faster than vehicle rats ($p<0.05$ log-rank tests). WM changes at P10 indicated increased fractional anisotropy (FA) in forceps minor of the corpus callosum and internal capsule in T4 rats as compared to vehicle group (t-test, $p<0.05$, 0.01, respectively). Whole brain group-wise FA histograms revealed significant shift of FA values in T4 group to the higher values. T4 treatment resulted in increased MBP concentration in brain homogenates as compared to vehicle treatment at P9-P11 ($p<0.01$, t-test). Moreover, when MBP data were correlated with whole brain DTI histograms, significant correlation between the data existed ($p=0.0008$, $r^2=0.77$) further strengthening the conclusion of accelerated myelination in T4 treated animals.
Taken together, presented behavioral, imaging and biomarker data indicate that this developmental myelination model is suitable to test therapeutic compounds for enhanced myelination.

Disclosures: L. Tolppanen: None. **K. Lariosa-Willinghama:** None. **D. Leonoudakis:** None. **D. Miszczuk:** None. **K. Lehtimäki:** None. **M. Flanagan:** None. **J. Gibson:** None. **A.J. Nurmi:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.12/F21

Topic: B.12. Demyelinating Disorders

Support: Biotechnology and Biological Sciences Research Council BB/J01026X/1
Wellcome Trust 110138/Z/15/Z

Title: Role of regulatory T cells in remyelination following cuprizone-induced demyelination

Authors: *R. G. PEÑALVA, N. DE LA VEGA GALLARDO, M. NAUGHTON, J. W. FALCONER, Y. DOMBROWSKI, D. C. FITZGERALD
Queen's Univ. Belfast, Belfast, United Kingdom

Abstract: In the central nervous system (CNS), demyelinating diseases such as multiple sclerosis (MS), can result in devastating neurological impairments. Remyelination is the natural process that regenerates myelin in the CNS. However, remyelination is impaired in MS and this

is partly due to the failure of oligodendrocyte progenitor cells (OPC) to differentiate into oligodendrocytes at the lesion sites. T cells play a crucial role in the pathogenesis of MS but interestingly, T cells are also required for efficient remyelination. From a wide spectrum of functionally different T cells subsets, the regulatory T cell (Treg) subset has been recently shown to play an important role in regeneration in various tissues. Therefore, we hypothesised that Treg are required for efficient remyelination in the murine brain.
To study the role of Treg in remyelination we used female and male C57Bl/6 (WT) and transgenic FoxP3-DTR mice, in which administration of diphtheria toxin (DT) induced specific depletion of $Foxp3^+$ Treg. Animals were exposed to a 0.2% cuprizone diet for 25 days to generate demyelinated lesions in the CNS. After this period, animals were returned to normal diet to allow remyelination to occur. Treg depletion was initiated at the start of remyelination. Both WT and FoxP3-DTR mice showed clear demyelination in the corpus callosum following cuprizone feeding compared to healthy controls. After cuprizone withdrawal, female and male WT and FoxP3-DTR mice showed a significant increase in differentiated oligodendrocytes ($Olig2^+CC1^+$ cells), indicating ongoing remyelination in the corpus callosum. However, both Treg-depleted females and males showed a significant reduction in $Olig2^+CC1^+$ cells after 2 weeks of remyelination in comparison with non-depleted animals or DT-treated control WT mice. Moreover, depletion of Treg impaired the expression of PLP mRNA in another brain area, the cerebellum, indicating an impaired remyelination response. Interestingly, a significant reduction in $Olig2^+Ki67^+$ proliferative OPCs was also observed in Treg-depleted mice compared to non-depleted animals, which is in contrast to our recent findings in spinal cord remyelination. We also observed gender differences in the kinetics of the regenerative response which was impacted by Treg depletion.
These results suggest that Treg depletion impacts oligodendrocyte proliferation and differentiation during remyelination in both males and females brain, highlighting the importance of Treg in CNS remyelination.

Disclosures: R.G. Peñalva: None. **N. De La Vega Gallardo:** None. **M. Naughton:** None. **J.W. Falconer:** None. **Y. Dombrowski:** None. **D.C. Fitzgerald:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.13/F22

Topic: B.12. Demyelinating Disorders

Title: An oral gavage model for cuprizone-induced brain demyelination: Improved repeatability along with robust and specific phenotype

Authors: *A.-M. KÄRKKÄINEN, K. LEHTIMÄKI, A. HAAPALA, T. PARKKARI
Charles River Discovery, Kuopio, Finland

Abstract: Cuprizone (CPZ) mouse model was originally established to model the loss of myelin sheath in brain white matter in diseases such as multiple sclerosis (MS). The model has conventionally been induced by feeding young mice with CPZ for 6 weeks. However, the dietary CPZ model has some disadvantages, including high variability of the amount of CPZ consumed during the study. In addition, the taste of chow containing CPZ combined with model-specific reluctance to eat may eventually lead to starvation, which in turn is a source of bias in motor behavioral readouts. To overcome these challenges, we have validated a model in which the mice receive CPZ in two daily oral gavages. Male C57Bl/6J mice (n = 15) at age of 8-10 weeks received two daily oral gavages of 150 mg/kg of CPZ for a 6-week period. The model was assessed according to the body weights, motor behavior and fractional anisotropy (FA), measured by diffusion tensor imaging (DTI). The readouts were evaluated at baseline and after 6 weeks of exposure.

Male mice were originally selected for the study due to our observation of fluctuating body weight (BW) in female mice, presumably due to natural hormone level fluctuation. In male mice, 6-week CPZ dosing induced a maximum of 10% decrease in BW, whereas with a higher dose or in dietary model, the critical weight loss of 25% was reached frequently. Accordingly, the termination rate (due to humane endpoint criteria) was pronouncedly diminished in oral gavage model versus the dietary model (1.5% vs 30%, respectively).

After 6 weeks of cuprizone exposure, the mice showed statistically significant increases in parameters of locomotor activity (traveled distance, rearing count, jump count and jump time) compared to vehicle-dosed controls. In addition, neophobia normally displayed by rodents (avoidance of open areas and preference of being close to walls etc.) was also significantly reduced in CPZ-exposed mice compared to the vehicle mice. Furthermore, at 6 full weeks of CPZ dosing, DTI showed highly significant decrease (15-18%) of fractional anisotropy (FA) in the genu, body and splenium of corpus callosum. In addition, a moderate, yet significant, FA decrease of 6-9% was observed in the forceps minor of corpus callosum, external capsule and anterior commissure (anterior part).

Taken together, we have characterized a cuprizone model with notable reproducibility. The oral gavage model of cuprizone exposure produced a model phenotype with significant motor hyperactivity along with significantly reduced neophobia and significant white matter loss in comparison to the vehicle mice. Combined with the shown low mortality, this model offers an excellent preclinical model of demyelination.

Disclosures: K. Lehtimäki: None. **A. Haapala:** None. **T. Parkkari:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.14/F23

Topic: B.12. Demyelinating Disorders

Support: Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology
Mayo Clinic Center for Biomedical Discovery

Title: High fat diet impacts behavioral deficits associated with cuprizone-induced demyelination

Authors: ***M. R. LANGLEY**[1], H. YOON[1,2], H. KIM[1], L. KLEPPE[1], W. SIMON[1], I. R. LANZA[2], N. K. LABRASSEUR[2], A. MATVEYENKO[2], I. A. SCARISBRICK[3]
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Abstract: We recently published that a diet high in fat and sucrose results in a loss of myelinating cells and their progenitors in the intact adult spinal cord (Yoon et al., 2016), however any differential effects of high fat or sucrose are unclear. To further explore the impact of dietary fat alone on myelin integrity in the adult CNS, 10 wk old male C57BL6J mice were fed a regular diet (RD) or a diet high in fat (HFD) for 4 wk. Mice fed a HFD for 4 wk had impaired glucose tolerance and increased caloric intake. Mice fed a HFD also showed significant decreases in vertical activity in the Open Field test and spent less time in the center of the field indicating an anxious phenotype. Supporting our previous findings in the spinal cord, there were significantly fewer Olig2+ oligodendrocyte lineage cells and increased signs of lipid peroxidation products (4-Hydroxynonenal-immunoreactivity) in the corpus callosum of HFD consuming mice compared to those fed a RD. To explore the effect of HFD on Cuprizone (CPZ)-induced demyelination, 10 wk old C57BL6 male mice were fed a RD or HFD for 4 wk prior to consumption of the same diets containing 0.2% CPZ for an additional 4 wk. Behaviorally, CPZ-HFD mice spent significantly more time engaging in stereotypic movements, such as grooming, during the Open Field test. Gait analysis by Catwalk also identified improvements in hind limb swing speed in the CPZ-HFD group when compared to CPZ-RD mice. Motor skills sequence (MOSS) revealed significant deficits in maximum velocity during complex wheel training in CPZ-administered RD or HFD-mice and in mice fed a HFD alone. However, CPZ-HFD mice were significantly faster than CPZ-RD mice during complex wheel running. Although 4 wk of CPZ exposure significantly depleted the number of Olig2+ oligodendrocyte progenitor cells, no significant difference between CPZ-RD and CPZ-HFD was observed. However, Eriochrome staining and qPCR for MBP and PLP in the corpus callosum revealed significant loss of myelin that was somewhat preserved in CPZ-HFD mice when compared to CPZ-RD. Moreover, GFAP immunoreactivity was significantly increased in CPZ fed mice, but to a lesser extent in the CPZ-

HFD group when compared to CPZ-RD. Together these studies suggest that HFD may have a deleterious effects on myelin in the intact CNS, but be protective in the context of CPZ-mediated demyelinating injury. How HFD affects myelin regeneration upon CPZ withdrawal is currently under study. A better understanding of cellular and molecular changes in response to HFD consumption is needed to help guide care for individuals with MS and other conditions in which myelin loss plays a pathological role and has the potential to identify new targets for intervention.

Disclosures: M.R. Langley: None. **H. Yoon:** None. **H. Kim:** None. **L. Kleppe:** None. **W. Simon:** None. **I.R. Lanza:** None. **N.K. LaBrasseur:** None. **A. Matveyenko:** None. **I.A. Scarisbrick:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.15/F24

Topic: B.12. Demyelinating Disorders

Support: NIH Grant 5R01GM120519

Title: Early postnatal exposure to general anesthesia disrupts oligodendrocyte development and myelin formation in hippocampus

Authors: *Q. LI, R. P. MATHENA, J. XU, C. D. MINTZ
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Abstract: Childhood exposure to general anesthetics may have harmful effects on cognitive function, but mechanisms underlying this phenomenon are unclear. Previous work has focused on the effects of anesthetics on CNS neuronal development. Here we demonstrate that early anesthetic exposure disrupts oligodendrocyte (OL) and myelin development in fimbria (FI) of hippocampus via actions on mTOR and related epigenetic dysregulation. At P7, 24 mice were exposed to 1.5% isoflurane carried in 100% oxygen and 12 to room air (control) for 4 hours. From P21-P35, rapamycin or vehicle was injected (i.p.) to isoflurane exposed animals. Animals were sacrificed at P35 for IHC and WB, or at P63 for EM. During P56-P63, behavior tests for learning ability (novel objective position recognition-NOPR and Y-maze) were performed. To determine the effect of isoflurane exposure on mTOR in OLs, pS6/APC labeled cells in FI were assayed. In control, 19% APC+ OLs were pS6+ and there was an increase to 51% in isoflurane exposed mice, which was ablated by rapamycin treatment (23%). In NOPR, control mice spent 58% exploration time with the novel object. The isoflurane exposed mice spent essentially equal exploration times at both objects. Rapamycin treatment restored the performance to near control levels (55%). In Y-maze, similar results were observed in novel arm (58% vs 50% vs 56%). 47%

BrdU+/NG2+ OPCs in FI were seen in control and 28% in isoflurane group. This number increased to 47% in isoflurane plus rapamycin group. The ratio of APC+ OLs over PDGFRα+ OPCs in isoflurane mice (234%) was lower than in control (346%) and rapamycin increased the ratio (339%). WB data indicated intensity of Nkx2.2 over β-actin was downregulated by isoflurane (64% vs 20%) and rapamycin attenuated this effect (40%). Expression of MBP was decreased by isoflurane (111% vs 60%) and it was restored with rapamycin (104%). In EM, the myelin thickness significantly decreased in isoflurane exposed animals than control (*g-ratio* 0.8 vs 0.76) and rapamycin increased thickness (0.76). For DNA methylation in OLs, 65% Olig2+ cells in control were double labeled with DNMT1 and only 37% in the isoflurane group. Rapamycin treatment increased this number (60%). Early isoflurane exposure in mice induces the activation of mTOR signal in OLs. Isoflurane decreases proliferation of OPCs, impedes differentiation of OPCs into mature OLs, inhibits the myelin formation in hippocampal white matter, and impairs the learning ability. Inhibition of mTOR pathway attenuates these effects. In addition, early isoflurane exposure reduces, and rapamycin treatment increases, DNA methylation level in OL lineage that contributes to OL and myelin development.

Disclosures: Q. Li: None. **R.P. Mathena:** None. **J. Xu:** None. **C.D. Mintz:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.16/DP04/F25

Topic: B.12. Demyelinating Disorders

Support: ANR grant OLGA

Title: Behavioral consequences of demyelination in a Xenopus laevis model of inducible-demyelination and myelin repair

Authors: *B. ZALC[1], E. HENRIET[2], A. MANNIOUI[2], A. S. KHAKHALIN[3]
[1]Sorbonne Université; Inserm, CNRS, Paris Cedex 13, France; [2]Sorbonne Université, Inserm, CNRS, ICM, Paris, France; [3]Biol., Bard Col., Annandale on Hudson, NY

Abstract: We have generated a *Xenopus laevis* transgenic line allowing conditional ablation of myelinating oligodendrocytes. In this *MBP-GFP-NTR* line the transgene, GFP reporter fused to *E. coli* nitroreductase (NTR) driven by the mouse 1.9kb upstream regulatory sequence of myelin basic protein, is specifically and selectively expressed in myelin forming oligodendrocytes. Since NTR converts the innocuous pro-drug metronidazole to a cytotoxin, to kill oligodendrocytes and induce conditional demyelination, metronidazole was introduced into the aquarium water. As tadpoles are transparent, demyelination can be monitored *in vivo* and quantified. For instance, in stage NF52-53 (i.e., 25 days post fertilization) *MBP-GFP-NTR* transgenic tadpoles treated for 10

days with metronidazole (10mM) the number of GFP+ cells per optic nerve significantly decreased from 13.9 $\pm$ 1.0 to 2.3 $\pm$ 2 ($p<0.01$). Upon cessation of metronidazole treatment, i.e., after returning tadpoles to normal water, spontaneous remyelination occurred rapidly: the number of GFP+ oligodendrocytes per optic nerve reached 8.3 $\pm$ 0.9 and 13.3 $\pm$ 1.5 at 3 and 8 days of recovery, respectively. We confirmed that counting the number of GFP+ cells is a reliable indicator of the extent of myelination/demyelination/remyelination by immunolabeling with myelin-specific antibodies and electron microscopy. Furthermore, we reasoned that demyelination should translate into loss of sensori-motor functions. To challenge this hypothesis, we measured the speed and distance traveled before and after demyelination and during the ongoing spontaneous remyelination. In addition, to test the functional consequence of demyelination and repair of the optic tract of *MBP-GFP-NTR* transgenic *Xenopus* tadpole we adapted a visual avoidance paradigm, based on a virtual collision test. Quantitative evaluation of behavioral perturbation was confronted to the degree of demyelination-remyelination assayed by counting the number of GFP+ oligodendrocytes in the optic nerve.

Disclosures: B. Zalc: None. **E. Henriet:** None. **A. Mannioui:** None. **A.S. Khakhalin:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.17/F26

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01 MH098742
NIH Grant T32 GM008076

Title: The effect of HIV and antiretroviral therapies on oligodendrocyte maturation

Authors: *L. ROTH[1,2], B. ZIDANE[3], C. AKAY ESPINOZA[3], K. L. JORDAN-SCIUTTO[3], J. B. GRINSPAN[1]
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Abstract: Despite combined antiretroviral therapy (cART), HIV-associated neurocognitive disorder (HAND) occurs in 30-50% of HIV-positive patients. Furthermore, white matter pathologies persist in HAND patients despite effective viral control through cART. The thinning of the corpus callosum and disruption of white matter microstructures seen in HIV-positive patients, on cART, suggest both HIV-infection and/or antiretroviral drugs may perturb myelin production and oligodendrocyte maturation. Thus, *we hypothesized that HIV-infection of macrophages and/or antiretroviral compounds alter oligodendrocyte differentiation, function,*

and/or survival, influencing the persistence of HAND in the post-cART era. To examine the effect of HIV-infection in the CNS on oligodendrocyte maturation, we stimulated primary rat oligodendrocyte precursor cells (OPCs) to differentiate into mature oligodendrocytes, and treated them with supernatants from HIV-infected monocyte derived macrophage (HIVMDM). To generate HIVMDM supernatants, primary monocytes were isolated and differentiated into macrophages, then infected with HIV. Using this model, HIVMDMs significantly inhibited the differentiation of OPCs, which may explain initial white matter loss in HIV-infected patients. To gain insight into the persistence of white matter changes in the post-cART era, we have previously demonstrated that ART compounds, lopinavir and ritonavir, both of the protease inhibitor (PI) class, inhibit oligodendrocyte precursor differentiation, while zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), did not. We have extended these analyses to examine other antiretroviral compounds including, another PI; darunavir, NRTIs; tenofovir alafenamide and tenofovir disoproxil, and integrase inhibitors (INSTI); elvitegravir and raltegravir. Darunavir, tenfovir alafenamide, and elvitegravir also inhibited oligodendrocyte differentiation, while tenofovir disoproxil and raltegravir did not affect oligodendrocyte differentiation. These studies suggest that further investigation into the effects of HIV and/or first line ART compounds are warranted to provide insights into the observed persistent white matter changes seen in HAND patients with implications for their contribution to cognitive impairment.

Disclosures: L. Roth: None. **B. Zidane:** None. **C. Akay Espinoza:** None. **K.L. Jordan-Sciutto:** None. **J.B. Grinspan:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.18/G1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CNPq
CAPES
Faperj

Title: Mycobacterium leprae accelerates myelin breadkdown in Schwann cells

Authors: *B. S. MIETTO[1], B. J. SOUZA[1], P. M. F. SANTOS[1], M. BERREDO-PINHO[1], P. S. ROSA[2], M. V. PESSOLANI[1], F. A. LARA[1], E. N. SARNO[1]
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Abstract: Leprosy neuropathy is a chronic disorder caused by the infection of the peripheral nerve by the obligate intracellular pathogen mycobacterium leprae (M. leprae). Among all non-neuronal cells present in the nerve, Schwann cells are the primary host that positively contributes

to M. leprae persistence in the nerve. While M. leprae binding to myelinated Schwann cells has been implicated in demyelinating phenotype, the mechanisms governing myelin dismantling during infection as well as its contribution to bacilli survival in Schwann cells remain elusive. Here, we provided strong evidence of close interaction between M. leprae with degenerating myelin profiles both *in vitro* and *in vivo*, by using a mouse model of leprosy infection and in human nerve biopsies. We also documented accelerated myelin breakdown trigged by M. leprae infection that was associated with a robust downregulation in positive myelin transcriptional regulators, along with upregulation of autophagy-related genes. Moreover, when we blocked myelin degradation by pharmacological inhibition of JNK/c-Jun pathway, we drastically reduced M. leprae viability in Schwann cells. Overall, these findings provide novel evidences of augmented autophagic-myelin destruction induced by M. leprae and, most relevant, that myelin breakdown favors M. leprae survival in Schwann cells.

Disclosures: B.J. Souza: None. **P.M.F. Santos:** None. **M. Berredo-Pinho:** None. **P.S. Rosa:** None. **M.V. Pessolani:** None. **F.A. Lara:** None. **E.N. Sarno:** None.

Poster

204. Myelin-Related Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 204.19/G2

Topic: C.08. Ischemia

Title: The role of oligodendrocyte precursor cells after cerebral ischemia

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Abstract: [Background] Stroke is the most leading cause of adult neurological disability worldwide. Although remarkable progress in the research of stroke has been made, most translational efforts into effective therapies have failed, except for thrombolytic therapy or intravascular thrombectomy that only benefits a small proportion of patients. Deeper understanding of the neurovascular injury and repair responses after stroke would lead to novel orchestrated therapeutic approaches. Among various cell types in neurovascular unit in the brain, oligodendrocyte precursor cells (OPCs) have been shown to play more diverse and crucial roles than previously appreciated. Besides serving as a reservoir for mature oligodendrocytes, OPCs display phenotypic heterogeneity, regulating neuronal, glial and vascular systems in a direct and reciprocal fashion. However, the detailed phenotypic changes of OPCs after cerebral ischemia remain largely enigmatic.

[Object] Our aim is to evaluate how OPCs contribute to neurovascular damage and regeneration after cerebral ischemia.
[Methods] A mouse stroke model was produced by transient middle cerebral artery occlusion (MCAO). Cerebral blood flow was monitored by laser speckle imaging. Immunohistochemistry was conducted to evaluate the behavior of OPCs at days 1, 3, 7, 14, and 28 after MCAO. Using primary rat OPC culture, RNA sequencing was performed to profile the alterations of gene expression in reactive OPCs after oxygen glucose derivation (OGD).
[Results]On day 1 after the surgery, PDGFR-α-positive OPCs decreased. Beginning on day 3, OPCs were increasing, especially at perivascular area in the ischemic area, and continued to increase on days 7 and 14. Increased "perivascular" OPCs were located closely to endothelial cells and coupled with post-stroke angiogenesis. Meanwhile, increased OPCs after cerebral ischemia could not fully differentiate into mature oligodendrocytes, as evaluated by fluoromyelin staining showing a decrease
in myelin integrity at the ischemic area where perivascular OPCs were increased. In vitro RNA-seq analysis of OPCs revealed substantial alterations in gene expression profiles after OGD.
[Conclusion]Our data suggest that reactive OPCs actively participate in the damage and repair reactions of neuronal, glial, and vascular systems after ischemic stroke. The modification of "pathological" OPCs would lead to novel therapeutic approach for stroke.

Disclosures: N. Kishida: None. **T. Maki:** None. **K. Yasuda:** None. **H. Kinoshita:** None. **K. Yoshida:** None. **H. Kataoka:** None. **Y. Takagi:** None. **S. Miyamoto:** None. **R. Takahashi:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.01/G3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: K01 AG050719
NSF DGE-1143954
Donors Cure Foundation New Vision Award
P01 NS080675

Title: *In vivo* deletion of Kir6.2 in a APP/PS1 mouse model abolishes hyperglycemic increase in interstitial fluid amyloid-beta but does not affect brain plaque burden

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Abstract: Alzheimer's disease (AD), the most common form of dementia, afflicts millions of Americans and people around the world and has no cure or efficacious treatment. Diabetes and non-diabetic hyperglycemia are both risk factors for AD. It has been previously shown by our lab that increased hyperglycemia leads to increased levels of interstitial fluid (ISF) amyloid beta (Aβ) and neuronal activity. We also demonstrated, pharmacologically, that ATP-sensitive potassium (KATP) channels modulate this increase in ISF Aβ and neuronal activity. In order to determine if active KATP channels are required for the resulting increases in Aβ and neuronal activity seen in hyperglycemic events, an AD mouse model (PSAPP) was crossed with mice deficient in the KATP channel subunits, Kir6.1 or Kir6.2. These PSAPP mice with genetic deletions of either Kir6.1-KATP or Kir6.2-KATP were also examined for any modulatory effects on the pathological features of AD. Mice brains were sectioned and stained for Aβ plaques then analyzed. When Kir6.2-KATP was deleted in PSAPP mice and a glucose insult was given, ISF Aβ and neuronal activity did not increase with elevated glucose levels. This change was not seen in PSAPP mice without the Kir6.1-KATP subunit. Next, Aβ burden in the cortex and hippocampus was found to be unchanged among PSAPP control mice and PSAPP mice with Kir6.1-KATP or Kir6.2-KATP deficiency. These results suggest that Kir6.2-KATP is necessary for hyperglycemic-associated Aβ and neuronal activity increases. The lack of plaque burden modulation with either Kir6.1-KATP or Kir6.2-KATP deletion in PSAPP mice brains suggests that further research must be done in order to determine if the Kir6.2-KATP deletion effects are only present during hyperglycemic events. Also, further examination is ongoing to determine whether other AD pathological changes were modulated by these deleted KATP channels, despite no change in Aβ plaque burden.

Disclosures: M. Pait: None. **W.R. Moritz:** None. **C.M. Carroll:** None. **M. Stanley:** None. **K. Winkey:** None. **C. Hollingsworth:** None. **M.S. Remedi:** None. **C.M. Yuede:** None. **C. Nichols:** None. **D.M. Holtzman:** None. **S.L. Macauley:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.02/G4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KAKENHI 18K17954

Title: Involvement of hippocampal insulin signaling in deterioration mechanisms of Alzheimer's disease with type 2 diabetes

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Abstract: Diabetes is associated with an increased risk for dementia including Alzheimer's disease (AD). Our recent studies show that cognitive dysfunction is accompanied by alterations in the hippocampal insulin receptor substrates (IRSs) signaling in diet induced obesity (DIO) mice for type 2 diabetes model and APP knockin (APP KI) mice for AD model. However, it is unclear whether type 2 diabetes affects memory functions, adult neurogenesis, and amyloid accumulation in APP KI mice through the hippocampal IRSs signaling.We found that the enhancement of hippocampal IRSs phosphorylation at serine residues, the reduction of hippocampal neurogenesis, and the exacerbation of cognitive dysfunction occur in APP KI mice with type 2 diabetes compared with APP KI mice with normal diet or DIO mice, whereas type 2 diabetes has no effect on amyloid accumulation in APP KI mice. These results suggest that the hippocampal IRSs signaling may play an important role in development of AD with type 2 diabetes independently of β-amyloid accumulation.

Disclosures: D. Tanokashira: None. **Y. Fukui:** None. **M. Kashiwada:** None. **K. Takei:** None. **M. Maruyama:** None. **S. Sato:** None. **T. Saito:** None. **T.C. Saido:** None. **A. Taguchi:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.03/G5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF Brain Research Program 2016M3C7A190439
BK21(Brain Korea 21 Plus)

Title: Energy metabolic regulation in Alzheimer's disease; Applied natural-derived protein

Authors: J.-S. PARK[1], M.-H. JO[1], R. ULLAH[1], M.-G. JO[1], M.-W. KIM[1], B. P. F. RUTTEN[2], *M.-O. KIM[1]
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Abstract: Numerous well known studies indicated that aberrant energy metabolism play key roles in Alzheimer's disease (AD) pathogenesis. Alzheimer's disease (AD) is a slow progressing

neurodegenerative disease that can remain asymptomatic for several decades. It has been widely approved that the production and deposition of Aβ are early events that precede the onset of memory impairment that occur during the late stage of AD. Therapeutic approaches targeting Aβ have been applied to halt disease progression, however satisfactory consequences remain limited because memory improvement and energy metabolic dysfunction were not completely recovered. Recently, promising evidences reported that metabolic imbalance might be fundamental cause of AD, indicating that metabolic regulator for glucose, lipid and insulin might be important interventions for AD. We investigate that our applied natural-derived protein attenuates AD and metabolic dysregulation via regulation of energy metabolism.

Disclosures: J. Park: None. **M. Jo:** None. **R. Ullah:** None. **M. Jo:** None. **M. Kim:** None. **B.P.F. Rutten:** None. **M. Kim:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.04/G6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FA55

Title: Basal forebrain afferent activation in response to homeostatically relevant stimuli

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Abstract: The basal forebrain is comprised of several nuclei including the substantia innominata, medial septum, nucleus basalis and diagonal band of Broca. These basal forebrain nuclei consist of several neuronal populations including cholinergic, GABAergic, and glutamatergic neurons. The cholinergic component, named the basal forebrain cholinergic system, comprises the largest source of cholinergic innervation of neocortical and subcortical limbic areas implicated in attention, learning, and arousal. Evidence suggests basal forebrain neurons are impacted in aging and, more dramatically, in diseases such as Alzheimer's. However, frank degeneration of basal forebrain cholinergic neurons appears to be a late-stage phenomonen associated with Alzheimer’s disease and other age-related dementias, suggesting that earlier manifestations of cholinergic dysfunction may reflect alterations in afferent regulation of this important neurotransmitter system. We investigate basal forebrain afferent activation during salient conditioned stimuli to reveal afferent projections directly affected by age. Both aged (26-28 months) and young (2-3 months) rats were administered 200 nl cholera toxin B (CTb), a retrograde tracer, in the ventral pallidum and substantia innominata region of the basal forebrain, and placed on an 80% food restricted diet. The following 7 days prior to perfusion with

paraformaldehyde, rats were either trained using a dark/food paired conditioned stimulus, known to activate basal forebrain cholinergic output, or not trained. On day 15, aged and young trained rats were either given a dark/food paired stimulus or only given a dark cue absent of the stimulus. Two hr later, animals were sacrificed and their brains processed for immunohistochemical detection of the neuronal activity marker, cFos, and CTb. Aged rats showed altered activation of basal forebrain afferents located in the medial prelimbic cortex, nucleus accumbens, central amygdala and ventral tegmental area when presented a dark/food stimulus compared to controls. Additionally, we investigated activation of heterogeneous cell populations within the basal forebrain to further elucidate potential circuits affected by age related loss of activation of basal forebrain cholinergic neurons. These data suggest that age-related changes in basal forebrain activation may stem from alterations in afferent regulation by brain regions implicated in reward, affect and attention.

Disclosures: B.L. Somera: None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.05/G7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5P01AG014930

Title: Mitochondrial and metabolic dysfunction in iPSC-derived neural precursor cells of Alzheimer’s disease-associated presenilin 1 mutation

Authors: *P. MARTIN-MAESTRO[1], H. MARTINEZ[2], A. SPROUL[3], S. NOGGLE[2], A. STARKOV[1]
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Abstract: Background: There is a consensus that mitochondrial dysfunction and mitochondria-originated oxidative damage are early events in the pathogenesis of Alzheimer's disease (AD). Moreover, abnormal mitochondrial dynamics and distribution as well as autophagy impairment are well characterized in the disease. Presenilin 1 (PSEN1) M146L gene mutation is the most prevalent in familial AD. Besides the generation of Aβ, little is known about PSEN1 implication in mitochondrial dysfunction and oxidative damage.
Methods: Mitochondria profile has been studied in isogenic PSEN1-modified iPSC-derived neural precursor cells.
Results: PSEN1-modified cells demonstrated a decreased metabolic activity in mitochondria in relation to changes in the activity of mitochondrial enzymes involved in energy metabolism

promoting glycolytic pathway. Moreover, PSEN1-modified cells exhibited a mitochondrial accumulation due to a mitochondrial recycling failure as consequence of an autophagy induction blockage. These results were accompanied by a deregulation of the proteins involved in mitochondrial dynamics that could be reflect an impairment of mitochondria distribution and its degradation.
Conclusions: Our findings indicate PSEN1-modified cells are a suitable model for the study of AD due to the recapitulation of features previously described in different AD models. Together, all these results point out the relevance of the mitochondrial abnormalities in the early stages of neural fate in the study of AD. It serves as a platform to unravel the role of PSEN1 in mitochondria metabolism and mitochondria quality control in a human neuronal model of AD, and to develop a useful in vitro screening system for existing and future AD-targeting drugs.

Disclosures: P. Martin-Maestro: None. **H. Martinez:** None. **A. Sproul:** None. **S. Noggle:** None. **A. Starkov:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.06/G8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant R00 AG044469
NIA Grant R01 AG055581
NIA Grant R01 AG056622
Alzheimer's Association NIRG-15-362799
The BrightFocus Foundation A2017457S
Wake Forest School of Medicine ADCC pilot grant
Wake Forest School of Medicine CTSI pilot grant

Title: Isoform-specific dysregulation of AMP-activated protein kinase signaling in a non-human primate model of Alzheimer’s disease

Authors: *X. WANG[1], C. SHIVELY[2], T. MA[3]
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Abstract: The etiology of Alzheimer’s disease (AD) is still unclear. Energy metabolic dysfunction has been found to be a distinct characteristic of AD, and may be the underlying pathogenic mechanism of Alzheimer’s disease. AMP-activated protein kinase (AMPK) is a master energy sensor that plays a critical role in maintaining cellular energy homeostasis, dysregulated of which has been linked to AD pathogenesis. AMPK has 3 subunits, the α, β and γ.

The α subunit is the catalytic subunit and has 2 isoforms, α1 and α2. Activity of AMPK is mainly regulated through phosphorylation on the catalytic α subunit. In this study we examined AMPK signaling in a non-human primate (vervet) model of pre-clinical Alzheimer's disease. Nine naturally aged female vervet monkeys were included in this study. Three AD-like monkeys showed high Aβ plaque burdens and Aβ dimers, while three control monkeys only showed very low Aβ plaque burdens and no Aβ dimers. Level of Aβ42 in CSF was lower in AD-like monkeys as compared to control monkeys. Behavior assessments showed AD-like monkeys were less alert and less energetic. Levels of AMPKα2 phosphorylation were significantly increased in the hippocampi of the AD-like monkeys as compared to control groups. Mass spectrometry-based proteomic studies showed that 31 proteins were up-regulated and 46 proteins were down-regulated in the hippocampi of the AD-like monkeys, many of which were indicated in metabolism process. Protein-protein interaction analysis suggested most of the up-regulated and down-regulated proteins are related to AMPKα through a network, indicating the pivotal role of AMPK in Alzheimer's disease. Taken together, AMPK signaling was dysregulated in the hippocampus of a vervet model of Alzheimer's disease, which contributes to our understanding of the molecular mechanisms underlying AD, thus may provide insights into development of novel diagnostic biomarker and therapeutic avenue for this devastating disease.

Disclosures: X. Wang: None. **C. Shively:** None. **T. Ma:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.07/G9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VA I21 BX003023-01
NIH R21 AG051103-01

Title: Reduced hyperemia with both K+-induced and ischemic spreading depression with age in CVN-AD Alzheimer's mice

Authors: *D. A. TURNER[1], C. COLTON[2], S. DEGAN[1], U. HOFFMANN[3], F. GALEFFI[1]
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Abstract: Alzheimer's mouse models (such as CVN-AD) may experience progressive neuronal death through loss of neurovascular coupling and substrate deprivation. We analyzed spreading depression (SD) episodes induced by K+ and anoxia to assess hemodynamic reactivity in variously aged CVN-AD and wild type control (WT) C57Bl mice (in weeks: young: < 24; mature: 30-40; aged > 50).
Methods: Spontaneously breathing mice were anesthetized with isofluorane (~1.5%), monitored

for pulse ox (> 75%, 30% fiO2), pulse rate (> 400/s), temp (> 37 C) and tail BP (> 80 mm Hg mean). Blood flow was measured by laser Doppler 3 mm in front of the glass micro-electrode (in posterior burr hole) measuring DC cortical responses. 1 M KCl was placed in an anterior burr hole to induce spontaneous SD events, measuring the hyperemic contour, magnitude, and cortical spread of blood flow responses, including transcranial reflectance imaging at 562 nm (IOS: Sensicam QE, 2.5-5X).
Results: SDs led to either monophasic hyperemia or a biphasic response with a brief decrease of blood flow followed by an overshoot. Peak SD-induced blood flow responses (% above baseline) were larger in both the mature (WT 109%, n=36 SDs vs. CVN 102%, n=25 SDs) and aged WT mice (WT 99%, n=36 SDs vs CVN 74%, n=41 SDs, p* <0.05) compared to CVN mice of the same age. A diminished hyperemic peak was also noted in aged vs young CVN mice (p*< 0.05 CVN aged, n =41 SDs vs. CVN young, n = 25 SDs). The number of SD events per animal (6.0) and inter-SD time interval (14.3 min) were similar, but SD physiological amplitude differed between WT and CVN: mature (-14.0 vs -9.59 mV) and aged (-9.29 vs -6.11 mV), respectively. SD conduction velocity averaged 6 mm/min. Terminal hypoxic-SD events (100% N2) showed less reactive blood flow response in the CVN mice (WT +7 % vs CVN -60 % of baseline). IOS imaging showed linear waves of front to back SD propagation at concordant conduction velocities with occasional deviation or conduction failure. The IOS wavefront showed a reduced reflectance followed by an enhanced signal, likely consisting of both hemodynamic and tissue changes.
Conclusions: In aging CVN mice there was a progressive age-related decrease of the hyperemic peak during spontaneous K+-SDs compared to wild type mice, and also a reduced reactive blood flow response to anoxia (100% N2). SD propagation patterns could be visualized transcranially with IOS to correlate with blood flow and physiological responses. These results show alterations in neurovascular coupling and reactivity in CVN-AD mice compared to aged controls both at the cortical blood flow level in response to SD events, as well as at the capillary and arteriole level when measured in vitro in tissue slices.

Disclosures: D.A. Turner: None. **C. Colton:** None. **S. Degan:** None. **U. Hoffmann:** None. **F. Galeffi:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.08/G10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Society
Academy of Medical Sciences
Wellcome Trust

Title: Investigating the effect of apolipoprotein ε4 on neurovascular function using two-photon microscopy

Authors: *O. BONNAR, K. SHAW, D. M. GRIJSEELS, L. BELL, C. N. HALL
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Abstract: Neurovascular coupling (NVC) is the mechanism by which increased energy demands from neurons are followed by localised increases in blood flow, a process thought to be dysfunctional in Alzheimer's disease (AD). The greatest genetic risk factor for AD, the gene for Apolipoprotein ε4 (APOE4), reduces pericyte coverage of the microvasculature via a cyclophilin A (CypA) mediated pathway, resulting in increased blood brain barrier (BBB) permeability even in young animals[1]. As pericytes are key players in the NVC response [2], we speculated that pericyte damage in APOE4 mice may impair capillary-level blood flow regulation. Such blood flow perturbation could promote AD by producing hypoxia, facilitating the formation of plaques and tangles. To test if young APOE4 animals exhibit neurovascular deficits in response to sensory stimulation, humanised APOE3 or APOE4 targeted replacement mice were bred with NG2-DsRed or Thy1-GCamp6f animals, allowing the visualisation of pericytes or excitatory neuronal activity. Two-photon imaging was employed to measure blood vessel diameter changes in response to visual stimulation in the visual cortex of awake head-fixed mice. Preliminary results suggest fewer capillaries respond to visual stimulation in APOE4 animals, although the size of dilations in responding capillaries does not differ between genotypes. Conversely, there is no difference in the frequency of responses in pial vessels, but these dilations are smaller in APOE4 mice. This is consistent with a scheme whereby smaller APOE4 pial dilations reflect net microvascular responses that have propagated upstream from a dysfunctional capillary bed [3]. Because the increase in BBB permeability can be mitigated by the CypA inhibitor, cyclosporine A (CsA), we tested if it could also improve NVC in APOE4 mice. Preliminary data suggests this may be the case. In conclusion, preliminary data suggests that there may be early perturbations in the vascular response to visual stimulation in the visual cortex of APOE4 mice. Fewer responses in the capillary bed and the resultant smaller vascular responses at the pia could result in a deficit in energy supply to this area. The possible restoration of function after administration of CsA presents a potential therapeutic strategy for early vascular changes in APOE4 carriers. 1. Bell, R. D. *et al. Nature* **485,** (2012). 2. Hall, C. N. *et al. Nature* **508,** (2014). 3. Longdean, T. A. *et al.* Nat Neurosci. **20,** (2017).

Disclosures: K. Shaw: None. **D.M. Grijseels:** None. **L. Bell:** None. **C.N. Hall:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.09/G11

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Loss of mitofusin 2 promotes mitophagy in neurons

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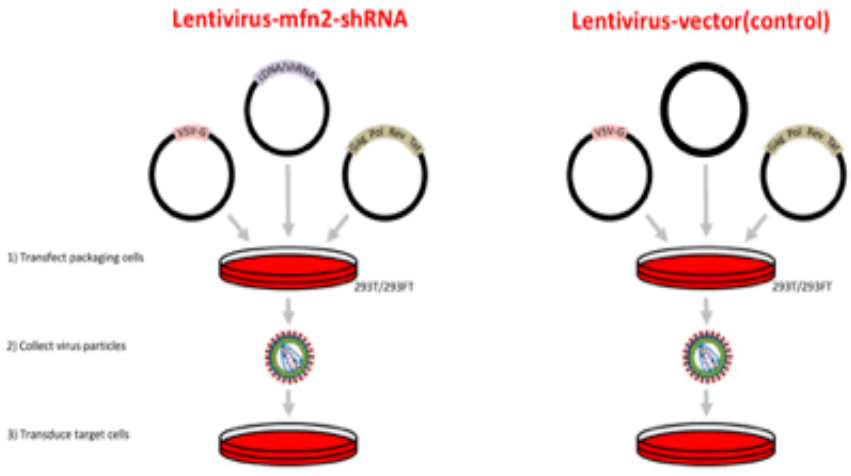
Abstract: Mitochondria are pivotal organelles for eukaryotic cells by providing energy, regulating Redox balance and modulate intracellular calcium homeostasis. Defected mitochondrial function results in cellular stress and eventually the cell death. Mitophagy is vital for the clearance of damaged mitochondria to maintain a healthy pool of mitochondria. A previous study has shown that mitofusin 2 (Mfn2) plays a key role in mediating mitophagy in cardiomyocytes by serving as a mitochondrial adaptor for Parkin. Of note, reduced expression levels of Mfn2 has been repeatedly identified to be a prominent change accompanying many neurodegenerative disorders such as Alzheimer's disease, which is characterized by brain mitochondrial dysfunction. In this regard, the accumulation of defected mitochondria in neurons in neurological diseases may be at least in part a result of lowered Mfn2 expression. However, whether Mfn2 is indispensable for the formation of mitophagosomes in neurons has not been comprehensively investigated yet. To address this question, we downregulated the expression of Mfn2 in primary cultured neurons and examined the status of mitophagy. Mfn2-downregulated neurons demonstrates severe mitochondrial dysfunction including increased fragmentation, increased oxidative stress and lessened energy production. Surprisingly, we have observed dramatically activated mitophagy in Mfn2-knockdown neurons, demonstrated by increased translocation of Parkin and LC3 as well as enhanced lysosomal engulfment of mitochondria. Such effects of loss of Mfn2 in potentiating mitochondrial dysfunction and mitophagy in neurons were further confirmed in genetic Mfn2 knockout mice. Therefore, our results suggest that Mfn2 is not likely to be a necessary protein facilitating mitophagy in neurons. Such discrepancy may arise from the heterogeneity of different cell types.



Disclosures: H. Chen: None. **H. Du:** None. **L. Guo:** None. **F. Xue:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.10/G12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P20 GM109098
P01 1AG027956
T32 AG052375

Title: Microvascular degeneration participates in the Alzheimer’s disease pathology in aged triple transgenic mouse model of Alzheimer’s disease

Authors: *D. D. QUINTANA, Y. ANANTULA, J. A. GARCIA, S. E. LEWIS, J. Z. CAVENDISH, S. SARKAR, C. M. BROWN, J. W. SIMPKINS
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Abstract: The architecture of the cerebrovascular system is inherently complex. The multitude of interconnected pathways that form a unidirectional distribution of blood flow contribute to a highly dynamic and stringently regulated system. The angioarchitecture is a major influential property that governs cerebral blood flow and thus guides the energetic states of the brain. Cerebrovascular hypoperfusion and hypometabolism are early manifestations of Alzheimer’s disease (AD) pathology, both of which worsen with age and disease progression. The precise role of cerebrovascular hypoperfusion and hypometabolism participate in the etiology and progression of AD is unknown. Cerebral amyloid angiopathy (CAA) is defined as a pathological accumulation of the amyloid-β peptide on cerebral blood vessels. CAA is reported in as many as 90% of all AD patients. Our unpublished studies demonstrate that the interaction between amyloid-β and cerebrovascular endothelial cells results in a number of metabolic and functional changes that suggest cellular stress. However, currently unknown is whether the accumulation of amyloid-β on the vasculature contributes to the cerebrovascular hypoperfusion and hypometabolism observed in AD patients. Thus, the goal of our study is to determine whether the progression of AD with age results in changes to the cerebrovascular architecture and function in a triple transgenic mouse model of AD. In our study, we used vascular corrosion casting to reconstruct the complete cerebrovascular system of the entire aged mouse brain at a sufficient resolution required to observe the microvasculature. Whole-brain vascular networks demonstrated complete vascular hierarchy, including geometrically complex microvascular networks. Regions specific assessment in aged triple transgenic AD mice demonstrated microvessel specific vascular deficits indicating vascular degeneration in aged triple transgenic mice compared to age matched wild type control mice.

Disclosures: D.D. Quintana: None. **Y. Anantula:** None. **J.A. Garcia:** None. **S.E. Lewis:** None. **J.Z. Cavendish:** None. **S. Sarkar:** None. **C.M. Brown:** None. **J.W. Simpkins:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.11/H1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG26572

Title: Effects of APOE genotype and obesity on metabolic and inflammatory outcomes in male mice

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Abstract: Genetic and environmental factors interact to regulate Alzheimer's disease (AD) risk. The strongest genetic risk factor for the development of late-onset AD is the ε4 allele of apolipoprotein E (*APOE*4). *APOE* encodes the apolipoprotein (apoE) cholesterol transporter, which has a role in lipid homeostasis. Obesity and the metabolic syndrome are primary modifiable risk factors for AD and may exacerbate these genetic vulnerabilities. Indeed, recent research from our lab demonstrated a significant interaction between obesity and *APOE* genotype in the regulation of AD-like pathology in EFAD mice in which obesogenic diet increased pathology in *APOE4* but not *APOE3* genotype. Because increased inflammation is implicated in driving AD pathogenesis and is associated with the deleterious effects of both obesity and *APOE4*, inflammation represents a compelling candidate mechanism by which obesity and *APOE4* interact to accelerate the development of AD. To gain insight into this possibility, the current research compared the effects of normal and obesogenic diet in male mice with *APOE3* versus *APOE4* genotype on inflammatory indices systemically and in brain. Further, we considered downstream effects of these interactions, focusing on metabolic and behavioral outcomes. Experimentally, adult male mice (N = 34) with knock-in of human APOE3 (E3) or APOE4 (E4) were maintained on Western diet (WD; high in saturated fat and sugars) or standard chow for 12 weeks beginning at age 3 months. Expression of microglia/macrophage markers, cytokines, and immune response factors were determined peripherally (e.g., plasma, adipose tissue) and in brain. In addition, mice were assessed on a range of metabolic (e.g., adiposity, glucose tolerance, fasting levels of glucose, insulin, and leptin) and behavioral (e.g., spontaneous alternation behavior, elevated plus maze) measures. Results from this investigation will provide novel insight into the interactions between *APOE* and diet-induced obesity, which

will inform on the mechanisms contributing to their cooperative actions in regulating AD pathology.

Disclosures: C.H. Sample: None. **V.A. Moser:** None. **C.J. Pike:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.12/H2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CB2015-1/ 257849 from CONACYT

Title: Effect of the consumption of hypercaloric diets on the integrity of the blood-brain barrier in hippocampus of rats

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Abstract: There is growing evidence that consumption of hypercaloric diets are associated with the development of metabolic syndrome (MS). Several studies have shown that MS promotes either cognitive impairment and the development of Alzheimer's disease (AD). The chronic inflammatory state that characterizes MS is proposed as the main promoter of damage in the Central Nervous System (CNS), with the blood-brain barrier (BBB) as one of the most vulnerable structures. The aim of this study is to evaluate the effect of the chronic consumption of hypercaloric diets (high in sucrose/HS or high in fat/HF) on the integrity of the BBB and the neuroinflammatory response in the Hippocampus. Newly weaned male Wistar rats were fed chow with hypercaloric diets during 2, 4 and 6 months. Body weight and abdominal fat accumulation were quantified, besides plasma levels of glucose, cholesterol and triglycerides. Expression of the tight junction proteins (ZO-1, Caludins-3 and -5) of the BBB were determined by western blot and qPCR; additionally, the levels of Fibrillar Glial Acid Protein (GFAP) as an indicator of neuroinflammation by immunohistochemistry. The results show an increased abdominal fat accumulation in rats fed with both hypercaloric diets. No differences in the plasma levels of glucose and cholesterol were find, however triglycerides increased in HS fed rats at 4 and 6 months. The expression of ZO-1 and Claudin-5 decreased in rats fed with both hypercaloric diets, been more evident in the group that consumed the high-fat diet. The levels of GFAP increased significantly. These results suggest that obesity leads to a loss in the integrity of the BBB, in addition to the neuroinflammatory response, furthermore could modify the function

of the BBB by altering its selectivity and favoring the entry of harmful molecules into the CNS. These events could explain, at least in part, the association between MS and the neurodegenerative process that characterizes AD.This project was supported by grand CB2015-1/ 257849 from National Council of Science and Technology (CONACYT)

Disclosures: C.F. Aguilar-Gammas: None. **E. Martinez-Abundis:** None. **E.N. De la Cruz-Hernández:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.13/H3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA P01AG026572
Arizona Alzheimer’s Consortium

Title: Perimenopausal aging brain is characterized by a bioenergetic-inflammatory transition state that indicates Alzheimer’s vulnerability

Authors: *Y. SHANG[1,2], J. BERGHOUT[2], Y. LUSSIER[2], F. YIN[1,3], R. D. BRINTON[1,3,4]
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Abstract: Perimenopause is a female aging transition that proceeds- and leads to reproductive senescence and is associated with multiple neurological symptoms, including those associated with increased Alzheimer’s risk. We previously demonstrated declined bioenergetic and synaptic functions in perimenopausal brains that are reminiscent of early stage AD phenotypes. Using pathway-centric bioinformatic approaches, the present study is aimed to determine the underlying biological processes that drive the transformation of perimenopausal brain and their contribution to AD vulnerability. Hippocampal and hypothalamic RNAs from six groups of female rats at different age and endocrine status were sequenced and analyzed through Principal Component Analysis (PCA), Differentially Expressed Gene (DEG) analysis and Gene Set Enrichment Analysis (GSEA). We developed a new ranking system for enriched pathways among biological groups by summarizing all pairwise GSEA results. Hierarchical clustering was applied to identify significant interactions between emerged pathways. PCA revealed that rats during perimenopause exhibited substantially higher variance in overall hippocampal gene expression, supporting the perimenopausal brain being at an unstable transition state. While PCA and DEG analyses of hippocampal RNA suggested significant differences among age-matched pre-/peri-/menopause brains, the difference in the hypothalamus was minor, suggesting hippocampus being more affected by endocrine aging than hypothalamus. GSEA further

revealed alterations in bioenergetic-, inflammatory-, and cell proliferation pathways during the transition featured by declining bioenergetic genes and low-grade activation of immune pathways. Moreover, nuclear- (nDNA) or mitochondrial DNA (mtDNA)-encoded bioenergetic genes are differentially regulated by chronological- and endocrine aging: mtDNA genes correlated closely with chronological aging whereas nDNA-encoded counterparts were largely endocrine dependent. Our findings suggest that hippocampal transcriptome during perimenopause is at a transition state characterized by perturbations to primarily bioenergetic- and inflammatory pathways, which could contribute to increased AD risk in women. This study provides novel mechanistic insights into the impact of perimenopausal transition on brain function, which could have implications for identifying phenotypes of AD risk for earliest detection in aging females.

Disclosures: Y. Shang: None. **J. Berghout:** None. **Y. Lussier:** None. **F. Yin:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.14/H4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA P01AG026572
Alzheimer’s Association SAGA-17-419459
Arizona Alzheimer's Consortium
Packer Wentz Research Endowment

Title: Impact of APOE genotype on the sex differences in bioenergetics and Alzheimer’s risks in aging mouse brain

Authors: *F. YIN[1,2], M. DESAI[5], Y. SHANG[1,3], Y. WANG[1,5], Z. MAO[1], A. MISHRA[1,5], R. D. BRINTON[1,2,4]
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Abstract: Age, APOE4 genotype, and female sex are among the top risk factors for Alzheimer’s disease (AD). Our previous studies demonstrated substantial sex disparities in brain bioenergetic trajectories in normal aging- and familial AD transgenic mice, and the bioenergetic deficits occurring in the perimenopausal brain could contribute to an increased AD risk in females. The goal of the present study is to determine the impact of APOE genotype on the sex-differentiated AD at-risk phenotypes during brain aging. With age-matched female and male humanized

APOE4 (hAPOE4) and hAPOE3 mice, we characterized their peripheral metabolic profile at 6- and 16 month-of-age, as well as their brain hippocampal transcriptome at 16 month-of-age. Our results indicated that at 6 month-of-age, APOE4 genotype elicited significantly lower plasma levels of glucose (in both females and males) but higher levels of ketone bodies (only in females) compared to age- and sex-matched hAPOE3 mice, and this pattern persisted to 16 month-of-age. At 16 month-of-age, the females had higher total triglyceride levels relative to genotype-matched males while APOE genotype did not elicit a difference. Moreover, hippocampal RNA-seq analysis of these mice suggested distinctive effects of APOE genotype and sex on regulating hippocampal gene expression: in terms of differentiated expressed genes (DEGs), variation in APOE genotype alone led to a more significant change than that of sex alone, and when these two factors combined, the most DEGs were identified between male hAPOE3 and female hAPOE4 mice. Furthermore, our pathway-centric bioinformatic analysis indicated that APOE4 genotype elicited a significant impact on the expression of bioenergetic- and inflammatory genes: Gene Set Enrichment Analysis (GSEA) suggested bioenergetic pathway being substantially suppressed while inflammatory pathway being activated, in both male- and female hAPOE4 mice relative to sex-matched hAPOE3 mice. These findings suggest that APOE4 genotype regulates the age-related decline in brain bioenergetic function and increased AD risk differentially in females and males. Outcomes of this study will provide mechanistic details of the APOE4 genetic burden on the sex-differentiated bioenergetic fluctuation during aging and its contribution to the onset of the prodromal AD endophenotype and higher AD risks in women.

Disclosures: F. Yin: None. **M. Desai:** None. **Y. Shang:** None. **Y. Wang:** None. **Z. Mao:** None. **A. Mishra:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.15/H5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH U54 HD029990
NIA P01 AG026572

Title: Chronic exposure to the therapeutic progestin nestorone promotes neurogenesis: Implications for sustaining regeneration in female brain

Authors: *S. CHEN[1], N. KUMAR[3], Z. MAO[1], T. WANG[1], R. SITRUK-WARE[3], R. D. BRINTON[1,2]
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Abstract: Neurogenesis is the principal regenerative mechanism to sustain the plasticity potential in adult brains. Decreased neurogenesis parallels the cognition decline with aging, and has been suggested as a common hallmark in the progression of many neurodegeneration diseases. We previously reported that acute exposure to Nestorone (NES, segesterone acetate), alone or in combination with 17β-estradiol (E2), increased rat neural progenitor/neural stem cell proliferation and survival in brain hippocampus both *in vitro* and *in vivo*. The present study expanded our previous findings to investigate the more clinical related chronic exposure NES alone or in combination with E2 on the regenerative capacity of adult brain. To mimic the chronic contraception exposure in women, 3 months old female mice (n = 110) were treated with NES, with or without co-administration of E2, for 4 weeks. Neural cell proliferation and survival and oligodendrocyte generation were assessed and the involvement of insulin-like growth factor 1 (IGF-1) signaling pathway was studied. Our results demonstrated that chronic NES and E2 alone or in combination increased neurogenesis by a comparable magnitude, with minimum to no antagonistic or additive effects between NES and E2. In addition, chronic exposure of NES or NES+E2 stimulated oligodendrocyte generation, indicating potential elevated myelination. IGF-1 and IGF-1 receptor (IGF-1R) were also upregulated after chronic NES and E2 exposure, suggesting the involvement of IGF-1 signaling as the potential underlined regulatory pathway transducing NES effect.These findings provide preclinical evidence and mechanistic insights for the development of NES as a neuroregenerative therapy to promote intrinsic regenerative capacity in female brains against aging and neurodegenerative disorders.

Disclosures: N. Kumar: None. **Z. Mao:** None. **T. Wang:** None. **R. Sitruk-Ware:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.16/H6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant P01-AG026572
NIA Grant U01-AG031115
NIA Grant U01-AG047222
NIA Grant UF1-AG046148

Title: Allopregnanolone rescues mitochondrial dysfunction in ovariectomized triple-transgenic Alzheimer’s mouse brain and familial Alzheimer’s neural stem cells

Authors: *T. WANG[1], J. YAO[4], C. M. SOLINSKY[5], S. CHEN[1], R. D. BRINTON[1,2,3]
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Abstract: We previously reported that reproductive senescence or ovarian hormone depletion by ovariectomy (OVX) significantly exacerbates glucose hypometabolism, mitochondrial deficits and AD pathology that features the female triple-transgenic Alzheimer's mouse brain (3xTgAD). We also demonstrated that the neurosteroid allopregnanolone (Allo) promotes neural stem cell regeneration, restores cognitive function and reduces AD pathology in female AD mouse brains. The present study was aimed to further investigate the potential therapeutic effect of Allo on the bioenergetic system of the female Alzheimer's brains and its underlying mechanism. Our results demonstrated that Allo reversed OVX-induced deficits in mitochondrial respiration and elevation in proton leak in 3xTgAD mice, which was supported by the increased expression and activity of key mitochondrial bioenergetic enzymes, pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (αKGDH). *In vitro* primary cultures suggested that Allo manifested a similar mitochondrial potentiating effect across multiple cell types including hippocampal neurons, mixed glia and neural stem cells (NSC). Consistent with the restored mitochondrial efficiency, Allo reversed OVX-induced increase in lipid peroxidation, an indicator of redox dysregulation and oxidative stress. Mechanistically, Allo enhanced brain metabolic activity, restored redox homeostasis and reduced amyloidogenesis via up-regulating genes involved in glucose metabolism, mitochondrial bioenergetics and the removal of reactive oxygen species (ROS) while simultaneously down-regulating genes involved in AD pathology, fatty acid metabolism and mitochondrial uncoupling and dynamics. Upstream regulator analysis predicted that Allo could effect through activating PPARGC1a and PPARG pathways while inhibiting the PSEN1, PTEN and TNF pathways. Further, the potential therapeutic effect of Allo on AD via promoting mitochondrial energy transduction was supported by assays performed with NSCs derived from induced pluripotent stem cells (iPSCs) of a familial AD patient with PSEN1 A431E mutation. Collectively, our findings suggest that Allo functions as a systems-biology regulator of bioenergetics, redox homeostasis, and β-amyloid metabolism in the female AD brains, thus providing a plausible rationale for Allo as a therapeutic strategy to promote female brain bioenergetic function that is compromised upon depletion of ovarian hormones, at natural menopause or after premenopausal oophorectomy.

Disclosures: T. Wang: None. **J. Yao:** None. **C.M. Solinsky:** None. **S. Chen:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.17/H7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA P01AG026572
SAGA-17-419459
Arizona Alzheimer's Consortium

Title: Sex differences in metabolic and inflammatory aging in humanized APOE-ε4 knock-in rat brain

Authors: *A. MISHRA[1], F. YIN[2], Z. MAO[2], Y. SHANG[3], L. DO[3], T. P. TROUARD[3], R. D. BRINTON[2]
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Abstract: Women APOE-**ε**4 carriers are susceptible to accelerated aging and undergo faster rates of conversion from Mild Cognitive Impairment (MCI) to Alzheimer's disease (AD) (Lin et al, Alzheimer's & dementia, 2015). Using humanized APOE-**ε**4 gene knock-in rat model, we conducted a longitudinal study to characterize the individual and combined impact of sex and APOE-ε4 genotype on the brain aging process. APOE-ε4 and wildtype (WT), female and male rats, were assessed at four aging windows: 7-8 months (m), 9-10 m, 12-13 m and 15-16 m. Reproductive cyclicity in female rats was assessed by vaginal lavage. During the longitudinal follow-up, we conducted ^{18}FDG-microPET/CT(18-fludeoxyglucose micro Positron Emission Tomography/Computational Tomography) to determine brain glucose uptake, and established peripheral metabolic profiles. Hippocampal RNA-Seq and magnetic resonance imaging (MRI) were conducted at end-of-study. MRI was conducted in fixed rat brain using a 3-dimensional high-resolution (100 micron isotropic) T2-weighted sequence. Diffusion-weighted MRI was also conducted using a segmented EPI sequence with b-values up to 6000 s/mm^2. Metabolically, female APOE-ε4 rats underwent an age-related decline in insulin with concomitant rise in plasma levels of ketone bodies. In comparison to WT-females, APOE-ε4 females exhibited significant decline in ^{18}FDG uptake at 12-13m, following reproductive senescence. The decline in glucose uptake in APOE-ε4 females worsened with age. Female APOE-ε4 rats had lower ^{18}FDG uptake than males across all time points. MRI-based quantitative volume assessment of brain regions revealed that white matter areas – anterior commissure and posterior commissure, in the APOE-ε4 female brain trended towards larger volume relative to APOE-ε4 males. Assessment of myelin integrity, via diffusion parameters, is currently underway. In the APOE-ε4 females, grey matter areas – neocortex ($p<0.05$) and hippocampus, were relatively smaller in comparison to APOE-ε4 males. RNA-seq analysis from the hippocampus revealed an upregulation of MHC-I, IL1R and IL6R in APOE-ε4 females. Upregulation of these genes may indicate activation of neuroinflammation in APOE-ε4 female brain. APOE-ε4 females also show an upregulation of PLA2G4 (cPLA2) indicating possible activation of the arachidonic acid pathway involved in breakdown of myelin (Klosniski et al, eLife, 2016). Thus far, the longitudinal data indicate that APOE-ε4, in combination with the aging endocrine transition state, worsens the metabolic trajectory which is associated with changes in regional brain volumes and neuroinflammation in the aging female brain.

Disclosures: A. Mishra: None. **F. Yin:** None. **Z. Mao:** None. **Y. Shang:** None. **L. Do:** None. **T.P. Trouard:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.18/H8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association SAGA Award
National Institute on Aging U01-AG047222
Arizona Alzheimer's Consortium

Title: Allopregnanolone restores cognitive function in APOE4+ females and males and promotes metabolism of fuels required for ATP generation

Authors: *M. K. DESAI[1], R. W. IRWIN[2], M. PRAJAPATI[1], K. PATHAK[3], P. PIRROTTE[3], R. D. BRINTON[4]
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Abstract: Sex differences in the effect of APOE4 on risk and progression of AD have been reported, with greater adverse impact in women. To address sex and APOE genotype impact on therapeutic efficacy of the regenerative neurosteroid Allopregnanolone (Allo), we investigated behavioral and metaboloic outcomes following Allo treatment in aged APOE4-/+ female and male mice. Female and male APOE3, E4, E3/4 mice were treated 1/week with intramuscular dose of 2 mg/kg Allo for 26 weeks or placebo from 10-16 months-of-age. Dose, formulation and duration of treatment were designed to reflect the human Phase 1b/2a clinical trial of Allo (ClinicalTrials.gov ID: NCT02221622). Behavior was assessed using Novel Object Recognition. Plasma and cortex were queried for 185 metabolites using ultra-performance-LCMS. Behavioral analyses indicated significantly increased novel object recognition in APOE4 females and males with greatest effect in APOE4 females, higher Discrimination Index (DI) and significantly better novel object recognition. Allo had no effect in APOE3/3 mice. Metabolomic analyses indicated changes in lipid and Arg metabolism between females and males within and across the three genotypes. In APOE3 and APOE4 females plasma glycerophospholipid metabolism was significantly downregulated ($p<0.05$). Glycerophospholipids were lowest in APOE3/4 females. In cortex, biogenic amines (α-aminoadipic acid, putrescine) and amino acids (Arg and Phe) were lowest in APOE3 and APOE4 females suggesting increased Arg catabolism. Following Allo treatment, APOE4 female plasma showed decreased glycerophospholipids and increased acylcarnitines, suggesting increased lipid catabolism. In APOE4 male plasma, Allo increased ADMA, ornithine, and acylcarnitines, indicating increased Arg and lipid catabolism. Allo exerted an APOE genotype dependent effect to improve cognitive function in APOE4+ female and male mice with APOE4+ females exhibiting greater response to Allo. Metabolomic data are

suggestive of an effect of Allo to increase lipid metabolism to generate acetyl-CoA to feed into the TCA cycle ATP generation in the mitochondria. Further, Allo treatment increased indicators of protein metabolism. In summary, efficacy of Allo was evident in both females and males and modified by APOE genotype. Further therapeutic development of Allo is underway. Research supported by Alzheimer's Association SAGA Award, National Institute on Aging U01-AG047222 and Arizona Alzheimer's Consortium.

Disclosures: M.K. Desai: None. **R.W. Irwin:** None. **M. Prajapati:** None. **K. Pathak:** None. **P. Pirrotte:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.19/H9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P01AG026572 to RDB

Title: Hormone loss and intervention initiated at different endocrine status differentially regulate brain bioenergetic function: Implications for Alzheimer's disease

Authors: *Z. MAO[1], F. YIN[1], Y. SHANG[2], R. BRINTON[3]
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Abstract: The perimenopause is an aging transition unique to females and is associated with multiple neurological symptoms. Our previous study in a rodent model of human perimenopause revealed the perimenopausal transition as a critical transition period characterized by a significant decline in bioenergetic and synaptic functions, that is reminiscent of early stage of Alzheimer's disease (AD). Combinations of 17β-estradiol (E2) and progestogens (P4) in varying regimens are widely used as hormone therapy for menopause-related climacteric symptoms. The present study was aimed to determine the efficacy and optimal intervention window of E2 in combination of cyclic P4 therapy on female rat brain at different stages of the perimenopausal transition, against bioenergetic deficits and AD risks. Placebo or E2+CyP4 therapy was initiated on female rats at 9-10 months with either pre- or perimenopause stages at the same age, and for each stage, ovariectomy (OVX) or Sham OVX surgery was performed before the intervention. Hormone therapy consisted of two 30-day cycles of continuous E2 and cyclic P4 (10 days/cycle) delivered by silastic capsules. Upon completion of the regime, rats were subject to transcriptomic, biochemical, immunocytochemical and brain metabolic investigations. We previously reported that a two-month treatment of E2+CyP4 on (OVX) young rats induced a

bioenergetic gene-expression profile comparable to the ovary intact females. Our data from this study indicate that the efficacy of E2+CyP4 therapy on brain bioenergetic functions in terms of glucose metabolism and mitochondrial respiratory capacity was differentially affected by the endocrine status of the rats when the intervention was initiated. In addition, our data also suggested that OVX initiated on pre- or perimenopausal stages elicited differentiated effects on bioenergetic-, inflammatory- and AD-related gene expressions. Immunocytochemistry study suggested that the E2+CyP4 therapy could effect through the PI3K-Akt pathway that was inhibited by OVX. Bioinformatic analysis of the hippocampal transcriptome identified interactions between the biological pathways being affected by hormone depletion, endocrine transition and E2+CyP4 therapy. Outcomes of this study will help determine the window of opportunity for preventing the at-AD-risk bioenergetic phenotype by hormone intervention in women and will provide mechanistic details for developing novel strategies to maintain neurological health and function throughout menopausal aging against AD vulnerability.

Disclosures: Z. Mao: None. **F. Yin:** None. **Y. Shang:** None. **R. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.20/H10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant UF1-AG046148
NIA Grant U01-AG031115
NIA Grant U01-AG047222
NIA Grant P01-AG026572

Title: Combining mitochondrial haplogroup, APOE genotype, and sex as a predictive responder identifier to regenerative therapeutic allopregnanolone for Alzheimer's disease

Authors: *Y. WANG[1], C. SOLINSKY[1], G. HERNANDEZ[2], L. SCHNEIDER[1], R. D. BRINTON[3]
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Abstract: Late onset Alzheimer’s disease (LOAD) is a systemic disease with multiple etiologies, and is associated with compromised brain metabolism and regenerative capacity. Allopregnanolone has been shown to promote brain mitochondrial function, neurogenesis, and memory in mouse models, and is currently being investigated as a regenerative therapeutic for AD (NCT02221622). While genetic markers such as APOE genotype may predict risk of AD, there is currently no genetic markers to predict therapeutic outcomes for AD. Because mitochondrial genetic variances and APOE genotype are known to be differentially associated

with respiratory capacity and cell proliferation, in this study, we evaluate whether they can be used as potential genetic markers to predict responders for Alzheimer's disease therapeutics. T-cells from allopregnanolone clinical trial participants were reprogrammed to iPSCs via a non-integrating, non-viral method, and then differentiated into NSCs using dual inhibition of SMAD signaling. Mitochondrial respiration and regenerative capacity were determined by metabolic analyzer and FACS. To determine mitochondrial haplogroups of the participants, DNA was extracted from whole blood of the participants, and Hypervariable region 1 and 2 of mitochondrial DNA were amplified, sequenced, and aligned to the Revised Cambridge Reference Sequence. Mitochondrial haplogroup was assigned using HaploGrep2 based on identified variants. Analysis revealed that allopregnanolone treatment preferentially increased maximum respiration in NSCs derived from participants of mitochondrial haplogroups A, L, M, and N compared to those from haplogroups H, HV, and J. Further, NSCs derived from male APOE4 carriers exhibited significantly different proliferation pattern relative to male non-APOE4 carriers following allopregnanolone treatment. Ongoing analyses will determine whether mitochondrial haplotype in combination with APOE genotype and sex can serve as predictive biomarkers of response to allopregnanolone on clinical level. Mitochondrial haplotype, APOE genotype, and sex in combination is a promising predictive biomarker to identify potential allopregnanolone responders. Predictive biomarkers will significantly contribute to a precision medicine strategy to identify responders to therapeutic agents for Alzheimer's disease.

Disclosures: Y. Wang: None. **C. Solinsky:** None. **G. Hernandez:** None. **L. Schneider:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.21/H11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant U01AG031115
NIA Grant U01AG047222
NIA Grant UF1AG046148
ADDF

Title: Allopregnanolone as a regenerative therapeutic for Alzheimer's disease: Phase 1 clinical trial outcomes

Authors: *G. D. HERNANDEZ[1], C. M. LOPEZ[1], C. M. SOLINSKY[3], N. KONO[4], R. W. IRWIN[5], K. E. RODGERS[2], B. AYDOGAN[6], Y. SHI[6], M. LAW[6], W. MACK[4], L. SCHNEIDER[7], R. D. BRINTON[2]
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Pharmaceut. Econ. & Policy, [4]Preventive Med., [5]Pharmacol. and Pharmaceut. Sci., [6]Radiology, [7]Psychiatry, USC, Los Angeles, CA

Abstract: Background

To date, no interventions have demonstrated substantial therapeutic efficacy to prevent, delay or treat Alzheimer's disease (AD) and several have accelerated disease progression. Current thinking in the field embraces the complexity of AD pathophysiology, which has enabled a more diverse therapeutic pipeline targeting multiple aspects of the disease. Targeting the regenerative system of the brain while simultaneously activating systems to reduce burden of AD pathology is a novel and innovative therapeutic approach. Allopregnanolone (Allo) is a first in class regenerative therapeutic for delaying progression and treating AD with a strong foundation of human safety exposure.

Methods

A randomized double-blind, placebo-controlled, multiple ascending dose, phase 1 clinical trial was conducted in patients with mild cognitive impairment due to AD or mild AD. Participants were age ≥ 55 years, had a MMSE score ≥ 20 and clinical dementia rating of 0.5-1. Participants were randomly assigned to receive weekly intravenous treatment of 2, 4 and 6mg of Allo or placebo. Primary outcome was to assess safety, tolerability and maximally tolerated dose (MTD) of Allo at the three doses administered intravenously once per week over 12 weeks. Secondary exploratory outcomes were the feasibility and impact of Allo on MRI indicators of regeneration and cognition. Lymphocyte derived iPSCs differentiated to neural stem cells were used to develop biomarker strategy to identify potential regenerative responders.

Results

A total of 24 patients were enrolled into the trial (18 Allo + 6 placebo). Peak plasma levels were reached within 30 minutes of start of infusion. Mean Cmax at 2, 4 and 6mg was 63±21 nM, 130±26 nM and 248±84 nM, respectively. The Cmax closely correlated (R=0.77) with Allo delivered in mg/kg dose. MTD was established by onset of sedation at doses >6mg. Twelve-week exposure to multiple doses of Allo once per week resulted in no reportable adverse effects, serious adverse events or ARIA. Structural analysis of MRI-based indicators of gray matter volume were consistent with regeneration in select brain regions. Subfield analysis indicated an increase in left hippocampal volume in the Allo 4mg cohort. Cognitive function measured by ADAS-cog14 was not improved. However, some Cogstate indicators were consistent with improvement. Biomarker of Allo response correlated with change in MRI structural volume.

Conclusion

Allopregnanolone is a first in class regenerative therapeutic for MCI and AD that targets endogenous neural stem cells and disease modifying mechanisms. Our data indicate a favorable safety and tolerability profile, and potential efficacy.

Disclosures: G.D. Hernandez: None. **C.M. Lopez:** None. **C.M. Solinsky:** None. **N. Kono:** None. **R.W. Irwin:** None. **K.E. Rodgers:** None. **B. Aydogan:** None. **Y. Shi:** None. **M. Law:** None. **W. Mack:** None. **L. Schneider:** None. **R.D. Brinton:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.22/H12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA P01AG026572
SAGA-17-419459
Arizona Alzheimer's Consortium

Title: Effect of sex and ApoE genotpye on regional brain volumes and white matter integrity in mice using high resolution MR imaging

Authors: *R. D. BRINTON[1], L. DO[2], A. S. BERNSTEIN[3], A. MISHRA[4], F. YIN[1], M. K. DESAI[4], T. P. TROUARD[2]
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Abstract: Sex differences in the progression of Alzheimer's disease (AD) in APOE4 carriers is eminent in the early stages. Early changes in white matter microstructure and alteration in regional brain volumes can be indicative of neurodegeneration during disease progression. APOE4 homozygotes have a higher accumulation of white matter hyperintensities, as seen on T2-FLAIR MRI, during normal aging, which is further increased after AD diagnosis. To establish translational validity of the humanized APOE mouse model for clinical findings, we conducted magnetic resonance imaging (MRI) on these mice. Male or female mice (n=11) with a targeted replacement of mouse APOE gene with either human APOE3 (ApoE3TR) or APOE4 (ApoE4TR) were used in the study. Fixed mouse brains were collected at their age of 16 months, and underwent high-resolution 3D T2-weighted RARE (75 micron isotropic voxels, 192x320x128 matrix) with TR/TE=1500/10ms. Multi-shell super-resolution diffusion-weighted MRI was also carried out on these brains with b=1000, 2000, 3000, 4000, 5000, 6000 s/mm^2, (200 micron isotropic voxels, 96x96x26 matrix). MRI was carried out on a 7T Bruker Biospec, using a volume coil for excitation and a 4-channel phased-array surface coil for reception. Images were processed using ITKsnap and MRIcron for brain extraction and biased corrected using the N4 routine in the Advanced Normalization Tools (ANTs). A T2-weighted reference image and atlas with 356 regions of interest (ROIs) (Steadman et. al., Autism Res, 2014) was registered to each animal using the SyN in ANTs. 14 regions of the brain, inclusive of white matter and grey matter areas were compared across all 4 groups. Female ApoE4TR mice had significantly larger cortical regions than the male ApoE4TR mice. Female ApoE4TRs trended to have larger white matter areas inclusive of anterior commissure, posterior commissure and corpus callosum. Other grey matter areas such as the hippocampus, striatal area and thalamus

also trended to be larger in the female ApoE4TR mice. The diffusion weighted MRI will be used for evaluation of brain microstructure including measures of white matter integrity and connectivity. The results from the study suggested sex differences in regional brain volumes in the ApoE4TR mice. The ongoing analysis of white matter integrity will provide further structural and functional information in understanding the tissue microstructure differences induced by sex or ApoE genotype in the aging brain, and its contribution to AD onset and progression.

Disclosures: R.D. Brinton: None. **L. Do:** None. **A.S. Bernstein:** None. **A. Mishra:** None. **F. Yin:** None. **M.K. Desai:** None. **T.P. Trouard:** None.

Poster

205. Altered Energy Homeostasis in Alzheimer's Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 205.23/H13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Illinois Department of Public Health Grant 83282002F
Center for Alzheimer's Disease and Related Disorders at SIU School of Medicine
Kenneth Stark Endowment
Fraternal Order of Eagles

Title: Soluble β-amyloid$_{42}$ stimulates gender specific hippocampal lactate release in C57BL/6 mice

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Abstract: Alzheimer’s disease (AD) is an age-related neurodegenerative disorder characterized by bioenergetic alterations, neurotransmitter dysfunction, synapse loss, and cerebral atrophy that eventually culminates in cognitive and functional decline. Accumulation of β-amyloid (Aβ)$_{42}$, the neurotoxic species associated with AD, begins decades prior to diagnosis and may precipitate the etiology. For example, we have previously demonstrated that soluble Aβ$_{42}$ elicits hippocampal glutamate release in a dose-dependent manner from male C57BL/6 mice. Since glial glutamate uptake is coupled to lactate release to support neuronal energy demands, we wanted to determine how soluble Aβ$_{42}$ affects hippocampal bioenergetics. To do this, we used an enzyme-based biosensor selective for lactate measurements to monitor extracellular levels in the dentate gyrus (DG), CA3, and CA1 of 3-6 month old male and female C57BL/6 mice. All solutions were prepared in 0.9% saline (pH 7.4) and pressure ejected to deliver consistent volumes of 25-75 nl. Local application of 0.1 μM Aβ$_{42}$ resulted in robust, reproducible lactate release in all three hippocampal subregions of male mice. The average lactate peak amplitude

(mean ± SEM) from 0.1 μM $A\beta_{42}$ (n=3) was elevated compared to 0.9% saline (vehicle control; n=4-5) and 0.1 μM scrambled $A\beta_{42}$ (peptide control; n=3) in the DG (4.9 ± 4.8, -1.3 ± 0.2, and -1.9 ± 0.9 mM, respectively), CA3 (15.7 ± 10.9, -1.6 ± 0.5, and 0.7 ± 0.9 mM, respectively), and CA1 (1.3 ± 0.8, -1.5 ± 0.5, and -0.7 ± 0.6 mM, respectively). Co-application of 0.1 μM $A\beta_{42}$ with 100 μM DL-*threo*-β-Benzyloxyaspartic acid (TBOA; a glutamate transport inhibitor; n=4) inhibited lactate release in the DG (-1.7 ± 0.9 mM), CA3 (-0.5 ± 0.9 mM), and CA1 (-0.6 ± 0.7 mM). Co-application of 0.1 μM $A\beta_{42}$ with 1 mM 2-Cyano-3-(4-hydroxyphenyl)-2-propenoic acid (CHC; a lactate transporter inhibitor; n=3) blocked lactate release in the DG (-1.2 ± 0.9 mM), CA3 (-0.8 ± 0.1 mM), and CA1 (0.1 ± 0.2 mM). In female C57BL/6 mice, lactate release from 0.1 μM $A\beta_{42}$ was only observed in the CA1 (7.0 ± 3.8 mM; n=5) and elevated compared to 0.9% saline (-1.5 ± 0.5 mM; n=6) and 0.1 μM scrambled $A\beta_{42}$ (-0.3 ± 0.6 mM; n=6). Again, co-application of 0.1 μM $A\beta_{42}$ with 100 μM TBOA (-0.5 ± 0.6 mM; n=6) or 1 mM CHC (0.6 ± 0.6 mM; n=5) blocked lactate release in female CA1 C57BL/6 mice. This preliminary data supports that soluble $A\beta_{42}$ alters hippocampal bioenergetics by eliciting glutamate uptake coupled lactate release that varies between genders of C57BL/6 mice. Further dose-response studies are needed to determine that $A\beta_{42}$ elicits glutamate release in the DG and CA3 of female C57BL/6 mice.

Disclosures: K.N. Hascup: None. **N. Esperant-Hilaire:** None. **E.R. Hascup:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.01/H14

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH
ALSA
MDA
F Prime
ALSFAC

Title: Specificity of nuclear pore complex abnormalities in C9orf72 ALS/FTD and Tau AD/FTD

Authors: A. COYNE[1], J. G. DAIGLE[2], B. EFTEKHARZADEH[3], *L. R. HAYES[4], J. CHEW[1], J. C. GLATZER[6], J. D. ROTHSTEIN[5]
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Abstract: Frontotemporal Dementia (FTD) is the second most common form of early onset dementia. Genetically, mutations in the microtubule associated protein Tau and an intronic hexanucleotide G_4C_2 repeat expansion in the C9orf72 gene account for a substantial proportion of FTD cases. Pathologically, FTD is characterized by either the accumulation of hyperphosphorylated Tau FTLD-Tau) or aggregation of the RNA binding protein TDP-43 (FTLD-TDP). Notably, most C9orf72 FTD cases are characterized by pathological TDP-43 inclusions suggesting the mechanisms underlying C9orf72 mediated FTD may be at least in part distinct from Tau mediated FTD. Impaired nucleocytoplasmic transport has recently been linked to multiple neurodegenerative diseases including ALS, HD, and AD. However, the precise mechanisms underlying these deficits in both Tau and C9orf72 mediated FTD remain largely unknown. Given the role of the nuclear pore complex in maintaining proper nucleocytoplasmic transport we hypothesis that nucleoporin alterations may contribute to transport deficits. Here, we use a combination of confocal and super resolution imaging techniques to assess the integrity of the nuclear pore complex and alterations in specific nucleoporins in post mortem tissue, mouse, and iPSC derived cortical neuron models of both C9orf72 and Tau mediated FTD. These experiments shed light on the specificity of nuclear pore abnormalities in disease subtypes and are poised to elucidate novel therapeutic targets for the treatment of specific subsets of patients.

Disclosures: A. Coyne: None. **J.G. Daigle:** None. **B. Eftekharzadeh:** None. **L.R. Hayes:** None. **J. Chew:** None. **J.C. Glatzer:** None. **J.D. Rothstein:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.02/H15

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Modeling of lysosome dysfunction due to progranulin deficiency

Authors: *F. PONTARELLI, J. JOYCE, A. W. DUNAH
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Abstract: Frontotemporal Dementia (FTD) is one of the most common forms of dementia in patients under the age of 65, and there are three major genetic causes of the disease: tau, C9ORF72, and progranulin (PGRN). Throughout their lives, patients that carry PGRN mutations typically express less than half of normal levels of the protein, and FTD-PGRN disease penetrance is 90% by 70 years of age. Initial efforts to characterize the function of progranulin predominantly described the protein as a neuroprotective growth factor that exerts influence over healing, oncogenesis, and inflammation. In a groundbreaking discovery, a small number of patients (N=3) were found to carry homozygous PGRN mutations and presented in their second

decade with the symptoms of a severe lysosomal storage disease, known as neuronal ceroid lipofuscinosis (NCL). Subsequently, the field has pivoted to describe the impact of progranulin on lysosome function. Homozygous and heterozygous PGRN mutation carriers alike have excessive electron-dense lysosomal storage material accumulated in many cell types, including eccrine cells, neurons, and microglia. FTD-PGRN patient lymphoblasts, have also been demonstrated to have NCL-like storage material that can be reduced by virus-based overexpression of PGRN. We have demonstrated that in vitro reduction of PGRN in cells has altered markers of lysosome function similar to what has been demonstrated in PGRN KO animals, NCL and FTD-PGRN patient brains. Ultimately, our goal is to determine if upregulation of PGRN in cells can reduce disease-related phenotypes to better predict the outcome of treating patients.

Disclosures: F. Pontarelli: None. **J. Joyce:** None. **A.W. Dunah:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.03/H16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1F99NS105182-01
NIH Grant 5T32AG020506-13
NIH Grant 5R25GM079300-07

Title: Progranulin-mediated deficiency of cathepsin D results in FTD and NCL-like phenotypes inneurons derived from FTD patients

Authors: *C. B. VALDEZ[1], Y. WONG[1], M. SCHWAKE[1], G. BU[2], Z. WSZOLEK[3], D. KRAINC[1]
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Abstract: Frontotemporal Lobar degeneration (FTLD) encompasses a group of neurodegenerative disorders characterized by cognitive and behavioral impairments. Heterozygous mutations in progranulin (PGRN) cause familial FTLD and result in decreased PGRN expression, while homozygous mutations result in complete loss of PGRN expression and lead to the neurodegenerative lysosomal storage disorder neuronal ceroid lipofuscinosis (NCL). However, how dose-dependent *PGRN* mutations contribute to these two different diseases is not well understood. Using induced pluripotent stem cell-derived cortical neurons from FTLD patients harboring *PGRN* mutations, we demonstrate that *PGRN* mutant neurons exhibit

decreased nuclear TDP-43 and increased insoluble TDP-43, as well as enlarged electron-dense vesicles, lipofuscin accumulation, and fingerprint-like profiles, suggesting that both FTLD and NCL-like pathology are present in FTLD *PGRN* patient neurons as compared to isogenic controls. Additionally, decreased lysosomal proteolysis and activity of the lysosomal enzyme cathepsin D in *PGRN* mutant neurons suggest that *PGRN* mutations may cause impaired lysosomal function. Furthermore, we find that PGRN interacts with cathepsin D, and that PGRN increases the activity of cathepsin D but not cathepsins B or L. Finally, we show that granulin E, a cleavage product of PGRN, is sufficient to increase cathepsin D activity. This functional relationship between PGRN and cathepsin D provides a possible explanation for overlapping NCL-like pathology observed in patients with mutations in PGRN or CTSD, the gene encoding cathepsin D. Together, our work identifies PGRN as an activator of lysosomal cathepsin D activity, and suggests that decreased cathepsin D activity due to loss of PGRN contributes to both FTLD and NCL pathology.

Disclosures: C.B. Valdez: None. **Y. Wong:** None. **M. Schwake:** None. **G. Bu:** None. **Z. Wszolek:** None. **D. Krainc:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.04/H17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Consortium for FTD Research/Bluefield Project to Cure Frontotemporal Dementia
NIH Grant K99AG056597
NIH Grant R01NS075487
NIH Grant P30NS047466

Title: The role of neuronal and microglial progranulin deficiency in FTD- and NCL-like pathology

Authors: *A. E. ARRANT[1], M. Q. HOFFMANN[1], A. R. PATEL[1], E. D. ROBERSON[2]
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Abstract: Loss of function mutations in progranulin (*GRN*) are a major cause of dominantly-inherited frontotemporal dementia (FTD), and individuals homozygous for *GRN* mutations develop a lysosomal storage disorder, neuronal ceroid lipofuscinosis (NCL). In the brain, progranulin is expressed primarily by neurons and microglia. Progranulin exerts neurotrophic effects on neurons, regulates inflammation in microglia, and is thought to maintain normal lysosomal function in both cell types. A major unanswered question in FTD due to *GRN*

mutations is the extent to which loss of progranulin's neurotrophic and anti-inflammatory effects contributes to disease. We and others have reported that mice with selective knockout of neuronal or microglial progranulin recapitulate some, but not all, of the pathology of global *Grn*$^{-/-}$ mice, which develop lipofuscinosis, gliosis, and accumulation of lysosomal proteins that may model the pathology of NCL. In this study, we tested whether knocking progranulin out of both neurons and microglia would recapitulate the pathology of global *Grn*$^{-/-}$ mice. We crossed *Grn*$^{fl/fl}$ mice expressing Cre recombinase under promoters targeting neurons (*CaMKII*, N-KO) and myeloid cells/microglia (*LysM*, Mg-KO) to generate dual neuronal/microglial progranulin knockout mice (D-KO), and assessed the pathological phenotypes of the mice at age 24 months. Cortical progranulin levels were reduced by roughly 50% in N-KO mice and 60% in D-KO mice, though Mg-KO mice did not exhibit a significant reduction in cortical progranulin levels. While knockout of both neuronal and microglial progranulin produced some pathologic abnormalities, the D-KO mice did not exhibit synergistic effects of progranulin knockout from both cell types. Unlike global *Grn*$^{-/-}$ mice, D-KO mice failed to develop lipofuscinosis, the hallmark pathology of NCL. These data show that partial progranulin insufficiency is sufficient to produce some deficits, and indicate that progranulin from other cell types is sufficient to prevent NCL-like pathology in neuronal/microglial progranulin knockout mice.

Disclosures: A.E. Arrant: None. **M.Q. Hoffmann:** None. **A.R. Patel:** None. **E.D. Roberson:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.05/H18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NINDS supported pre-doctoral T32 on Interdisciplinary Training in Movement Disorders and Neurorestoration T32-NS082168
National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR001427
Barbara's Dream Fund for FTD Research and Education
University of Florida, McKnight Brain Institute, and Center for Translation Research in Neurodegenerative Disease

Title: Progranulin deficiency causes early lipofuscinosis and structural abnormalities in the periphery of knockout mice

Authors: *A. WALKER[1], S. RAYAPROLU[3], J. GASS[4], J. HOWARD[1], C. DUFFY[1], L. PETRUCELLI[4], J. LEWIS[2]

[2]Dept Neurosci., [1]Univ. of Florida, Gainesville, FL; [3]Neurosci., UF Col. of Med., Gainesville, FL; [4]Neurosci., Mayo Clin., Jacksonville, FL

Abstract: Lipofuscin is a complex mixture of proteins, lipids, and metals that is autofluorescent and periodic-acid Schiff (PAS) positive. It progressively accumulates in post-mitotic cells with increasing age, making it a reliable marker of cellular aging. Excessive accumulation of lipofuscin in the brain or other organs at an early age is a pathological hallmark of a family of inherited lysosomal storage diseases termed neuronal ceroid lipofuscinosis (NCL). One form of NCL is an adult-onset neuronal ceroid lipofuscinosis-11 (CLN11) caused by homozygous loss-of-function mutations in the granulin gene (*GRN*). CLN11 is characterized by progressive retinal degeneration, seizures, ataxia, cognitive decline, and accumulation of lipofuscin in the skin. *GRN* encodes for the secreted glycoprotein progranulin, which has anti-inflammatory and neuroprotective roles, and functions as a growth factor in the brain. Peripherally, progranulin plays an important role in tissue repair, development, and anti-inflammation. Complete loss of progranulin in the brain leads to lipofuscinosis and inflammation in humans and mice, indicating that progranulin plays a significant role in maintaining brain integrity and successful aging. Published data from progranulin deficient mice at 22 months of age has shown cytological within the liver, however, the extent and progression of lipofuscinosis and other pathologies throughout the periphery has not been explored at the younger ages. Given this, we sought to determine if progranulin deficient mice developed lipofuscinosis and pathologies indicative of accelerated aging in peripheral organs that could potentially serve as biomarkers of disease progression. We assessed the liver, spleen, and kidney from 7 and 12 month old *Grn*-knockout and *Grn*-wildtype mice for structural changes, inflammation, and lipofuscinosis. The knockout livers showed accumulation of PAS-positive inclusions, consistent with lipofuscinosis, and enlarged lysosomes at both ages, while wild-type mice lacked any pathology. The knockout spleens displayed disorganization of the red and white pulp boundaries at both ages compared to wildtype mice, and an abundance of inflated megakaryocytes, which were mainly in the 12-month *Grn*-knockout spleens. Lastly, preliminary data has suggested that the *Grn*-knockout kidneys show possible abnormalities in glomerular morphology and other structures at both ages, while wild-type glomeruli appeared normal. These data demonstrate that there are consequences of progranulin deficiency in organs outside of the brain thus indicative of a more global disease that has not yet been investigated in humans with progranulin loss.

Disclosures: A. Walker: None. **S. Rayaprolu:** None. **J. Gass:** None. **J. Howard:** None. **C. Duffy:** None. **L. Petrucelli:** None. **J. Lewis:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.06/I1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FONDECYT 1181645 (BvZ)
CARE-UC AFB 170005 (BvZ)
NUCLEO UNAB DI-4-17/N (BvZ, LVN)
FONDECYT 1150933 (LVN)

Title: Characterization of epigenetic histone marks in the hippocampus of a mouse model of amyotrophic lateral sclerosis and frontotemporal dementia

Authors: *M. V. GUERRA[1], A. HERRERA-SOTO[1], I. DIAZ[1,2], N. JURY[1,2], B. VAN ZUNDERT[1,2], L. VARELA-NALLAR[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are progressive neurodegenerative diseases. An aberrant hexanucleotide repeat expansion (HRE) in the C9ORF72 gene is linked to both pathologies. Recent studies show aberrant gene expression in ALS astrocytes, which may involve epigenetic dysregulation that has been evidenced in different neurodegenerative diseases. Epigenetic modifications regulate gene expression via chromatin remodeling without affecting the DNA sequence. Here we investigated if critical histone post-translational modifications (HPTMs) are altered in neurons and astrocytes in the hippocampus of the C9ORF72-HRE transgenic mouse model of ALS/FTD. HPTMs can either activate or repress genes depending on the residues being modified. Brain tissues obtained from 6 and 9 month-old C9ORF72-HRE mice were analyzed by immunofluorescence staining with specific antibodies that detect repressive and active HPTMs. Nucblue was used to visualize heterochromatin distribution, and NeuN and GFAP staining were used to identify neurons and astrocytes, respectively. A strong reduction in the number and intensity of foci immunoreactive for repressive HPTMs was found in neurons and astrocytes in the hippocampal regions CA1, CA3 and dentate gyrus of transgenic ALS/FTD mice compared with age-matched wild-type mice. No differences were found for DNA staining or activation histone marks between transgenic and wild-type mice. These results suggest that loss of epigenetic control contributes to pathogenesis and disease development in ALS and FTD. Currently, the expression of histone modification enzymes, which can be considered as potential therapeutic targets, is being tested in the brain of C9ORF72-HRE mice.

Disclosures: M.V. Guerra: None. **A. Herrera-Soto:** None. **I. Diaz:** None. **N. Jury:** None. **B. van Zundert:** None. **L. Varela-Nallar:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.07/I2

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: AG-017586
AG-010124

Title: Gene expression profile and comparative pathway analysis in FTLD-TDP and FTLD-tau pathological cases

Authors: E. SUH[1], S. PROKOP[1], K. R. MILLER[2], E. B. LEE[1], J. Q. TROJANOWSKI[1], *V. M. VAN DEERLIN[1]
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Abstract: Frontotemporal Lobar Degeneration (FTLD) is a group of complex neurodegenerative diseases which comprise two major proteinopathies characterized most commonly by protein inclusions of TDP-43 (FTLD-TDP) and tau (FTLD-tau). FTLD-TDP and FTLD-tau present clinically as a heterogeneous spectrum of phenotypes with progressive changes in behavior, language, and cognition. Behavioral variant frontotemporal degeneration (bvFTD) is the most of frequent clinical phenotype and has a range of underlying neuropathology commonly associated with tauopathies or TDP-43 proteinopathies. While some FTLD-tau cases carry mutations in the gene of the microtubule associated protein tau (*MAPT*), FTLD-TDP is associated with mutations in multiple genes including *C9orf72*, *GRN*, *TBK1*, and others. Despite the molecular links with genetics, the pathological processes in FTLD, and its heterogeneous clinical phenotypes are not well elucidated. The aims of this study were to investigate the gene expression signatures and pathways that underlie the neuropathological process in cases with mutations resulting in FTLD-TDP or FTLD-tau neuropathologic changes. To this end, we selected normal control subjects with no significant clinical or neuropathological changes and FTLD cases with pathogenic mutations in genes such as *C9orf72* (FTLD-TDP-C9orf72), *GRN* (FTLD-TDP-GRN), or *MAPT* (FTLD-tau-MAPT*)* and total RNA was obtained from formalin fixed paraffin embedded (FFPE) hippocampus sections with 30-50% neuronal loss. Using the Nanostring nCounter Neuropathology gene expression panel, we assessed expression profiles of 760 genes and 23 pathways and processes associated with neurodegenerative diseases and compared mutation specific changes among the mutation groups and normal controls. The analysis revealed that the FTLD-TDP-GRN and the FTLD-tau-MAPT hippocampi showed significant downregulation of genes involved in a number of pathways such as autophagy, oxidative stress, vesicle trafficking,

axon and dendrite structure, and activated microglia scores, whereas the FTLD-TDP-C9orf72 hippocampi did not, suggesting that distinct molecular mechanisms lead to the TDP-43 pathology observed in cases with C9orf72 repeat expansion. In conclusion, our findings demonstrated mutation specific changes in gene expression signatures and pathways in FTLD cases with mutations in *GRN*, *MAPT*, or *C9orf72*, among which *MAPT* presented most differences compared with normal controls.

Disclosures: E. Suh: None. **S. Prokop:** None. **K.R. Miller:** A. Employment/Salary (full or part-time):; Nanostring Technologies. **E.B. Lee:** None. **J.Q. Trojanowski:** None. **V.M. Van Deerlin:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.08/I3

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant R01AG054025
NIH Grant R01NS094557

Title: TDP-43 and tau oligomer interactions in ad pathology

Authors: *S. A. MCALLEN, A. ELLSWORTH, N. BHATT, M. MONTALBANO, U. SENGUPTA, R. KAYED
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Abstract: TDP-43 is a protein that binds to both DNA and RNA and is present mostly in the nucleus of the cell. This protein is required in many cell functions such as microRNA biogenesis and RNA splicing. In neurons, TDP-43 has a much more critical role in synaptic plasticity and axonal transport. The neurodegenerative diseases of frontotemporal dementia (FTLD-TDP) and amyotrophic lateral sclerosis (ALS) are characterized by cytoplasmic inclusion bodies of ubiquitinated and hyperphosphorylated TDP-43 aggregates. Moreover, recent studies demonstrated the presence of TDP-43 pathology in Alzheimer’s disease (AD) and other tauopathies. The role of TDP-43 aggregation in AD and its interactions with other proteins, especially its interactions with the main pathological amyloidogenic proteins Aβ and Tau, is still unclear. The goal of this study is to investigate and characterize TDP-43 oligomers in AD and their direct interactions with Tau oligomers. We demonstrate that both TDP-43 and Tau form toxic oligomers in AD. Based on these results and studies demonstrating the regulation of tau by other RNA binding proteins (RBPs), we are further investigating the interactions of TDP-43 and Tau in AD and other tauopathies. We also look to determine the formation of highly toxic hybrid

oligomers, their effects on cellular clearance mechanisms, and the aggregation profile on both TDP-43 and Tau. Determining the interactions between TDP-43 and Tau could lead to a better understanding of the role of these proteins in AD pathology and drug development.

Disclosures: S.A. McAllen: None. **A. Ellsworth:** None. **N. Bhatt:** None. **M. Montalbano:** None. **U. Sengupta:** None. **R. Kayed:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.09/I4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Aberrant interaction between FUS and SFPQ in the nucleus of neurons in sporadic FTLD/ALS and PSP brains

Authors: *Y. FUJIOKA[1], S. ISHIGAKI[1], Y. RIKU[1,3], M. ISHIBASHI[2], S. YOKOI[1], K. ENDO[1], N. IWADE[1], K. KAWAI[1], H. WATANABE[1], M. KATSUNO[1], M. YOSHIDA[3], G. SOBUE[2]
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Abstract: Fused in sarcoma (FUS) is an RNA binding protein which is genetically and pathologically linked to frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). We have reported that FUS and SFPQ regulate alternative splicing of *Mapt* gene at exon10 which generates two pathogenic isoforms of neural microtubule-associated protein tau (Tau) protein. Silencing of FUS or SFPQ in mice resulted in the increased ratio of 4-repeat tau (4R-tau)/ 3-repeat tau (3R-tau) followed by FTLD-like behavioral impairments, accumulation of phosphorylated tau, and neuronal loss. To clarify the functional role of FUS/SFPQ in sporadic FTLD/ALS and progressive supranuclear palsy (PSP) cases, the interaction between FUS and SFPQ in postmortem autopsied brains was investigated (FTLD/ALS: n = 14, PSP: n = 20, Control: n = 17). The immunohistochemical analysis revealed that the intra-nuclear co-localization of FUS and SFPQ was significantly reduced in FTLD/ALS and PSP compared to controls. The co-localization level of FUS and SFPQ was negatively correlated with age in control cases. However, there was no correlation between the co-localization level and age in FTLD/ALS and PSP cases. Immunoprecipitation analysis using postmortem frozen brain tissues showed reduced interactions between FUS and SFPQ in the brains of FTLD/ALS and PSP patients compared to control cases. Our findings suggest that altered interaction between FUS/SFPQ is involved in the pathogenesis of FTLD/ALS and 4R-tauopathies.

Disclosures: Y. Fujioka: None. **S. Ishigaki:** None. **Y. Riku:** None. **M. Ishibashi:** None. **S. Yokoi:** None. **K. Endo:** None. **N. Iwade:** None. **K. Kawai:** None. **H. Watanabe:** None. **M. Katsuno:** None. **M. Yoshida:** None. **G. Sobue:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.10/I5

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: Brain/MINDS

Title: Silencing of FUS in the caudate nucleus of non-human primates induces disruption of its fiber bundles

Authors: *K. ENDO[1], S. ISHIGAKI[1], N. HATANAKA[3], J. HATA[4], H. WATANABE[1], M. KATSUNO[1], A. NAMBU[3], H. OKANO[5], G. SOBUE[2]
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Abstract: [Objective] Frontotemporal lobar degeneration (FTLD) is one of the devastating dementia syndromes characterized by abnormal social cognitions and behaviors. Volume loss of the caudate nucleus and decreased size of its fiber bundles were observed in early FTLD patients, suggesting that structural change of the caudate nucleus could be an early pathological event of FTLD. FUS, an RNA binding protein, has been identified as a causative molecule, which is dislocated from the nucleus to the cytoplasm in the affected neurons of FTLD. We aimed to clarify whether FUS-silencing in the caudate nucleus affects neuronal networks and/or brain structure and to establish a non-human primate model of FTLD. [Methods] The AAV vector encoding shRNA against FUS (AAV-shFUS) was stereotaxically injected into the caudate nucleus of two adult female marmosets, while AAV vector encoding control shRNA (AAV-Cont) was injected into the contralateral side. At 6 or 10 weeks post-injection, the brain was removed after euthanasia. An ex-vivo 9.4 T magnetic resonance imaging (MRI) study was performed followed by immunohistochemical examination. [Results] Global tractography using 3 shell data (b=1000, b=3000, and b=5000) revealed the reduced size of fiber bundles from the caudate nucleus in the AAV-shFUS injection side compared to the AAV-Cont injection side (mean length 8.51 mm vs. 9.96 mm; $p < 0.0001$). Immunohistochemical examination validated that approximately 80 % of endogenous FUS was downregulated accompanied with marked glial inflammation in the AAV-shFUS injected cortex and caudate nucleus. [Conclusions] Our results

indicated that caudate-specific FUS silencing in marmoset recapitulates structural changes observed in FTLD patients. Further investigation is necessary to determine whether the higher behavioral and cognitive functions are affected as well.

Disclosures: K. Endo: None. **S. Ishigaki:** None. **N. Hatanaka:** None. **J. Hata:** None. **H. Watanabe:** None. **M. Katsuno:** None. **A. Nambu:** None. **H. Okano:** None. **G. Sobue:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.11/I6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Whole exome sequencing (WES) of DNA from a patient with disinhibition, stereotypy and frontolobar degeneration reveals a rare but deleterious SNP in MAPT gene associated with frontotemporal dementia (FTD)

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Abstract: FTD is a significant clinical problem affecting a younger (age 40-65) population and often masquerading as a treatment resistant psychiatric disorder such as depression or psychosis. It is highly heritable and mutations in microtubule associated protein tau (*MAPT*), progranulin (*PGRN*) and chromosome 9 open reading frame 72 (*C90rf72*) expansion mutations have been found in familial FTD. It has been proposed that clinical presentations and treatment responsivity of FTD patients vary depending on variant genes present (Young et al., 2017). Thus, *MAPT* mutation carriers tend to deteriorate when treated with ACh inhibitors and it has been suggested that *PGRN* mutation effects could be mitigated by small molecule drugs (De Muynck and Van Damme, 2015). To further explore the genotype-phenotype association, we performed WES of DNA extracted from a blood sample from a proband, a 56 year old Chinese female, with previously well characterized behavioral FTD (bvFTD) syndrome (Pospos et al. 2018), and her symptom-free son, 33. The Ethic's Committee of Xijing Hospital approved the study. SureSelect Human All Exon V6 64M (Agilent) was used to capture target DNA and HiSeq X Ten System (Illumina) was used for sequencing. Paired-end alignment to the 1000 genomes hg19/GRCh37 reference genome was performed using BWA ALN. SAM files were sorted, converted to BAM, and duplicates were marked with Picard. GATK was used for local realignment and base quality score recalibration, variants were called jointly in all samples using the GATK's HaplotypeCaller in the "GENOTYPE_GIVEN_ALLELES" mode. PROVEAN, SIFT, PolyPhen2 HDIV, PolyPhen2 HVAR, MutationTaster, M-CAP and REVEL were used to predict

deleteriousness of amino acid changes. MaxEntScan was used for splicing defect prediction. Data showed a rare (MAF=0.014, *China Thousand Human Genomes*) missense single nucleotide variant c.689(exon6)A>G in *MAPT* gene resulting in amino acid change (p.Q230R), which was deleterious by several predictors. Patient's son had no pathogenic *MAPT* variants. Our findings elucidate genotype-phenotype association in bvFTD and lend support to clinical applications of advanced technologies such as Next Generation Sequencing to improve diagnostic accuracy and minimize unnecessary investigations and treatments.

Disclosures: M. Xi: None. **R. Zhang:** None. **H. Wang:** None. **Y. Cai:** None. **A. Baskys:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.12/I7

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Tau pathology, type 2 diabetes, and serum/glucocorticoid regulated kinase 1 (SGK1) in tauopathy mice

Authors: *M. ELAHI[1,2], Y. MOTOI[2], N. HATTORI[2]
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Abstract: Background: Type 2 diabetes mellitus (T2DM) is one of the risk factors for Alzheimer's disease (AD), however, the molecular mechanism remains poorly defined. T2DM animal model showed an increased level of glucocorticoids and tau phosphorylation in the brain and SGK1 can be activated by glucocorticoids or by impairment in insulin signaling pathway. SGK1 is a member of the Ser/Thr protein kinase that has been reported to be involved in tau phosphorylation at Ser214. In this report, we examined the effects of T2DM on AD using in vivo and in vitro tauopathy model focusing SGK1.
Methods: 10-month-old tauopathy model mice, Tg601 (overexpressing 2N4R human tau) and non-transgenic mice were fed with high fat diet (HFD, 35% fat) for 5 months (N = 14, respectively). The glucose tolerance test (IPGTT), and intraperitoneal insulin tolerance test (ITT) were conducted at 12 months. The Morris water maze test (MWM) and elevated plus maze test (EPM) were performed at 15 months prior to sacrifice. Brain protein levels of tau phosphorylation, AKT/pAKT, PI3K, GSK-3β, CDK5 and PP2A were measured using the western blotting. The expression and activation of SGK1 were evaluated by both at RNA and protein level. Stable wild-type 2N4R tau expressing SH-SY5Y cells were treated with palmitic acid-BSA conjugate to assess the SGK1 induction by in vitro insulin resistance. To analyze the function of SGK1, siRNA mediated sgk1 down regulation and SGK1 overexpression were

analyzed using the same cell line.
Results: HFD-treated mice demonstrated longer escape latency in the MWM, and spent shorter time than non-treated mice in the EPM. HFD-fed mice showed impaired insulin resistance with increased phosphorylation of AKT (Ser473), high amount of sarkosyl insoluble and oligomeric tau, and impaired microtubule (MT) polymerization. Tau pathology in HFD mice were characterized by increase in tau phosphorylation at Ser214 and a five-fold increase in SGK1 expression and activation (phosphorylation at Thr256), while there was no difference in the protein level of phosphor-S9 GSK-3β, Cdk5 and PP2A. In vitro study with palmitic acid-BSA-treated stable tau cell lines showed impaired insulin resistance by impaired AKT phosphorylation and increase in Ser214 tau phosphorylation,SGK1 expression and activation. SGK1 specific siRNA treatment into stable tau cells decreased tau phosphorylation at Ser214 and SGK1 overexpression elevated pSer214-tau.
Conclusion: Our findings indicated that SGK1 might be involved in tau phosphorylation at Ser214 leading to the development of T2DM mediated AD.

Disclosures: M. Elahi: None. **Y. Motoi:** None. **N. Hattori:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.13/I8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant AG051556

Title: Cognitive and biochemical abnormalities in diabetic mice are age and sex dependent

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Abstract: Numerous studies report an association of type 2 diabetes (diabetes) with late onset Alzheimer’s disease and vascular dementia. Diabetes is a risk factor for small vessel cerebrovascular disease, a core feature of vascular cognitive impairment. We modeled and evaluated these human conditions in mice by comparing microvascular resting flow, peak microvascular responses to post-occlusive reactive hyperemia (PORH), behavior, synaptic plasticity, and histopathology in leptin knockout (db/db, diabetes) and normoglycemic

db/heterozygous mice (controls). Six groups of mice (males and females) were analyzed: db/db mice at young-adult age (3-5 m.o.), old age (10-12 m.o.), db/db mice treated for 5 months with metformin and their controls. Behavioral analysis was conducted with two hippocampal dependent tasks, active place avoidance (APA) and novel object recognition (NOR). The conflict variant of APA assay assesses cognitive flexibility (APA conflict) by challenging mice to learn the location of a new shock zone that is opposite to its initial location. APA conflict evaluates prefrontal cortex-ventral hippocampus functional integrity. Young diabetic mice had normal APA and NOR values at baseline as compared to control mice. However, we observed deficits in old age in db/db mice compared to controls; APA was measured by averaging the number of times mice entered the shock zone across all eight trials. Speed of movement and total path length were also compared across groups. ANOVA shows ($F_{(4)}$=4,69; p=0.031) and a genotype X sex interaction $F_{(4)}$=5.2; p=0.022). The effect at old age of db/db mice was observed mainly in female mice. The cognitive deficits in db/db metformin treated mice were less pronounced than non-treated diabetics. Immunohistochemistry analyses of neuronal integrity, glia activation, the endothelium and amyloid angiopathy, p-tau, and beta-amyloid pathologies demonstrated differences in several markers in db/db mice, but also mainly observed at old age. Microvascular flow was evaluated with a Laser Speckle Contrast Imaging (LCSI) system in combination with transient occlusion of common carotid artery and continuous measurement of changes in laser speckle cortical microvascular perfusion units (LSPU) coupled with PORH. These measurements and electrophysiological profiles of the CA3-CA1 synapsis are being performed at the time of this submission and a detailed analysis will be shown at the final presentation of this abstract.

Disclosures: D. Cepeda: None. **V. Escobar:** None. **D. Gonzalez:** None. **L. Buitrago:** None. **J. Li:** None. **F. Barone:** None. **A.M. Brickman:** None. **J.A. Luchsinger:** None. **H.W. Moreno:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.14/I9

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIRG-15-363477 (DBV)
AARF-16-44060 (SF)
MNIRGD-15-363229
2013-A-016-FEL (DBV)
2016-A-016-FEL (ACM)
NIH/NIA AG027544 (FML)
AG00538 (FML and CWC)

Title: Role of tau on synaptic and cognitive deficits in type 1 and type 2 diabetes mellitus

Authors: *L. TRUJILLO-ESTRADA[1,2], C. NGUYEN[1,2], R. KUANG[1,2], C. DA CUNHA[1,2], S. FORNER[1,2], A. C. MARTINI[1,2], R. AGER[1,2], A. PRIETO[1], C. W. COTMAN[1,2], D. BAGLIETTO-VARGAS[1,2], F. LAFERLA[1,2]
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Abstract: Diabetes mellitus (DM) is one of the most devastating diseases that currently affect the aging population. Important evidences indicate that this metabolic disorder is a risk factor for many brain disorders and significantly affect cognition leading to dementia. New findings have shown that the microtubule associated protein tau is pathologically processed in DM, however, it remains unknown whether pathological tau modifications plays a central role in the cognitive deficits associated with DM. In this study, we hypothesized that alterations in the protein tau represent a pathological mechanism by which DM induces synaptic/cognitive impairments. Previous work from our lab has demonstrated that reducing tau levels mitigates memory/synaptic deficits in T1DM-like mice, suggesting that T1DM requires of tau to induce the deficits. Herein, we sought to further investigate whether tau is an important component for the synaptic/memory dysfunction associated with T1DM and to determine if tau is also required for T2DM to impair cognition. We have used two diabetic models: (1) for T1DM we administrate streptozotocin (STZ) in our wild type htau mice and (2) for T2DM-like condition we crossed our htau mice and tauKO mice with db/db mice, a diabetic model. We observed that T1DM causes cognitive and synaptic deficits by tau-dependent mechanisms as only the deficits are detected in htau mice under STZ treatment. However, for T2DM, tau does not exacerbate the cognitive/synaptic impairment (as introduction of htau in db/db mice does not exacerbate the deficits and the ablation of tau does not recover it) and we propose that inflammation may play a main role. Our results show that tau has a differential effect in the cognitive/synaptic deficits in T1DM and T2DM. While T1DM induces tau-dependent deficits, in T2DM these deficits are not associated to tau. These novel findings show for the first time that different molecular mechanisms underlying the cognitive and synaptic impairments associated with T1DM and T2DM.

Disclosures: L. Trujillo-Estrada: None. **C. Nguyen:** None. **R. Kuang:** None. **C. Da Cunha:** None. **S. Forner:** None. **A.C. Martini:** None. **R. Ager:** None. **A. Prieto:** None. **C.W. Cotman:** None. **D. Baglietto-Vargas:** None. **F. LaFerla:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.15/I10

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: France Alzheimer
Vaincre alzheimer
Inserm
Université Lille
LabEx (excellence laboratory)
DISTALZ (Development of Innovative Strategies for a Transdisciplinary approach to ALZheimer's disease)
Région Hauts-de-France

Title: Brain insulin sensitivity and peripheral metabolic changesin tau transgenic mice

Authors: *E. FAIVRE[1], A. LEBOUCHER[1], T. AHMED[2], E. CARON[1], A. TAILLEUX[3], S. RAISON[4], A. JOLY-AMADO[5], E. MARCINIAK[1], K. CARVALHO[1], M. HAMDAME[1], K. BANTUBUNGI[3], S. LANCEL[3], S. EDDARKAOUI[1], R. CAILLIEREZ[1], E. VALLEZ[3], B. STAELS[3], D. VIEAU[1], D. BALSCHUN[2], L. BUÉE[1], D. BLUM[1]
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Abstract: Accumulation of hyper-phosphorylated and aggregated Tau protein is a neuropathological hallmark of Alzheimer's Disease (AD) and Tauopathies. AD patient brains' exhibit insulin resistance (Talbot et al., 2012). Whereas, under normal physiological conditions insulin signaling in the brain mediates plasticity and memory formation, it can also regulate peripheral energy homeostasis (Gratuze, Joly-Amado et al., 2018 for review). Thus, brain insulin resistance, in AD, affects both cognitive and metabolic changes described in these patients. While a role of Aβ and APOE4 towards the development of brain insulin resistance emerged, contribution of Tau pathology was largely overlooked. Our recent data (Marciniak et al., 2017) demonstrated that one of the physiological function of Tau is to sustain brain insulin signaling. We postulated that under pathological conditions, hyper-phosphorylated/aggregated Tau is likely to lose this function and to favor the development of brain insulin resistance. This hypothesis was substantiated by observations from patient brains with pure Tauopathies (Yarchoan et al., 2014). To address the potential link between Tau pathology and brain insulin resistance, we have evaluated the brain response to insulin in a transgenic mouse model of AD-like Tau pathology (THY-Tau22). This murine model overexpresses mutated human Tau under the control of a neuronal promoter and mice progressively develop hippocampal Tau pathology and cognitive deficits. Using electrophysiological and biochemical evaluations, we observed that at a time when Tau pathology and cognitive deficits were overt and obvious, the hippocampus of THY-Tau22 mice exhibited enhanced response to insulin. In addition, we demonstrated that the ability of i.c.v. insulin to promote body weight loss was enhanced in THY-Tau22 mice. In line with this, THY-Tau22 mice exhibited a lower body weight gain, hypoleptinemia and hypoinsulinemia and finally a metabolic resistance to High Fat Diet. Collectively, these data indicate that the

development of Tau pathology in THY-Tau22 mice does not associate with brain insulin resistance but rather enhanced brain response to the hormone. These data open the debate on the relationship between Tau pathology and brain insulin resistance but also point a possible bias regarding the use of transgenic mouse models that overexpress Tau.

Disclosures: A. Leboucher: None. **T. Ahmed:** None. **E. Caron:** None. **A. Tailleux:** None. **S. Raison:** None. **A. Joly-Amado:** None. **E. Marciniak:** None. **K. Carvalho:** None. **M. Hamdame:** None. **K. Bantubungi:** None. **S. Lancel:** None. **S. Eddarkaoui:** None. **R. Caillierez:** None. **E. Vallez:** None. **B. Staels:** None. **D. Vieau:** None. **D. Balschun:** None. **L. Buée:** None. **D. Blum:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.16/I11

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Fatty acid damages astrocytes and induced diabetes encephalopathy

Authors: *X. WANG, F. MA
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Abstract: Diabetes might cause central nervous system lesions and functional changes including loss of learning and memory abilities as well as brain structure and function changes, namely diabetes encephalopathy (DE), which is a risk factor to induce Alzheimer's disease. We used KK-Ay mice and showed typical high glucose, high fat and high insulin symptoms with learning and memory dysfunction from 3 to7 month old. Compared with control group (C57BL / 6J mice), till 7 months KKay mice showed no obvious loss in cortex and hippocampus neurons, and no obvious damage of cell. However, at 5 and 7 month astrocytes in cortex and hippocampal of KK-Ay mice were significantly damaged. In the cell based studies we found that high glucose (till 35mM) treatment had no obvious damage effect on neurons, but 35mM glucose could significantly reduce the cell activity of astrocytes, especially astrocytes were sensitive to sodium palmitate (PA). The activity of astrocytes decreased markedly even at the low concentration of PA. Further, we investigated the mechanisms of PA induced damage of astrocytes. We found that the transporter CD36 played an important role in palmitic acid-induced apoptosis of astrocytes. The protein expression of CD36 in astrocyte was 5 fold as it expressed in neurons. Therefore, CD36 played a key role in the process of PA uptake by astrocytes. CD36 inhibitor SSO reduced the uptake of palmitate, as the results it also inhibited the generation of ROS and the calcium overload. SSO showed significant protective effects on PA-induced cell death of astrocytes. In conclusion, fatty acid induced injury of astrocyte might be an important cause of

DE. CD36 mediates the translocation of PA into astrocytes, which leads to damage and cell apoptosis. CD36 located on astrocytes might be the target to prevent dementia induced by diabetes.

Disclosures: X. Wang: None. **F. Ma:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.17/I12

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: SBRC Foundation Grant 7069
Alzheimer Society of Canada

Title: Secreted amyloid precursor protein alpha as a therapeutic for diabetic encephalopathy

Authors: *Y. HUANG[1,2], B. D. AULSTON[2], G. L. ODERO[2], G. W. GLAZNER[2,1]
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Abstract: Secreted amyloid precursor protein alpha (sAPPα) is produced by the cleavage of full length amyloid precursor protein (APP). A designated sAPPα receptor has yet to be discovered, but there is evidence that sAPPα protein is an insulin receptor agonist which can modulate the neuronal AKT-mediated neurotrophic insulin pathway. When phosphorylated, AKT protects the call by inhibiting GSK3 kinase and phosphorylation of tau. Hyperphosphorylation of tau causes aggregation, creating neurofibrillary tangles that predisposes the brain to neurodegeneration. The ability for sAPPα to be effective in the absence of insulin (type 1 diabetes) was tested by comparing diabetic transgenic sAPPα overexpressing mice to diabetic wildtype mice. Mice were rendered diabetic via injection of streptozotocin to reduce the beta cells in the pancreas. After 16 weeks post injection, cortical tissue was collected and western blots were completed to observe levels of AKT, GSK3 and pTau. Decreased levels of pAKT, GSK3, and pTau were detected in the transgenic diabetic in comparison to wildtype diabetic animals. This indicates that sAPPα can ameliorate the effects of insulin loss in the brain, and is a potential therapeutic for diseases that involve tau hyperphosphorylation.

Disclosures: Y. Huang: None. **B.D. Aulston:** None. **G.L. Odero:** None. **G.W. Glazner:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.18/I13

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Extensive white matter changes and brainstem calcification in an autopsy case of bilateral striopallidodentate calcinosis (Fahr's syndrome)

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Abstract: Bilateral striopallidodentate calcinosis, also known as Fahr's syndrome, is a rare but well-known neurological disorder characterized by extensive symmetrical brain calcification, specifically in the basal ganglia and cerebellar dentate nuclei. Fahr's disease referes to familial idiopathic calcification of the basal ganglia. Fahr's syndrome is sometimes used to encompass both Fahr's disease and basal ganglia calcification secondary to other disorders. In most cases, brain calcification is detected by computed tomography; thus white matter changes and the brainstem calcification have not been described well. In this study, we investigated the exact distribution and extent of the calcifications, and their impact on the brain tissue. Brain and spinal cord from an autopsied 85-year-old patient of Alzheimer's disease with Fahr's syndrome were neuropathologically investigated. Computed tomography revealed symmetrical extensive intracranial calcification and severe cerebral atrophy, however, brainstem calcification was not detected. The formalin-fixed paraffin-embedded sections stained with hematoxylin-eosin, Klüver-Barrera, Dahl, von Kossa, Berlin blue and immunostainings for β-amyloid, phosphorylated tau and α-synuclein were used. Alzheimer's disease pathology and massive vascular calcification in the basal ganglia and dentate nuclei of the cerebellum were found. In addition, we clarified extensive white matter changes and brainstem calcification. The vascular calcification continuously spread over the surrounding white matter and occasionally into the cortex (the depths of cerebral cortical sulci and cerebellar folia). The distribution of vascular calcification in the white matter was very similar to the area of attenuated myelin staining. Vascular calcification in the brainstem was found in the medulla and pontine tegmentum. Calcified capillaries were frequently observed in the red nucleus. Neuronal loss in the substantia nigra without α-synuclein pathology was found. We should recognize extensive white matter changes associated with the continuity of the areas of vascular calcification and brainstem calcification as a cause of neuropsychiatric symptoms in Fahr's syndrome.

Disclosures: T. Iwase: None. **M. Yoshida:** None. **I. Yazawa:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.19/I14

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: NIH Grant R01 AG054456-02

Title: The effects of aquaporin-4 mislocalization on tau accumulation

Authors: *M. SMITH, J. J. ILIFF
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Abstract: Tauopathies such as Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD) are neurodegenerative disorders associated with the aggregation of hyper-phosphorylated tau (p-tau). Recent experimental studies suggest that tau aggregates propagate along neural pathways, accounting for the stereotypical neuroanatomical spread of pathology that is a feature of tauopathies. The cause for tau accumulation is currently unknown, however studies suggest that the perivascular localization of the astroglial water channel aquaporin-4 (AQP4) supports the clearance of interstitial tau along the glymphatic pathway. In the present study, we tested whether loss of perivascular AQP4 localization promotes the development of tau pathology in the P301S (PS19) mouse line. The P301S line was crossed with a line harboring deletion of the AQP4-interacting alpha syntrophin gene (*Snta1-/-* mice) which lack perivascular AQP4 localization and exhibit impaired glymphatic pathway function. Immunofluorescence demonstrated that perivascular AQP4 localization is reduced between 12 to 36 weeks of age, and is further reduced in the presence of the P301S transgene. Immunofluorescence using the AT8 p-tau-specific antibody demonstrated to effect of *Snta1* gene deletion on cortical or hippocampal p-tau immunoreactivity at 12, 24 or 36 weeks of age. Western blot using the AT8 antibody demonstrated no difference in soluble or insoluble AT8 levels. In the Morris water maze, *Snta1* gene deletion did not alter cognitive function beyond the impairment observed in the P301S animals. These data demonstrate that loss of perivascular AQP4 localization does not alter the rate of tau aggregation or neurocognitive decline in the P301S transgenic mouse line. Whether the loss of perivascular AQP4 localization alters the rate of tau aggregate propagation remains unknown.

Disclosures: M. Smith: None. **J.J. Iliff:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.20/I15

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: Innovation Fund Denmark Industrial Post Doc Grant

Title: The importance of the glymphatic system in the migration of therapeutic monoclonal antibodies

Authors: *P. C. CHRISTENSEN[1,2,3], M. NEDERGAARD[3], J. T. PEDERSEN[2]
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Abstract: The glymphatic system is a functional waste clearance pathway for the mammalian CNS (Jessen et al., 2015) where CSF from the subarachnoid space exchanges with the ISF throughout the brain via paravascular influx (Iliff et al., 2012) facilitating the efficient clearance of pathologically relevant macromolecules (e.g. Aβ and tau) from the brain interstitium (Iliff et al., 2012, 2014). Immunotherapy has become a successful treatment outside the CNS, however, mAbs for CNS disorders faces as the BBB hinder large molecules like antibodies to enter the brain (Banks, 2010). The intention of mAb therapy in neurodegenerative diseases is for the drug to enter the CNS at a relevant concentration and "mop up" abnormal pathological thus preventing ongoing propagation of pathology.
First, we evaluate the glymphatic system in naïve and transgenic mice (rtg4510 mice) modeling tau pathology in Alzheimer's disease (AD) by injecting a fluorescent tracer into the CSF followed by histology and fluorescent imaging. Second, we investigate the impact of the BBB on mAb penetration in the brain by comparing levels of mAb bound to target (abnormal tau) administered either via the cisterna magna or intravenously. Therapeutic mAbs are injected into the CSF or intravenously in naïve and rtg4510 mice and the penetration of mAbs is temporally and anatomically mapped using histology and fluorescent imaging. Thirdly, we investigate clearance over the BBB by examining the pharmacokinetic after administration of mAbs via cisterna magna and intravenously, by temporally measuring plasma levels of mAbs by LC-MS and ELISA.
Failure to fully understand and address BBB and clearance issues could be underlying factors for clinical trials not meting clinical endpoints (Abbott and Dolgin, 2016; Le Couteur et al., 2016). CNS immunotherapy may simply fail if the drugs never reach their intended target at sufficient

concentrations. If drug delivery over the BBB becomes successful, many failed drugs may get second chances.

Disclosures: P.C. Christensen: A. Employment/Salary (full or part-time):; H.Lundbeck A/S. 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.; H. Lundbeck A/S. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); H. Lundbeck A/S. **M. Nedergaard:** None. **J.T. Pedersen:** A. Employment/Salary (full or part-time):; H.Lundbeck A/S. 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.; H. Lundbeck A/S. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); H. Lundbeck A/S. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); H.Lundbeck A/S.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.21/DP05/I16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: EPSRC Grant EP/N034864/1

Title: Pharmacological blockade of aquaporin-4 inhibits glymphatic flow and clearance of tau from the mouse brain

Authors: *I. F. HARRISON, O. ISMAIL, Y. OHENE, P. NAHAVANDI, J. A. WELLS, M. F. LYTHGOE
Univ. Col. London, London, United Kingdom

Abstract: Introduction The glymphatic clearance system is a brain-wide pathway for removal of waste solutes, which depends upon the presence of aquaporin-4 (AQP4) channels, on the endfeet of paravascular astrocytes in the brain. Glymphatic function has been shown to be impaired in mouse models of Alzheimer’s disease (AD), and both amyloid-β and tau have been shown to be cleared from the brain via this system. Until now however, it is unknown whether the glymphatic pathway presents as a suitable drug target. Here we demonstrate that a novel AQP4 inhibitor, suppresses glymphatic function and clearance of tau from the brain, suggesting that pharmacological manipulation of AQP4 function may present as a novel drug target for the treatment AD. **Materials and Methods** Mice were treated with either AQP4 inhibitor (TGN-

020) or vehicle 15mins prior to either, 1) quantification of glymphatic inflow via dynamic contrast-enhanced MRI (intracisternal administration of MRI contrast agent (Gd-DTPA) and concurrent acquisition of whole brain T1-weighted MR images), or 2) assessment of parenchymal tau clearance (intracerebral infusion of tau-containing brain homogenate and subsequent cerebrospinal fluid collection). **Results** Glymphatic inflow of Gd-DTPA into the parenchyma was significantly ablated after TGN-020. Furthermore, intrastriatal infusion of tau-containing brain homogenate revealed that TGN-020 treatment significantly reduced tau clearance from the brain. Comparable TGN-020 induced inhibition of parenchymal inflow of MR contrast agent, and clearance of tau from the brain were observed, suggestive that TGN-020 inhibits arterial and venous associated AQP4 equally. **Conclusions** Pharmacological blockade of AQP4 suppresses both glymphatic inflow of MR contrast agent, into the brain, and clearance of tau from the brain, via inhibition of arterial and venous associated AQP4 channels respectively. These findings suggest that pharmacological manipulation of AQP4 alters the function of the glymphatic clearance pathway in its removal of tau from the brain, positioning AQP4 as a novel drug target for the treatment of AD.

Disclosures: I.F. Harrison: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly and Company. **O. Ismail:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly and Company. **Y. Ohene:** None. **P. Nahavandi:** None. **J.A. Wells:** None. **M.F. Lythgoe:** 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.; Eli Lilly and Company. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly and Company.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.22/I17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CGL2015-71498-P

Title: Neurodegeneration in dolphins and whales: Newcomparative naturalmodels?

Authors: *S. SACCHINI[1], A. ESPINOSA DE LOS MONTEROS[1], J. DÍAZ-DELGADO[2], Y. PAZ[1], Y. BERNALDO DE QUIRÓS[1], A. FERNÁNDEZ[1]
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Abstract: Spontaneous animal models of AD should possess 2 histopathological hallmarks: beta-amyloid (Aβ) deposition and neurofibrillary tangles (NFT) formation. However, no natural animal models that fulfill these conditions have been reported and most research into Alzheimer's disease (AD) has been performed using transgenic rodents. The order Cetacea comprises two extant suborders: Mysticeti (or baleen whales) and Odontoceti (or toothed whales). Cetacea, along with manatees (Sirenia), are the only mammals that are fully adapted to life in water. Cetaceans are homeotherms, long-lived top predators, which are at high risk from bioaccumulation and biomagnification of a variety of organic and metallic pollutants. Neuronal intranuclear Aβ immunopositivity, senile plaques in the frontal cortex, and NFT granulovacuolar degeneration in the Purkinje neurons of the cerebellum were the most striking observed hallmarks.On the other side, a recent study on the morphology of the *locus coeruleus* (LC) complex of the family *Delphinidae* (Sacchini, et al., 2018) highlighted for the first time, the existence of a large amount of neuromelanin (NM) within the LC neurons.The NM accumulates over a lifetime and has been described mainly in human brain, but also in neurons of monkey, horse, giraffe, cattle, sheep, goat, dog, rat, and even frog. While in most of the mammals, the NM shows the histochemical and ultrastructural features typical of lipofuscins, in the human brain, melanin is confined within cytoplasmatic organelles that are surrounded by a double membrane, suggesting an autophagic origin. Transmission electron microscopy demonstrated in two toothed whales, the existence of melanin granules associated with lipid droplets and membranes, something very near to human NM. Finally, in view of the often observed polyglucosan-like bodies in the cetacean brain, mainly in NM-containing neurons, two antibodies against alpha-synuclein were used in order to investigate the possible existence of Lewy bodies, the hallmark of Parkinson’ s disease. Some immunoreactivity has been observed and all these findings may answer the question: may cetacean be a new comparative, Spontaneous, natural model for NDDs? In addition, dolphins and whales may also show atypical hallmarks of neurodegeneration.

Disclosures: A. Espinosa de los Monteros: None. **J. Díaz-Delgado:** None. **Y. Paz:** None. **Y. Bernaldo de Quirós:** None. **A. Fernández:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.23/J1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH GRANT 1R01AG053060-01A1
VA GRANT 1I01 BX002478-01A1
NIH GRANT 5R01NS073899-07

FLORIDA DEPARTMENT OF HEALTH GRANT 5AZ07

Title: Critical validation of reagents in CHCHD10 and CHCHD2 research

Authors: *C. L. TROTTER[1,2], T. LIU[1,2], X. ZHAO[1,2], C. FANG[1,2], J. WOO[1,2], D. KANG[1,3]
[1]Univ. of South Florida, Tampa, FL; [2]Byrd Alzheimers Inst., Tampa, FL; [3]Byrd Alzheimers Inst., Tampa, DC

Abstract: Immunochemical techniques are a cornerstone of neuroscience research. Their reliability is completely dependent on the specificity and reproducibility of the antibodies used. It is well known that antibodies and other reagents such as interfering RNAs commonly exhibit cross-reactivity. However, validation of reagents has yet to become standard practice in many labs. This is suspected to be a major contributor to lack of reproducibility in the field. Here we provide data on the specificity of commercially available antibodies and shRNAs targeting two highly similar mitochondrial proteins of approximately equal size, coiled-coil-helix-coiled-coil-helix domain containing proteins 10 and 2 (CHCHD10 and CHCHD2). These proteins are implicated in amyotrophic lateral sclerosis / frontotemporal dementia and Parkinson's disease, respectively. Despite increased risk of cross-reactivity due to their similarity, many recent publications regarding these proteins have failed to provide evidence on the specificity of reagents used. Our data indicate that many CHCHD10 antibodies used in the field also detect high levels of CHCHD2 and vice versa. Furthermore, we show that in rodents, the CHCHD2 sequence is duplicated and fused with a neighboring gene, Zinc-finger BED type-containing 5 (ZBED5), resulting in a fusion protein whose N-terminus contains most of the amino acid sequence of CHCHD2. This greatly complicates the interpretation of data which were obtained by using CHCHD2 RNA interference or immunostaining in rodents or rodent-derived cell lines. Taken together, our data highlight the importance of reagent testing and validation in CHCHD10/CHCHD2 research as well as neuroscience research in general.

Disclosures: C.L. Trotter: None. **T. Liu:** None. **X. Zhao:** None. **C. Fang:** None. **J. Woo:** None. **D. Kang:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.24/J2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UH2NS100606

Title: Identifying novel fluid and imaging biomarkers for small-vessel disease-mediated vascular cognitive impairment and dementia (VCID)

Authors: *T. L. SUDDUTH, O. M. AL-JANABI[1], A. A. BAHRANI[2], C. D. SMITH[2], Q. CHENG[2], B. T. GOLD[2], G. A. JICHA[2], D. M. WILCOCK[2]
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Abstract: Vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia and often occurs co-morbidly with Alzheimer's disease (AD). VCID is also the most common co-morbidity with AD pathology in the late-onset sporadic AD population. Currently, diagnosis for VCID is limited to clinical signs of cognitive impairment along with white matter disease identified on MRI imaging. As novel therapeutics are developed aimed at disease modification, there is an emerging need for biomarkers to accurately identify the patient population that will benefit from the therapies. As part of the MarkVCID Consortium, we have been exploring novel fluid and imaging biomarkers that may be predictive of VCID in a clinical cohort enriched for individuals with high cerebrovascular disease.
In a cohort of 115 individuals with longitudinal clinical, cognitive, and MRI volumetric white-matter hyperintensities from MR FLAIR sequences, we examined 29 proteins in the CSF and plasma. These proteins ranged from vascular injury responses, angiogenesis mediators, neuroinflammation, and matrix remodeling proteins. The MSD V-PLEX assays were used and the assays included four individual samples that were replicated on every plate to attain our coefficient of variance (CV). Our CV ranged from 5-20%, depending on the individual protein. The data was analyzed using standard machine learning approaches with AdaBoost and Random Forest being applied for feature selection. We identified a collection of 7 features that predicted cognitive impairment in our VCID cohort with an 86% accuracy. These features include angiogenic and inflammatory proteins from CSF and plasma. We also have three features that provide a 50% predictive value for white matter hyperintensity volume, and we are actively working to further enhance this.
In summary, we have identified a series of novel fluid biomarkers that are predictive, in a machine learning model, of severity of VCID.

Disclosures: T.L. Sudduth: None. **O.M. Al-Janabi:** None. **A.A. Bahrani:** None. **C.D. Smith:** None. **Q. Cheng:** None. **B.T. Gold:** None. **G.A. Jicha:** None. **D.M. Wilcock:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.25/J3

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Title: Evaluation of an innovative inhibitor of tau toxicity and aggregation in pre-clinical models of fronto- temporal dementia

Authors: *L. FIORITI, A. LEVINE, L. COLNAGHI
Plico Biotech Inc, New York, NY

Abstract: Plico Biotech is developing first in class biotherapeutics (Plico Biotherapeutics: PLBs) to inhibit the toxicity of proteins such as tau, alpha-synuclein, SOD1 and HTT. PLBs target toxic proteins inside of cells and are designed to be extremely stable while emulating ubiquitin-like proteins that participate in a natural process of proteostasis inside cells. Our **lead candidate, PLB002**, has showed *in vitro* good inhibitory properties against the toxicity of tau and other proteins that cause neurodegeneration. PLB002 is active at very low concentration, with an IC50 in the nanomolar range. Once administered to mice (intravenous, intranasal, intraperitoneal) PLB002 readily reaches the brain at a therapeutic concentration and improves the behavior performance in an AD/FTD clinical murine model, the transgenic TauP301L mutant strain (Lewis et al., 2000).

Disclosures: A. Levine: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Plico Biotech Inc. **L. Colnaghi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Plico Biotech Inc.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.26/J4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH
Packard Center for ALS Research

Title: Determining whether splicing repression is a major function of TDP-43 in forebrain neurons

Authors: *X. WEN, B. PANG, A. N. DONDE, J. P. LING, P. REDDY, H. WU, P. C. WONG
Pathology, Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Nuclear depletion of Tar DNA-binding protein 43 (TDP-43), an RNA binding protein which represses aberrant splicing, may underlie neuron loss in neurodegenerative disease associated with TDP-43 pathology, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). As multiple functions are ascribed to TDP-43, its major role(s)

in forebrain neurons, cells that are impacted in these human diseases remains elusive.
To test the hypothesis that splicing repression is a major function of TDP-43 in forebrain neurons, we take advantage of a previously characterized chimeric splicing repressor termed CTR (comprised of the N-terminal RNA-recognition domain of TDP-43 fused with an unrelated but well-known splicing repressor, RAVER1) for its ability to rescue neurodegeneration occurring in a mouse model lacking TDP-43 in forebrain neurons.
Employing an AAV9 viral vector approach to deliver CTR or GFP by intracerebroventricular injection at postnatal day 0 into our previously described conditional Tdp-43 knockout (CaMKIIα-CreER;Tdp-43F/F) mice, we showed expression of CTR ranged from 30 - 72% of the hippocampal neurons in CA1 and CA2/3 areas. Expression of CTR, but not GPF, restored TDP-43 mediated splicing repression as judged by cryptic exon incorporation using semi-quantitative RT-PCR [AAV9-CTR (n=3) vs. AAV9-GFP (n=3) treated CaMKIIα-CreER;Tdp-43F/F mice; $p < 0.01$] or RNA *in situ* hybridization (via the "Basescope" method) analysis of a TDP-43 downstream target RNA, *Synaptojanin 2 Binding Protein (Synj2bp)* [AAV9-CTR (n=3) vs. AAV9-GFP (n=2) treated CaMKIIα-CreER;Tdp-43F/F mice; $p < 0.05$].
Since we previously showed that neurons in CA2/3, but not CA1 area, were more vulnerable to depletion of Tdp-43 in CaMKIIα-CreER;Tdp-43F/F mice, we assessed in these mice the ability of CTR to rescue CA2/3 neuron loss. We will present data to determine whether the AAV9-CTR, but not AAV9-GFP, treated CaMKIIα-CreER;Tdp-43F/F mice would ameliorate loss of CA2/3 neurons.
Thus, positive outcomes from these studies will support the idea that TDP-43 mediated splicing repression is a major function of TDP-43 in forebrain neurons and identify a novel mechanism-based therapeutic target for neurodegenerative disease exhibiting TDP-43 pathology.

Disclosures: X. Wen: None. **B. Pang:** None. **A.N. Donde:** None. **J.P. Ling:** None. **P. Reddy:** None. **H. Wu:** None. **P.C. Wong:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.27/J5

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: MOST 104-0210-01-09-02
MOST 105-0210-01-13-01
MOST 106-0210-01-15-02

Title: Characterization of the effects of adenosine augmentation compound (J4) on AD mouse models of amyloidogenesis (APP/PS1) and tauopathy (THY-Tau22)

Authors: *C.-P. CHANG[1], C.-C. LEE[1], Y.-G. CHANG[1], S.-J. CHENG[2], H.-M. CHEN[1], L. BUEE[3], D. BLUM[3], J.-M. FANG[4], Y. CHERN[1]
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Abstract: Alzheimer's disease (AD) is the most common progressive neurological disease characterized by two main pathological hallmarks (extracellular β-amyloid deposits and intracellular neurofibrillary tangles), which lead to cerebral dystrophy and cognitive decline in aging population. Adenosine is a neuromodulator involved in multiple fundamental physiological functions in the CNS. Dysfunction of adenosine homeostasis in the brain has been observed in various neurological disorders (including AD; and Huntington's disease, HD). In the present study, we assessed whether adenosine tone augmentation by chronic treatment with the an inhibitor (J4) of a nucleoside transporter (ENT1) is of valuable therapeutic interest in the context of AD-like amyloid pathology and tauopathy using AD mouse models of amyloidogenesis (APP/PS1) and tauopathy (THY-Tau22), respectively. Here, we demonstrated that chronic treatment with J4 improved the detrimental phenotypes of both APP/PS1 and THY-Tau22 mice. Using *in vivo* (Morris water maze) and *in vitro* (electrophysiology and biochemical analyses) approaches, we further showed that adenosine augmentation ameliorated 1) spatial memory deficiency, 2) synaptic plasticity impairment, 3) upsurge astrocytic $A_{2A}R$, 4) accumulations of β-amyloid and hyperphosphorylated Tau, and 5) abnormal kinase activities in the hippocampus of APP/PS1 and THY-Tau22 mice. Collectively, adenosine tone augmentation is beneficial to AD and may pave the way for the development of a novel therapeutic treatment for AD.

Disclosures: C. Chang: None. **C. Lee:** None. **Y. Chang:** None. **S. Cheng:** None. **H. Chen:** None. **L. Buee:** None. **D. Blum:** None. **J. Fang:** None. **Y. Chern:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.28/J6

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: Université de Lille (AAP Internationalisation)
Fondation pour la Recherche Médicale (SPF20160936000)
LabEx DISTALZ
Région Hauts de France (PARTENAIRR COGNADORA)
ANR ADORATAU

Title: Adenosine A_{2A} receptor dysregulation in Alzheimer's disease impact of astrocytic A_{2A}R upsurge in a mouse mode of tauopathy

Authors: *V. GOMEZ MURCIA[1], E. FAIVRE[1], K. CARVALHO[1], J. COELHO[2], L. CELLAI[1], C. MERIAUX[1], M. DUMOULIN[1], D. TAILLEU[1], D. VIEAU[1], M. HAMDANE[1], L. BUÉE[1], L. V. LOPES[2], D. BLUM[1]
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Abstract: Neuronal accumulation of hyperphosphorylated and aggregated Tau proteins is correlated with cognitive decline in Alzheimer's disease but mechanisms underlying Tau-induced memory deficits remain unclear. Previous epidemiological and experimental studies pointed out that chronic caffeine consumption reduces AD risk and associated cognitive deficits. These protective effects were ascribed to the blockade of adenosine A2A receptors (A2ARs), which are found upregulated in the brain of AD patient's brains in correlation with Tau pathology development and cognitive deficits. These post-mortem observations suggest a link between A2AR dysregulation, Tau pathology and memory in AD. Both neuronal and astroglial A2AR appear to be dysregulated in AD. To get insights towards this relationship, we aimed at evaluating the pathophysiological impact of neuronal (see abstract from Kevin Carvalho, this meeting) and astrocytic (this abstract) A2AR upsurge in a transgenic model of AD-like Tauopathy (THY-Tau22 mice) To address the role of astrocytic upsurge, we have developed a conditional model (Tet-Off) allowing A2AR overexpression in GFAP-positive astrocytes. This model was crossed with THY-Tau22 mice, who develop a progressive hippocampal Tau pathology associated with cognitive decline. In the different groups of animals, we evaluated Tau pathological changes (phosphorylation, aggregation) and functional impairments (learning and memory) at 5-6 months of age, when pathology is expressed but not maximal in the THY-Tau22 model. We found that astrocytic A2AR overexpression worsens spatial memory impairments of THY-Tau22 mice. These effects were associated to an increased of Tau phosphorylation and aggregation as well as to the upregulation of hippocampal neuroinflammatory processes induced by Tau pathology. Altogether, these data suggest that neuronal A2AR dysregulation seen in the brain of AD patients contributes to the development of Tau-induced cognitive impairments by modulating Tau pathology and neuroinflammation.

Disclosures: V. Gomez Murcia: None. **E. Faivre:** None. **K. Carvalho:** None. **J. Coelho:** None. **L. Cellai:** None. **C. Meriaux:** None. **M. Dumoulin:** None. **D. Tailleu:** None. **D. Vieau:** None. **M. Hamdane:** None. **L. Buée:** None. **L. V. Lopes:** None. **D. Blum:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.29/J7

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: ANR ADORATAU, Région Hauts de France (PARTENAIRR COGNADORA)
LabEx DISTALZ
Université de Lille (AAP Internationalisation)
Fondation pour la Recherche Médicale (SPF20160936000)

Title: Adenosine A_{2A} receptor dysregulation in Alzheimer's disease: Impact of neuronal A_{2A} receptor upsurge in a mouse model of tauopathy

Authors: *K. CARVALHO[1], E. FAIVRE[1], V. GOMEZ-MURCIA[1], J. E. COELHO[2], L. CELLAI[1], C. MERIAUX[1], A. DELEAU[1], S. EDDARKAOUI[1], S. LE GRAS[3], M. DUMOULIN[4], S. BÉGARD[1], D. TAILLIEU[4], D. VIEAU[1], M. HAMDANE[1], L. BUEE[1], A.-L. BOUTILLIER[5], L. V. LOPES[2], D. BLUM[1]
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Abstract: Neuronal accumulation of hyperphosphorylated and aggregated Tau proteins is correlated with cognitive decline in Alzheimer’s disease but mechanisms underlying Tau-induced memory deficits remain unclear. Previous epidemiological and experimental studies pointed out that chronic caffeine consumption reduces AD risk and associated cognitive deficits. These protective effects were ascribed to the blockade of adenosine A_{2A} receptors (A_{2A}Rs), which are found upregulated in the brain of AD patient’s brains in correlation with Tau pathology development and cognitive deficits. These post-mortem observations suggest a link between A_{2A}R dysregulation, Tau pathology and memory in AD. Both neuronal and astroglial A_{2A}R appear to be dysregulated in AD. To get insights towards this relationship, we aimed at evaluating the pathophysiological impact of neuronal (this abstract) and astrocytic (see abstract from Victoria Gomez-Murcia, this meeting) A_{2A}R upsurge in a transgenic model of AD-like Tauopathy (THY-Tau22 mice) To address the role of neuronal upsurge, we have developed a conditional model (Tet-Off) allowing A_{2A}R overexpression in CAMKII-positive neurons. This model was crossed with THY-Tau22 mice, who develop a progressive hippocampal Tau pathology associated with cognitive decline. In the different groups of animals, we evaluated Tau pathological changes (phosphorylation, aggregation) and functional impairments (learning and

memory) at 5-6 months of age, when pathology is expressed but not maximal in the THY-Tau22 model. We found that neuronal $A_{2A}R$ overexpression worsens spatial memory impairments of Tau transgenic mice. This detrimental effect was associated with an increased tau phosphorylation at some epitopes, a decreased expression of the Brain-Derived Neurotrophic Factor (BDNF) and an altered NMDA receptor phosphorylation. Interestingly, following RNA sequencing, we uncovered that neuronal $A_{2A}R$ overexpression in Tau mice led to a significant altered hippocampal gene expression mostly ascribed to microglial cell function, underlying a functional link between neuronal A_{2A} dysregulation and microglia in a Tau pathology context. Altogether, these data suggest that neuronal $A_{2A}R$ dysregulation seen in the brain of AD patients contributes to the development of Tau-induced cognitive impairments by modulating the interplay between neurons and glial cells.

Disclosures: E. Faivre: None. **V. Gomez-Murcia:** None. **J.E. Coelho:** None. **L. Cellai:** None. **C. Meriaux:** None. **A. Deleau:** None. **S. Eddarkaoui:** None. **S. Le Gras:** None. **M. Dumoulin:** None. **S. Bégard:** None. **D. Taillieu:** None. **D. Vieau:** None. **M. Hamdane:** None. **L. Buee:** None. **A. Boutillier:** None. **L.V. Lopes:** None. **D. Blum:** None.

Poster

206. Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 206.30/J8

Topic: C.05. Tauopathies, Tau-dementias, and Prion diseases

Support: France Alzheimer
Vaincre alzheimer
Inserm
Université de Lille
LabEx (excellence laboratory) DISTALZ (Development of Innovative Strategies for a Transdisciplinary approach to ALZheimer’s disease)
Région Hauts-de-France
DN2M

Title: Characterization of two new humanized tau knock-in models

Authors: *D. BLUM, S. EDDARKAOUI, T. BOSCHETTI, L. DURIEUX, H. BENDERRADJI, C. MACHALA, E. FAIVRE, K. CARVALHO, A. BOGDANOVA, S. BEGARD, L. MORANT, S. HALLIEZ, M.-L. CAILLET-BOUDIN, N. SERGEANT, L. BUEE, V. BUEE-SCHERRER
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Abstract: Tau proteins are missorted, aggregated, and found as Tau inclusions in many pathological conditions associated with neurodegenerative disorders, which are collectively known as tauopathies. In some of them, mutations on *MAPT* gene that encodes isoforms of Tau proteins have been shown to promote Tau aggregation, decrease its affinity for microtubules or modify alternative splicing. Tau mis-splicing can also occur in Tauopathies in the absence of *MAPT* mutations. Most mouse models of Tauopathies are based on transgenic mouse models overexpressing a single isoform of WT or mutated human Tau. On one side, with regards to the recognized role of Tau in different neuronal functions, these models underestimate a presumable impact of Tau overexpression on the mouse phenotype; and on the other side, these models do not allow the precise study of human Tau splicing *in vivo*. In order to get new insights into the study of human Tauopathies, using animal closely mimicking the pathophysiological context, we have recently generated two original knock-in mouse models (KI), by inserting the transgene into the *Mapt* murine locus. In these KI models, Tau transgene expression is under the control of the endogenous murine promoter. Two lines have been created 1) the TauKI-V5 model which consists in the insertion of a human Tau cDNA (1N4R) bearing a mutation (P301L) and a V5 tag and 2) the Tau-MG model which consists in the insertion of a human Tau minigene coding for the constitutive and two alternatively spliced exons (2 and 10) including flanking intronic regions responsible for their alternative splicing. In both models, transgene expressions were validated at the mRNA and protein levels, and mostly found in the central nervous system, but also, as expected, in some peripheral organs such as heart and muscle. Molecular and biochemical characterization of both models are ongoing and results will be presented.

Disclosures: D. Blum: None. **S. Eddarkaoui:** None. **T. Boschetti:** None. **L. Durieux:** None. **H. Benderradji:** None. **C. Machala:** None. **E. Faivre:** None. **K. Carvalho:** None. **A. Bogdanova:** None. **S. Begard:** None. **L. Morant:** None. **S. Halliez:** None. **M. Caillet-Boudin:** None. **N. Sergeant:** None. **L. Buee:** None. **V. Buee-Scherrer:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.01/J9

Topic: C.03. Parkinson’s Disease

Support: NSFC 81371256
NSFC 81171061
NSFC 81361128012

Title: Properties of oscillatory neuronal activity in the basal ganglia and thalamus in patients with Parkinson’s disease

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Abstract: Objective: To characterize the firing rate and pattern of oscillatory neurons in the basal ganglia and motor thalamus in patients with Parkinson's disease (PD). Methods: Twenty-nine patients with PD undergoing stereotactic neurosurgery were studied. Microelectrode recordings in the subthalamic nucleus (STN, n=16), the globus pallidus internus (GPi, n=9) and the ventral oral posterior/ventral intermediate nucleus of thalamus (the Vop/Vim, n=9) were performed. Electromyography (EMG) of the contralateral limbs was simultaneously recorded. Single unit analysis and measurements of interspike intervals (ISI) were carried out. Spectral analysis and coherence analysis were assessed to study oscillatory neurons in relation to limb muscle activity. Mean spontaneous firing rate (MSFR) of oscillatory neurons were calculated. Analysis of variance (ANOVA) and X^2 test were performed. Results: Of 76 STN neurons, 39.5% were tremor frequency band neurons (TFB) and 28.9% were β frequency band neurons (βFB). The MSFR was 44.2 ± 7.6 Hz. Of 62 GPi neurons, 37.1% were TFB neurons and 27.4% were βFB neurons. The MSFR was 80.9 ± 9.6 Hz. Of 44 Vop neurons, 65.9% were TFB neurons and 9.1% were βFB neurons. The MSFR was 24.4 ± 4.2 Hz. Of 30 Vim oscillatory neurons, 70.0% were TFB neurons and 13.3% were βFB neurons. The MSFR was 30.3 ±3.6 Hz. Further comparison indicated that proportion of βFB oscillatory neurons in the STN and GPi was significantly higher than that of similar neurons in the Vop and Vim of thalamus ($P<0.05$). Conversely, the proportion of TFB neurons and tremor related neurons in Vim and Vop was significant higher than that of STN and GPi ($P<0.05$). ANOVA indicated significant differences of MSFR of oscillatory neurons in four nuclei. The highest MSFR was GPi oscillatory neurons whereas the lowest MSFR was Vop oscillatory neurons ($P<0.05$). Conclusion: The altered firing rate and pattern of oscillatory neurons in basal ganglia structures play a critical important role in generation of parkinsonian motor symptoms, and findings here are generally in support of the "classic model" of basal ganglia dysfunction in PD. β oscillatory activity, thought to be antikinetic, is more prominent in the basal ganglia than in the thalamus suggesting that the oscillation most likely result from dopaminergic depletion. While both basal ganglia and thalamus have tremor activity, the thalamus appears to play a more important role in tremor production, basal ganglia β oscillatory activity might be the trigger.

Disclosures: P. Zhuang: None. **M. Hallett:** None. **G. Du:** None. **Y. Zhang:** None. **Y. Li:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.02/J10

Topic: C.03. Parkinson's Disease

Support: Swedish Research Council
Parkinson Fonden
G.S hold a position partially founded by the Karolinska Institutet

Title: NMDA receptors in the substantia nigra pars reticulata

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Abstract: The substantia nigra pars reticulata (SNr) is involved in movement and action control. This brain region is the main output of the basal ganglia, providing GABAergic projection to thalamic and brainstem regions. The SNr receives glutamatergic innervation primarily from the subthalamic nucleus (STN). In Parkinson's disease, neurons in SNr and STN are hyperactive and their firing pattern is altered. The exact mechanisms responsible for this modified activity are still incompletely identified, but might involve an altered NMDA receptor (NMDAR) function. This type of glutamate receptor plays key roles in synaptic transmission and long-term synaptic plasticity. In the SNr, NMDARs contribute to induction of long-term depression. Given that the subunit composition of the NMDAR is critical for its biophysical, pharmacological and signaling properties, we sought to investigate the composition of synaptic NMDARs in GABAergic SNr neurons. We measured evoked NMDAR-mediated excitatory postsynaptic currents (NMDA-EPSCs) in SNr neurons recorded in brain slices from male C57/BL6 control mice (aged 7-10 weeks). To identify the contribution of GluN2A to synaptic NMDARs we bath applied the GluN2A antagonist TCN-201 (10 µM). This antagonist decreased the amplitude of NMDA-EPSCs (to 67.01±4.42 of baseline) only in a subset of recorded neurons (n = 5/10). The GluN2B antagonist Ro 25-6981 (1 µM) induced a robust decrease of the NMDA-EPSCs (to 61.07±4.8 % of baseline) in the majority of recorded neurons (n = 17/18). The GluN2D antagonist DQP-1105(20 µM) decreased the NMDA-EPSCs only in a subset of recorded neurons (to 63.98±3.8 % of baseline in n =9/16 neurons tested). Altogether, our results demonstrate that two distinct populations of GABAergic neurons in the SNr have different NMDARs: one with GluN2B/GluN2A and the other with GluN2B/GluN2D. Our ongoing work investigates the possible contribution of tri-heteromeric NMDARs in the SNr GABAergic neurons and evaluates the subunit composition of NMDARs in these neurons in mouse models of Parkinson's disease.

Disclosures: G. Sitzia: None. **K. Chergui:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.03/J11

Topic: C.03. Parkinson's Disease

Support: Min. San. RF-2013-02356215
Cariplo Foundation 2014-0660
PRIN2015FNWP34
Umberto Veronesi Foundation Post-doctoral Fellowship 2015

Title: GluN2D-containing NMDA receptors are involved in the pathophysiology of levodopa-induced dyskinesias

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Abstract: The central role of dopamine (DA) in Parkinson's disease (PD) and levodopa-induced dyskinesias (LIDs) is clear. However, increasing work support the involvement of other neurotransmitter systems. Indeed, DA depletion and prolonged treatment with levodopa lead to adaptive changes in the glutamatergic transmission from the cortex to the striatum, resulting in the aberrant localization and function of striatal glutamate receptors. An emerging concept is that cell-type and subunit specific alterations of NMDA receptors (NMDARs) in the striatum may differently contribute to the pathological events underlying PD and LIDs. While previous work investigated modifications of GluN2A- and GluN2B-NMDARs in spiny projection neurons, GluN2D-NMDAR, a less represented subtype mainly expressed by striatal cholinergic interneurons, has gained researchers' interest. This work aims at characterizing the role of GluN2D-NMDARs in the synaptic changes in PD and after chronic treatment with levodopa. To this, the 6-hydroxydopamine rat model of PD was used to reproduce degeneration of the nigrostriatal pathway. Then, parkinsonian animals were chronically treated with levodopa. An array of biochemical, immunohistochemical and pharmacological tools were applied. Our results indicate that GluN2D-NMDARs synaptic localization is augmented in the striatum of dyskinetic rats compared to parkinsonian and control animals. This event is associated to a dramatic increase in GluN2D binding to PSD-95. Importantly, treatment with a selective GluN2D antagonist can ameliorate the severity of established dyskinesias. Our findings confirm the involvement of GluN2D-NMDARs in LIDs. In the search for novel approaches that go beyond DA replacement therapy, different NMDAR subtypes may represent effective therapeutic candidates for LIDs.

Disclosures: M. Mellone: None. **E. Zianni:** None. **J. Stanic:** None. **A. Longhi:** None. **M. Thiolat:** None. **Q. Li:** None. **E. Bezard:** None. **M. Di Luca:** None. **F. Gardoni:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.04/J12

Topic: C.03. Parkinson's Disease

Support: Lundbeck Foundation R248-2016-2518
Michael J Fox foundation
Aarhus University
Dandrite

Title: Detection and quantification of alpha-synuclein aggregates in models of synucleinopathies and human pathological tissue by aggregate-specific antibodies

Authors: *C. BETZER[1], S. ELFARRASH[1], L. LASSEN[1], E. GREGERSEN[1], R. KOFOED[1], Y. FU[2], G. HALLIDAY[2], P. JENSEN[1]
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Abstract: Deposition of aggregated alpha-synuclein in cytoplasmic inclusions e.g. Lewy bodies is a characteristic hallmark for neurodegenerative disorders as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. The inclusions are likely to develop over a long period, perhaps decades and during this period, different soluble neurotoxic aggregates are hypothesized to exist. Detection and quantification of these soluble aggregates is not trivial, but slowly techniques are emerging. We present two novel methods based on the commercially available antibody MJF14-6-4-2 that specifically bind aggregated alpha-synuclein.
The alpha-synuclein oligomer ELISA allows detection and quantitative comparison of alpha-synuclein oligomers in *in vivo* and *in vitro* experiments, including alpha-synuclein transgenic cell lines and human alpha-synuclein transgenic mouse models. Moreover, we present a MJF14-6-4-2 proximity ligation assay that allows site specific detection and semi-quantitative evaluation of alpha-synuclein aggregates in alpha-synuclein overexpressing cells, animal models overexpressing human alpha-synuclein, and human pathological brain tissue. These techniques holds potential of quantifying the potential effects of therapeutic interventions in different models.

Disclosures: C. Betzer: None. **S. Elfarrash:** None. **L. Lassen:** None. **E. Gregersen:** None. **R. Kofoed:** None. **Y. Fu:** None. **G. Halliday:** None. **P. Jensen:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.05/J13

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS078247
NIH Grant NS088206
NIH Grant ES026892

Title: Tweak promotes NLRP3 inflammasome activation via PKC delta and mitochondria dependent oxidative stress mechanisms in astrocytes

Authors: *A. KANTHASAMY, C. GOMEZ-ESTRADA, V. LAWANA, H. JIN, V. ANANTHARAM, A. G. KANTHASAMY
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Abstract: Impairment in mitochondrial function and heightened oxidative stress dependent inflammatory response have been linked to PD pathogenesis. However, the triggers for mitochondrial dysfunction remain poorly characterized. Therefore, targeting proteins that regulate mitochondrial function could lead to the discovery of novel therapeutics for PD. We recently identified that Protein Kinase C delta (PKCδ), a redox sensitive kinase, may be involved in the microglial activation response following exposure to Parkinsonian toxins. In the current study we examined the mitochondrial function of PKCδ and its involvement in NLRP3 inflamamsome activation using a Tumor Necrosis Factor-(TNF) like weak inducer of apoptosis (TWEAK)-induced neuroinflammation cell culture model. We show that TWEAK stimulation of U373 astrocytic cells induces a time dependent increase in ROS generation, mitochondrially derived ROS, collapse of mitochondrial membrane potential (MMP) and PKCδ activation. These effects were accompanied by the upregulation of NLRP3 inflammasome and the resulting increase in the secretion of IL-1β and IL-18, proinflammatory cytokines. Notably, down regulation of PKCδ by siRNA-mediated gene silencing attenuated TWEAK-induced NLRP3 inflammasome activation via amelioration of mitochondrial dysfunction. Likewise, a mitochondrial targeted antioxidant, mitoapocynin, attenuated mitochondrial impairment with a concomitant suppression of NLRP3 inflammasome activation in a PKCδ dependent manner. Our study suggests that activation of PKCδ via mitochondrial oxidative stress dependent mechanisms might serve as a critical determinant of NLRP3 inflammasome activation in TWEAK treated cells. Taken together, our studies suggest that manipulating PKCδ activation may represent a novel therapeutic strategy in PD.

Disclosures: A. Kanthasamy: None. **C. Gomez-Estrada:** None. **V. Lawana:** None. **H. Jin:** None. **V. Anantharam:** None. **A.G. Kanthasamy:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.06/J14

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS R37 NS067525-09

Title: The role of ISP1 in PAR-dependent cell death (parthanatos) and regulation

Authors: *S.-C. CHOU[1], T.-I. KAM[3], H. PARK[2], Y. WANG[4], T. M. DAWSON[5], V. L. DAWSON[6]
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Abstract: Abstract
Parthanatos is a Poly (ADP-ribose) (PAR)-dependent cell death mechanism that is involved in many neurological disorders including Parkinson's disease (PD) and stroke. Iduna/RNF146 is a first-in-class PAR-dependent ubiquitin E3-ligase. Iduna prevents parthanatos. However, the underlying mechanism is largely unknown. To begin to understand the mechanism of how Iduna attenuates parthanatos, we screened a comprehensive human protein chip containing approximately 17,000 proteins for proteins that were ubquitinated by Iduna. We found 79 proteins that are potential PAR-dependent Iduna substrates from the protein chip array. This was followed by screening these Iduna substrates for their ability to prevent parthanatic cell death using specific siRNAs to the 79 proteins. We identified 6 proteins including Iduna Substrate Protein 1 (ISP1) that prevent parthanatos. We are currently characterizing IPS1's role in parthanatos. ISP1 is a PAR binding protein that is ubiquitinated by Iduna and degraded by the proteasome in a PAR-dependent manner. Mutation on specific residues of ISP1 lead to loss of PAR binding and disrupt ubiquitination by Iduna. Expression of ISP1 is increased following treatment with the DNA damaging agent, MNNG. Knockout of ISP1 substantially reduces MMNG-induced parthanatos. Studies are ongoing to understand the mechanism accounting for ISP1's role in parthanatos in cell-based and primary neuron-based models.

Disclosures: S. Chou: None. **T. Kam:** None. **H. Park:** None. **Y. Wang:** None. **T.M. Dawson:** None. **V.L. Dawson:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.07/K1

Topic: C.03. Parkinson's Disease

Title: Quantitative study of electrical activities in subthalamic nucleus neuron: Role of MDMA as a modulator in Parkinson's disease

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Abstract: As the emergence of abnormal burst discharge in subthalamic nucleus (STN) cells is a pathological hallmark of the Parkinson's disease. Here our goal is to study the effect of 3,4-Methylene-dioxy-*N*-methylamphetamine (MDMA, 'ecstasy') at the level of abnormal bursting patterns in a computational model of STN cell with proper validation. The nine ionic currents are incorporated in terms of maximal conductances and voltage-dependent activation/inactivation gating variables. Synaptic events (MDMA) is formalized with an instantaneous rise of the synaptic conductance $g_{syn}(t)$ from 0 to maximum value at time t_0 followed by an exponential decay. The STN cell fires spontaneous action potentials (AP) in the single spike mode with a resting membrane potential (RMP) of approximately ─50 mV. The mean firing rate is 17 Hz in our model. The MDMA with high dose increased both RMP and firing rate. The rising phase of AP is built up by Ca^{2+} conductances until enough slowly activated K^+ channels are open to repolarize it. Moreover, the same MDMA with zero doses decreased the AP firings significantly in our model. As MDMA elevates the RMP of STN cell to generate more APs, proper dosing of MDMA inhibitors might be an effective new non-dopaminergic alternative in parkinsonian patients.

Disclosures: C. Mahapatra: None. **R.M. Manchanda:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.08/K2

Topic: C.03. Parkinson's Disease

Support: DFG GRK2162

Title: Rotenone triggers senescence in human astrocytes

Authors: *K. SIMMNACHER, P. KLEIN, B. WINNER
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Abstract: One major risk factor of Parkinson`s disease (PD) is aging. Core pathomechanisms of PD, such as oxidative stress and mitochondrial dysfunction, are increased also with age and even healthy subjects show aging related neurodegeneration in the substantia nigra. This study aims to link senescence, as one major aspect of aging, to PD. Senescent cells accumulate with age, they accelerate aging in organs and they are linked to aging related diseases such as Sarcopenia or Arteriosclerosis. In addition to aging, which strongly connects PD and senescence, oxidative stress and mitochondrial dysfunction are closely linked to both PD pathology and senescence induction.
The aim of this project was to analyze if PD relevant stressors are able to induce a senescent phenotype in brain cells. For this, fetal astrocytes were exposed to the PD relevant stressor Rotenone. Senescent markers such as IL6, senescence-associated beta-galacotsidase and p16 were analyzed in those cells. We were able to measure an increase in senescence markers within cells treated for short term as well as long term with Rotenone.
An increase in IL6 might indicate a proinflammatory effect of senescent astrocytes in the brain with higher inflammation being one pathomechanism of PD. Senescence might also impair astrocyte function related to neuroprotection, neurotoxicity, transmitter release or blood-brain-barrier function and that way contribute to disease progression.

Disclosures: K. Simmnacher: None. **P. Klein:** None. **B. Winner:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.09/K3

Topic: C.03. Parkinson’s Disease

Support: Veteran Affairs Merit Award I01BX002477
NIH Grant AG048205
NIH Grant NS073670

Title: Neurotoxin MPTP-induced Parkinson’s disease: Mast cells, inflammatory mediators and neuroinflammation

Authors: *K. DURAISAMY[1,2], G. P. SELVAKUMAR[1,2], R. THANGAVEL[1,2], M. E. AHMED[1,2], S. A. ZAHEER[1], S. P. RAIKWAR[1,2], I. DUBOVA[1], G. GILER[1], S. HERR[1], K. KUKULKA[1], H. ZAHOOR[1], D. SAEED[1], S. S. IYER[1,2], A. ZAHEER[1,2]

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Abstract: Inflammatory mediators released from activated microglia, astrocytes, neurons, mast cells and T-cells-induce neuroinflammation-mediated neurodegeneration in neurodegenerative diseases. Parkinson's disease (PD) is characterized by neurodegeneration of dopaminergic neurons in substantia nigra of the midbrain. Mast cells are implicated in neuroinflammation and neurodegeneration in the central nervous system (CNS). However, the exact mechanism involved in this process is not yet clearly known. Neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induces PD like-symptoms in animals. 1-methyl-4-phenylpyridinium (MPP^+), a toxic metabolite of MPTP activate glial cells, neurons and mast cells to release various inflammatory mediators in the CNS. In this study, we analyzed neuroinflammation and mast cells activation in the brains of acute MPTP-induced Parkinsonian mice. Brain mast cells were stained with toluidine blue staining. Brains from MPTP-injected mice showed increased mast cell numbers as well as increased mast cell activation when compared with the control mice brains. Immunofluorescence staining showed increased protease-activated receptor-2 (PAR-2), receptor for mast cell released proteases in MPTP-induced PD mice brains. Further, immunofluorescence staining showed increased PAR-2 expression in primary mouse astrocytes cultured in vitro and incubated with MPP^+, inflammatory protein glia maturation factor (GMF), mouse mast cell protease-6 (MMCP-6) and MMCP-7. Injury associated cytokine interleukin-33 expression increased in the midbrain and striatum of human PD brains as compared with age and gender matched human control subjects' brains. We suggest that mast cell interaction with glial cells and neurons during neuroinflammation can be explored as a new therapeutic target for PD and other neuroinflammatory disorders.

Disclosures: K. Duraisamy: None. **G.P. Selvakumar:** None. **R. Thangavel:** None. **M.E. Ahmed:** None. **S.A. Zaheer:** None. **S.P. Raikwar:** None. **I. Dubova:** None. **G. Giler:** None. **S. Herr:** None. **K. Kukulka:** None. **H. Zahoor:** None. **D. Saeed:** None. **S.S. Iyer:** None. **A. Zaheer:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.10/K4

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS101134
NIH Grant AT006868

Title: Oxidative stress-mediated dysregulation of PP2A

Authors: H.-J. PARK[1], M. GRUDNIEWSKA[1], I. JUNG[1], R. YAN[1], J. ZHANG[1], S. ZHANG[2], K. HUBER[3], J. STOCK[2,3], *M. M. MOURADIAN[1]
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Abstract: The formation of pathologic aggregates of hyperphosphorylated, misfolded α-synuclein and tau is a common feature in α-synucleinopathies and tauopathies, respectively. Our recent postmortem brain studies of Parkinson's disease, Dementia with Lewy Bodies, Alzheimer's disease and Progressive Supranuclear Palsy revealed that dysregulation of the phosphatase that dephosphorylates these two proteins, protein phosphatase 2A (PP2A), is a common feature among these disorders. PP2A, which is a major serine/threonine phosphatase in the brain, is a trimeric holoenzyme that includes a catalytic C subunit and one of several regulatory B subunits that confer substrate specificity. The PP2A isoform that dephosphorylates α-synuclein and tau is B55alpha containing, and its assembly and activity are tightly regulated by reversible carboxyl methylation of the C subunit. In α-synucleinopathies and tauopathies, we found an imbalance in the expression levels of the two PP2A modulating enzymes that control its methylation, namely leucine carboxyl methyltransferase (LMCT-1) and protein phosphatase methylesterase (PME-1), creating conditions that favor inactivation of PP2A. However, the mechanism underlying dysregulation of PP2A methylation and its decreased activity in neurodegenerative diseases is not fully understood. Another common feature among these disorders is oxidative stress. Therefore, here we sought to address whether oxidative stress contributes to the altered state of PP2A methylation and the expression of its methylation modulating enzymes. Challenging human neuroblastoma SH-SY5Y cells with hydrogen peroxide resulted in significant changes in the expression levels of both LCMT-1 and PME-1, associated with demethylation of PP2A. Through changes in the methylation status of PP2A, its activity is also significantly reduced under conditions of oxidative stress. These findings support a role for oxidative stress in modulating PP2A activity, and consequently, the accumulation of hyperphosphorylated protein aggregates in neurodegenerative diseases.

Disclosures: H. Park: None. **M. Grudniewska:** None. **I. Jung:** None. **R. Yan:** None. **J. Zhang:** None. **S. Zhang:** None. **K. Huber:** A. Employment/Salary (full or part-time):; Signum Biosciences. **J. Stock:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signum Biosciences. **M.M. Mouradian:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.11/K5

Topic: C.03. Parkinson's Disease

Support: NRF-2018R1A2B2003955
HI17C-0936-010018

Title: Identification of Parkinson's disease-associated STUB1 as a novel target for covalent ISG15 conjugation and modulation of its ubiquitin E3 ligase activity during type 1 interferon-mediated inflammatory signaling

Authors: L. YOO[1], Y. H. LEE[1], *H. RHIM[2], K. C. CHUNG[1]
[1]Dept Systems Biol., Yonsei Univ., Seoul, Korea, Republic of; [2]Korea Inst. Sci. Tech. (KIST), Seoul, Korea, Republic of

Abstract: Abstract: An ubiquitin-like protein, ISG15 (interferon-stimulated gene 15), is one of the major type I interferon effector systems. ISG15 is expressed in cells in response to a variety of stress conditions (i.e., viral and bacterial infections or genotoxic stress) and present in its free form or is conjugated to cellular proteins. ISGylation is the covalent attachment of the ISG15 to lysine residues on target proteins via a pathway similar to ubiquitination. In addition, conjugated ISG15 can be removed from target proteins by UBP43. All components of the ISG15 system are induced by type I interferons. Here, we identified Parkinson disease-associated and the U-Box-containing ubiquitin E3 ligase STUB1 protein as a novel target for covalent ISG15 modification. STUB1 is modified by ISG15 in response to type I IFNs, which is mediated by ISG15 E3 ligase, Herc5, when the components of ISGylation were overexpressed or the type I interferon were treated. We have also mapped the major ISGylation sites within the STUB1. Moreover, ISGylation somehow affects the biochemical and functional activity of STUB1. At the meeting, additional data linking of its altered regulation to the cellular processes and disease occurrence would be presented.

Disclosures: L. Yoo: None. **Y.H. Lee:** None. **H. Rhim:** None. **K.C. Chung:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.12/K6

Topic: C.03. Parkinson’s Disease

Title: Microglial activation-dependent increase in protein kinase C-δ and pro-inflammatory cytokines reduces the length and number of fibers in the primary mesencephalic neurons

Authors: *S. MISHRA, C. RAJPUT, A. K. MISHRA, M. P. SINGH
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Abstract: Microglial activation is found to be decisivein the progressive nigrostriatal dopaminergic neurodegeneration leading to Parkinsonism. However, the mechanism of

microglial activation-dependent dopaminergic neurodegeneration has not yet been shown. The study aimed to investigate the role of a variety of mediators involved in the interaction of microglia and mesencephalic neurons in order to decipher the underlying mechanism. The primary microglial cells were isolated from 1-2 days old pups while mesencephalic neurons were isolated from embryo (Wistar rats) during the embryonic days 14-18 employing standard procedures. Microglial cells and mesencephalic neurons were treated with cypermethrin independently at various doses to go for a dose at which microglial cells got activated but the same dose was not toxic to mesencephalic neurons. At the selected dose (0.25 μM), the expression of activation markers, such as protein kinase C-δ (PKC-δ), inducible nitric oxide (iNOS) and pro-inflammatory cytokines, were measured to reassurethe activation of primary microglia. Cypermethrin augmented the level of PKC-δ, iNOS, tumor necrosis factor-α and interleukin-β proteins in the primary microglia cells. Moreover, the level of caspase-8 and caspase-3/7 were also increased in the treated microglia. Cypermethrin-treated microglial cell-conditioned media reduced the length and number of axon fibers in the primary mesencephalic neurons. Minocycline (50 nM), a pharmacological inhibitor of microglial activation, reduced the level of pro-inflammatory cytokines, PKC δ and caspases in the microglial cells and rescued from reduced length and number of axon fibers in the mesencephalic neurons.. The results demonstrate that microglial-activation dependent upregulation of PKC-δ and pro-inflammatory cytokines can be responsible for cypermethrin-induced neurodegeneration.
Keywords: Parkinsonism; Microglial activation; Mesencephalic neurons

Disclosures: S. Mishra: None. **C. Rajput:** None. **A.K. Mishra:** None. **M.P. Singh:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.13/K7

Topic: C.03. Parkinson’s Disease

Support: MSCRF 2014-MSCRFE-0587
NINDS R03NS087338-01A1

Title: The PARK10 gene USP24 negatively regulates autophagy through the ULK1 and type III PI3-kinase pathway

Authors: *J. A. THAYER[1], O. AWAD[2], N. U. HEGDEKAR[3], C. SARKAR[5], C. BURT[4], H. TESFAY[4], R. FELDMAN[4], M. M. LIPINSKI[6]
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Abstract: Autophagy is a lysosome-dependent intracellular degradation pathway essential for neuroprotection. Defects in autophagy are linked to neurodegenerative diseases, including Parkinson's disease (PD) but the mechanisms causing its disruption are not fully understood. The deubiquitinating enzyme *USP24* is located on chromosome 1 in the *PARK10* locus associated with late-onset PD and was identified as a negative regulator of autophagy by our lab. We confirmed increased USP24 protein and mRNA levels in the substantia nigra of a subpopulation of idiopathic PD patients. In human cell lines and iPS cell derived dopaminergic neurons, *USP24* knock-down led to up-regulation of cellular autophagy flux. This was assessed by increased LC3-II levels and by lysosomal translocation of the mCherry-GFP-LC3 autophagy reporter. To determine where *USP24* functions in the autophagy pathway we studied its effect on the upstream regulators of autophagy. Lack of change in the phosphorylation of mTORC1 target, ribosomal protein S6, after knock-down of *USP24* indicates that *USP24* acts independent or downstream of mTOR. *USP24* knock-down caused accumulation of PtdIns3P (type III PI3-kinase product), demonstrated by quantification of the FYVE-dsRed reporter. Inducing autophagy by loss of *USP24* function was attenuated in the presence of type III PI3-kinase inhibitors, spautin1 or 3MA. Furthermore, *USP24* knock-down lead to ULK1 protein stabilization and increased ULK1 activity. Our data suggests that *USP24* alters ULK1 protein stability, potentially by impacting ubiquitination. Together our data demonstrate that *USP24* regulates autophagy via ULK1 and the type III PI3-kinase pathway. Induction of autophagy following *USP24* knock-down was not associated with loss of cell viability. *USP24* was able to regulate autophagy in PD relevant cells, iPS cell derived dopaminergic neurons. Interestingly, *USP24* knock-down enhanced long-term survival and increased neurite length of iPS cell derived dopaminergic neurons, suggesting potential neuroprotective function. Our data highlight the mechanisms of *USP24* in regulation of autophagy and its potential role in PD.

Disclosures: J.A. Thayer: None. **O. Awad:** None. **N.U. Hegdekar:** None. **C. Sarkar:** None. **C. Burt:** None. **H. Tesfay:** None. **R. Feldman:** None. **M.M. Lipinski:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.14/K8

Topic: C.03. Parkinson's Disease

Support: Parkinson's Foundation
NIH R01 NS105432
Van Andel Research Institute

Title: Tau neuropathology and dopaminergic neurodegeneration in a D620N VPS35 knockin mouse model of Parkinson's disease

Authors: *X. CHEN[1], J. KORDICH[1], E. T. WILLIAMS[1], N. LEVINE[1], A. COLE-STRAUSS[2], J. LIPTON[2], D. J. MOORE[1]
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Abstract: Mutations in the *vacuolar protein sorting 35 ortholog (VPS35, PARK17)* gene were recently identified as a new cause of late-onset, autosomal dominant familial Parkinson's disease (PD). A single missense mutation, AspD620Asn (D620N), has so far been identified to segregate with disease in multiple PD families, thereby proving the pathogenicity of this disease variant. At present, the mechanism(s) by which familial VPS35 mutations precipitate neurodegeneration in PD are incompletely understood and a demonstration of interactions between VPS35 and other PD-linked gene products in rodent models is lacking. In the current study, we employed a new germline *D620N VPS35* knockin (KI) mouse model to determine the pathogenic impact with chronic aging of the D620N mutation at physiological expression levels. Our data provide evidence that a heterozygous or homozygous D620N mutation is sufficient to reproduce neuropathological hallmarks of PD as indicated by an age-dependent degeneration of nigrostriatal pathway dopaminergic neurons and widespread axonal pathology. Given the central role of α-synuclein in PD pathogenesis and prior data linking VPS35 function to α-synuclein homeostasis, we assessed changes in α-synuclein levels or aggregation. We find that D620N VPS35 expression does not induce α-synuclein neuropathology and has no effect on the lethal neurodegenerative phenotype induced by the expression of human A53T-α-Syn in transgenic mice. However, D620N knockin mice instead exhibit tau pathology with advancing age as indicated by hyperphosphorylation and abnormal conformations of tau in different brain regions. Our data raise the tantalizing possibility of a pathogenic interplay between VPS35 and tau to induce neurodegeneration in PD. Our ongoing studies will address the mechanisms by which PD-linked mutant VPS35 induces tau pathology, which may represent an important and early feature of VPS35-induced neuronal degeneration in PD. The current *D620N VPS35* knockin mouse model will provide an important tool for understanding neurodegenerative mechanism(s) underlying *VPS35*-linked PD.
FUNDING SOURCES: The authors are grateful for funding support from the Parkinson's Foundation, NIH R01 NS105432 and Van Andel Research Institute.

Disclosures: X. Chen: None. **J. Kordich:** None. **E.T. Williams:** None. **N. Levine:** None. **A. Cole-Strauss:** None. **J. Lipton:** None. **D.J. Moore:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.15/K9

Topic: C.03. Parkinson's Disease

Support: MOST 106-2314-B-182A-012 -MY3
CMRPG3F1821

Title: Investigation of the role of RAB39B in the pathogenesis of Parkinson's disease

Authors: *C.-C. CHIU[1], T.-H. YEH[2], H.-L. WANG[3]
[1]Chang Gung Mem. Hosp., TAOYUAN, Taiwan; [2]Dept. of Neurology, Taipei Med. Univ. Hosp., Taipei, Taiwan; [3]Dept. of Physiology, Chang Gung Univ. Sch. of Med., Kwei-San, Tao-Yuan, Taiwan

Abstract: RAB39B, a member of small GTPases, is participates in vesicular trafficking. Mutations in RAB39B cause X-linked Parkinson's disease (PD). In the present study, we searched for genetic variants in RAB39B in 250 patients with PD. In the present study, rotenone-induced cellular model of PD was used to investigate pathogenic mechanism of mutant (T168K) RAB39B-induced PD. Compared to rotenone-treated control cells, expression of wild-type (WT) Rab39B significantly attenuated rotenone-induced cell death, whereas overexpression of (T168K) RAB39B was ineffective in preventing rotenone-induced cytotoxicity. Overexpression of WT RAB39B ameliorated rotenone-induced apoptotic death of SH-SY5Y cells. (T168K) RAB39B failed to prevent rotenone-induced activation of mitochondrial apoptotic pathway. Protein expression of ER stress, including Grp78 and CHOP, was upregulated in SH-SH5Y cells expressing (T168K) RAB39B. The protein level of autophagic proteins, including Atg7 and LC3II, was upregulated SH-SY5Y cells expressing (T168K) RAB39B, suggesting that (T168K) RAB39B mutation causes autophagy impairment.

Disclosures: C. Chiu: None. **T. Yeh:** None. **H. Wang:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.16/DP06/K10

Topic: C.03. Parkinson’s Disease

Title: Converging pathways in genetic and sporadic Parkinson’s disease: Using unbiased network analysis to connect the dots

Authors: *A. D. LEE, J. C. HALL, J. W. RYAN, B. BEHROUZ
Neuroinitiative, Jacksonville, FL

Abstract: Genetic discoveries over the last twenty years provide clues into the process and systems involved in Parkinson’s disease pathogenesis. While genetic mutation can explain about 10% of cases, the remaining 90%, referred to as sporadic cases, have unknown etiology. Interestingly, several diverse starting points lead to similar motor symptoms caused by

progressive degeneration of dopamine neurons in in the substantia nigra pars compacta, a hallmark pathology of disease which suggests that there might be convergence of biochemical pathways.
In this study we used protein-protein interaction data from Biogrid, IntAct, Reactome, Pathway Commons, and SEED to construct a Bayesian network graph of known interactions. Using this network we computed all simple paths between a starting point (e.g. genetic causes) and end point (e.g. post-mortem genomic variation) using an implementation of Dijkstra's algorithm. Further aggregate analysis ranked intermediate steps by connectedness, measured by how many times a given protein occurred across all possible paths and normalized to the total number of known interactions for each protein in the source data. Pathfinding was repeated for each permutation resulting from autosomal mutations and risk factors associated with Parkinson's disease as sources (including but not limited to SNCA, LRRK2, VPS35, PARK2, PINK1, PARK7, ATP13A2, FBXO7, PLA2G6, EIF4G1, DNAJC6, ATP6AP2, COQ7, SYNJ1, DNAJC13, PTRHD1, PODXL, RAB39B, CHCHD2, TMEM230, and GBA) and transcriptomic differences observed in post-mortem sporadic Parkinson's patient brains as targets. Top hits implicate specific target proteins within membrane homeostasis and trafficking, mitochondrial, and lysosomal pathways which may be further exploited to understand disease process and for therapeutic intervention.

Disclosures: **J.C. Hall:** A. Employment/Salary (full or part-time):; NeuroInitiative LLC. **J.W. Ryan:** A. Employment/Salary (full or part-time):; NeuroInitiative LLC. **B. Behrouz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroInitiative LLC.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.17/K11

Topic: C.03. Parkinson's Disease

Support: NIH Grant AG048205
VA Merit Award I01BX002477

Title: Molecular control of autophagy by glia maturation factor in rat dopaminergic N27 neurons: A role for endoplasmic reticulum stress and MAPK activation

Authors: *S. GOVINDHASAMY PUSHPAVATHI[1,2], M. AHMED[1,2], K. DURAISAMY[1,2], S. S IYER[1,2], T. RAMASAMY[1,2], S. RAIKWAR[1,2], S. A ZAHEER[1], A. ZAHEER[1,2]
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Abstract: Parkinson's disease (PD) is a prevalent neurodegenerative disease, mainly characterized by progressive loss of dopaminergic neurons in the substantia nigra of the midbrain. Neurodegeneration is brought about due to dysregulation of autophagy and accumulation of cytoplasmic inclusion in the dopaminergic neurons. However, the mechanisms that impair autophagy remains poorly understood. Glia maturation factor (GMF), a brain-localized inflammatory protein induces dopaminergic neurodegeneration in PD. 1-methyl-4-phenylpiridium ion (MPP^+), a toxic precursor from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces experimental PD *in vitro*. Using rat dopaminergic N27 cells, primary neurons from wild type and GMF-KO mice we show that GMF and MPP^+ enhance the expression of p38 and ERK1/2 mitogen-activated protein kinases (MAPKs), increased mTOR activation, endoplasmic reticulum stress markers p-PERK, IRE1α and reduced Beclin1, FIP200 and autophagy related proteins (ATGs) 3, 5 and 12. The combined results demonstrate that GMF affects autophagy through autophagosome formation and maturation with significantly reduced lysosomal-associated membrane proten1/2 (LAMP1/2), and the number of autophagic acidic vesicles. In the mouse primary neurons we show that MPP^+ treatment leads to differential expression and localization of p62/sequestosome and in GMF-KO neurons there was a marked increase in p62 staining implying autophagy deficiency with very little co-localization of α-synuclein and p62. Collectively, in this study, we provides an evidence of bidirectional role for GMF in executing dopaminergic neuronal death mediated by autophagy that is relevant to PD.

Disclosures: S. Govindhasamy pushpavathi: None. **M. Ahmed:** None. **K. Duraisamy:** None. **S. S Iyer:** None. **T. Ramasamy:** None. **S. Raikwar:** None. **S. A Zaheer:** None. **A. Zaheer:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.18/K12

Topic: C.03. Parkinson's Disease

Support: CONACYT 239516

Title: Gas1 induces neurodegeneration via apoptosis by the formation of nitric oxide and activation of JNK/c-Jun in a model of Parkinson's disease

Authors: *E. BAUTISTA[1,2], R. CASTANEDA-ARELLANO[1], P. VERGARA[1], R. O. GONZALEZ[3], J. V. SEGOVIA-VILA[1]
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Abstract: Growth arrest-specific 1 (Gas1) is a pleiotropic protein that induces apoptosis of tumor cells and has important roles during the development of the nervous system. Previously, we showed that Gas1 participates in the differentiation of neurons and that it is expressed in the dopaminergic cells of the *substantia nigra* (SN). Based on these data, we studied the role of Gas1 in a Parkinson's disease (PD) model. First, we induced the overexpression of Gas1 in SH-SY5Y-AR cells (differentiated cells with retinoic acid) treated with the neurotoxin 6-hydroxydopamine (6-OHDA). In these experimental conditions, we found that the over-expression of Gas1 produced a marked reduction in the number of viable cells related with an increase of the active form of caspase 3 in SH-SY5Y-AR cells treated with the 6-OHDA. This pro-apoptotic effect of Gas1 was associated with the formation of reactive nitrogen species, and the activation of JNK/c-Jun. In an *in vivo* PD model, we unilaterally injected 6-hydroxydopamine (6-OHDA) into the striatum and five min after Gas1 was administrated into the SN ipsilateral to the lesion (6-OHDA). Seven days post-injury, we found that Gas1 increased the injury caused by 6-OHDA. Since, it incremented the ipsilateral turnig behavior in response to apomorphine, decreased the levels of tyrosine hydroxylase (TH) in the SN and increased the immunoreactivity to GFAP in the striatum and SN of mice lesioned with 6-OHDA. Together, these data suggest the mechanism by which Gas1 could participate in the neurodegenerative process associated with Parkinson's disease.

Disclosures: E. Bautista: None. **R. Castaneda-Arellano:** None. **P. Vergara:** None. **R.O. Gonzalez:** None. **J.V. Segovia-Vila:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.19/K13

Topic: C.03. Parkinson’s Disease

Support: NMRC-Translational Clinical Research Program in Parkinson's disease and Collaborative Basic Research Grant
NNI CG Pilot Grant (NCG PA07)

Title: Parkin modulates brain lipid metabolism through lipoprotein lipase - Implications for Parkinson's disease

Authors: *W. TANG[1], J. THUNDYIL[1], S. Q. Z. YEOW[2], A. NAIR[2], G. G. Y. LIM[1], C. CHAI[1], T.-P. YAO[3], K. LIM[2]
[1]Res., Natl. Neurosci. Inst., Singapore, Singapore; [2]Natl. Univ. of Singapore, Singapore, Singapore; [3]Sch. of Med., Duke Univ., Durham, NC

Abstract: Abnormal lipid metabolism has been observed in the brains of patients with neurodegenerative diseases, including Parkinson's disease (PD). Intriguingly, a recent study reported an unconventional role of parkin, which is implicated in juvenile-onset PD, in the regulation of fat uptake via stabilizing the fatty acid translocase, Cluster of Differentiation 36 (CD36). Yet, the role of parkin-mediated lipid regulation in the brain and any consequences caused by its dysregulation on neurodegeneration remain to be elucidated. To investigate these questions, we employed both biochemical and fluorescence imaging approaches to robustly determine the functional relationship between parkin and lipoprotein lipase (LPL), a triglyceride lipase expressed in the brain and a CD36 interactor. Using independent study models - human neuroblastoma cell lines and brain cells derived from parkin knockout (KO) mice - we demonstrate that parkin expression levels correlate positively with the levels of transcript, protein, and activity of LPL. Interestingly, parkin effect on LPL seems to be independent of its canonical E3 ligase function; rather, our data indicate that parkin regulates LPL at the transcriptional level. Accordingly, our genetic screening of LPL modulators identified Sterol Regulatory Element Binding Protein 2 (SREBP2), a major transcription factor involved in cholesterol and fatty acid biosynthesis, as a potential mediator in parkin-LPL pathway. Finally, our results show that disruption of this pathway during PD-linked cellular stress affects the dynamics of two organelles associated with neurodegeneration: mitochondria and lipid droplets. Altogether, our findings identify a novel pathway implicating parkin in brain lipid metabolism via its regulation on SREBP2-LPL axis. At the same time, our results pave the way for a potential next generation therapeutic strategy against PD.

Disclosures: J. Thundyil: None. **S.Q.Z. Yeow:** None. **A. Nair:** None. **G.G.Y. Lim:** None. **C. Chai:** None. **T. Yao:** None. **K. Lim:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.20/K14

Topic: C.03. Parkinson’s Disease

Support: NIH Grant 1R15GM117501

Title: Through the nose: Acne bacteria and Parkinson's disease

Authors: *C. A. BIEGEL, S. F. GOTTLIEB, V. CIMINO, K. KULASON, K. CHU, D. ORSHAN, P. PRABHU, G. H. OTAZU, J. R. LEHESTE
NYIT Col. of Osteo. Med., Old Westbury, NY

Abstract: There is increasing evidence for a specific microbial signature associated with Parkinson’s disease (PD). While cause and effect are still unclear, there is growing consensus

about the unfavorable nature of this association and its disease-promoting potential. It has become evident that the human microbiome is in constant communication with the human body through metabolites and other components and that it can either promote well-being or disease. Brain health and neurodegeneration are no exception and first evidence is now pointing toward cranial nerves as fast-track for harmful bacterial species and their metabolites into the human brain. According to Braak's staging system for PD, the first intracranial cellular signs of the disease are found in the olfactory bulb as well as the lower midbrain – both structures that are connected to areas of high bacterial content via cranial nerves.
This work is focused on the opportunistic potential of the Gram-positive anaerobe, *Propionibacterium acnes* (*P. acnes*) primarily investigating histological and mechanistic aspects involved in bacterial invasion via the intranasal-olfactory route. In addition, it examines the effects of bacterial brain entry on dopaminergic (DA) neurons in the nigro-striatal pathway of the midbrain and whether this paradigm can recapitulate the loss of DA neurons seen in PD. This work is inspired by our previous findings of intra-neural *P. acnes* in post-mortem human PD brain tissue.
To study aspects of bacterial invasion via the intranasal-olfactory route and the cellular consequences, we introduced clinically relevant isolates of *P. acnes* and bacterial controls (*Staphylococcus epidermidis*, *Propionibacterium freudenreichii*) intranasally into wild-type C57Bl6J mice. Overall we found *P. acnes*-specific reduced sensitivity to odors along with widespread biofilm formation in the olfactory bulb and evidence of inflammation and axonal degeneration at the olfactory nerve.
To study the effect of *P. acnes* on DA neurons, we delivered the bacterium or controls unilaterally into the striatum. Post-injection outcomes were determined at 24h and 14 days post-infection with immunohistochemical, DNA/RNA and protein-based techniques. While the initial molecular response to experimental and control bacteria was very similar, only *P. acnes* prevailed after 14 days showing extensive biofilm, inflammation and ipsilateral DA neuron degeneration.
This work recapitulates important signs and symptoms associated with PD such as hyposmia seen during the early course of the disease as well as DA neuron degeneration. These results support the possibility of a *P. acnes*-based disease etiology for PD.

Disclosures: C.A. Biegel: None. **S.F. Gottlieb:** None. **V. Cimino:** None. **K. Kulason:** None. **K. Chu:** None. **D. Orshan:** None. **P. Prabhu:** None. **G.H. Otazu:** None. **J.R. Leheste:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.21/K15

Topic: C.03. Parkinson's Disease

Support: NYU Fresco Institute's RFA - Basic Science Research Grant
Unicredit Funding

Title: Pathological features of midbrain organoids of GBA-mutated patients

Authors: *E. FRATTINI[1,2], F. CRIBIÙ[3], G. MONZIO COMPAGNONI[2], A. PITTARO[3], G. ERCOLI[3], R. TACCHI[3], M. AURELI[4], M. SAMARANI[4], S. SALANI[2], A. BORDONI[2], A. BELLUCCI[5], G. FAUSTINI[5], S. DUGA[6], L. STRANIERO[6], M. TOSI[2], R. SILIPIGNI[7], L. LAZZARI[8], M. BARILANI[9], S. CORTI[2], N. BRESOLIN[2], A. DI FONZO[2]
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Abstract: Background: Parkinson’s Disease (PD) is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons (DaNs) in the substantia nigra of the midbrain. Mutations in GBA gene, historically linked to Gaucher’s Disease (GD), are the most frequent genetic risk factor for PD. However, the link between GBA mutations and neurodegeneration is still not clear. In this project, the potential of human stem cell-derived midbrain organoids was exploited to shed light on this lacking point.
Materials and methods: Fibroblasts derived from skin biopsies of a PD patient with a heterozygous GBA mutation, a GD patient with a homozygous GBA mutation, and two healthy controls were reprogrammed into iPSCs with Sendai virus (Thermofisher). Expression of stem cell markers was assessed with immunofluorescence (IF). Karyotype analysis was carried out to exclude genetic rearrangements during reprogramming. Protocols for the generation of brain organoids by Lancaster et al. (2013) and Jo et al. (2016) were modified to generate 3D cultures containing a high amount of DaNs with midbrain identity. Samples collected at various time points underwent extensive RNA, western blot (WB), enzymatic, IF, and immunohistochemical (IHC) analyses. Sphingolipids analyses were performed by metabolic labelling with radioactive precursors [1-3H]sphingosine. Sphingolipid pattern was evaluated by HPTLC, and radioactive lipids were visualized by digital autoradiography.
Results: GBA and control iPSC lines stained positive for stem cell markers. Karyotype analysis of reprogrammed iPSCs was normal. Progressive expression of neuronal and DaN markers (TUJ1, MAP2, TH) over time reflected the embryologic development and full maturation of midbrain structures. IHC staining showed the presence of several cell types, including neurons

(NF, TH) and astrocytes (GFAP). Schmorl's method detected positive staining for neuromelanin, suggesting a mature dopaminergic identity. GCase protein amount and enzymatic activity were decreased in GBA organoids. Sphingolipids analyses revealed the same feature described during the development of human brain, reaching an important enrichment of polisialogangliosides. Interestingly an accumulation of glucosylceramide is observed in GBA-mutated organoids. Discussion: Midbrain organoids may recapitulate some molecular events and biochemical dysfunctions underlying GBA-related neurodegeneration. This model may represent a comprehensive human platform that could be exploited for the elucidation of mechanisms involved in PD and for the screening of potential therapeutic strategies.

Disclosures: E. Frattini: None. **F. Cribiù:** None. **G. Monzio Compagnoni:** None. **A. Pittaro:** None. **G. Ercoli:** None. **R. Tacchi:** None. **M. Aureli:** None. **M. Samarani:** None. **S. Salani:** None. **A. Bordoni:** None. **A. Bellucci:** None. **G. Faustini:** None. **S. Duga:** None. **L. Straniero:** None. **M. Tosi:** None. **R. Silipigni:** None. **L. Lazzari:** None. **M. Barilani:** None. **S. Corti:** None. **N. Bresolin:** None. **A. Di Fonzo:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.22/K16

Topic: C.03. Parkinson's Disease

Title: ATF4 regulates neuronal death in cellular models of Parkinson's disease

Authors: *M. D. DEMMINGS, S. P. CREGAN
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Abstract: Parkinson's Disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra. However, mechanisms underlying this neuronal loss remain largely unknown. ATF4, a key mediator of the Integrated Stress Response (ISR), is a transcription factor that during prolonged activation can induce the expression of several downstream pro-apoptotic target genes. Both oxidative stress and mitochondrial dysfunction are associated with PD and these factors are known to activate the ISR. Therefore, we investigated whether prolonged activation of ATF4 by PD neurotoxins promotes pro-apoptotic gene induction and neuronal cell death. To address this, we treated mouse primary cortical neurons with the PD neurotoxins 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenylpyridinium (MPP+) and found that both drugs caused a sustained elevation of ATF4 protein levels as well as the persistent induction of several pro-apoptotic genes including Chop, Trb3, and the Bcl-2 family member Puma. To determine whether ATF4 is necessary for PD neurotoxin-induced neuronal cell death, ATF4 +/+ and ATF4 -/- primary cortical neurons were treated with 6-OHDA or MPP+. We found that transcript levels of the pro-apoptotic factors Chop, Trb3, and Puma were significantly reduced in

ATF4-/- neurons as compared to wild-type neurons ($p<0.05$). Furthermore, we found that neuronal death induced by both 6-OHDA or MPP+ was markedly reduced in ATF4 -/- neurons ($p<0.05$) as assessed by Hoechst morphology and Live-Dead assays. Thus, our loss of function study clearly demonstrates that ATF4 is necessary for apoptotic neuronal loss in 6-OHDA and MPP + paradigms and highlights the Integrated Stress Response as a potential therapeutic target in PD.

Disclosures: M.D. Demmings: None. **S.P. Cregan:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.23/K17

Topic: C.03. Parkinson's Disease

Support: NINDS F31 Grant NS098630
NIEHS R01 Grant ES024745

Title: Nlrp3 is required for microglial activation in MPTP treated mice

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Abstract: Neuroinflammation is associated with the progression of Parkinson's disease (PD), however, mechanisms driving PD-associated neuroinflammation are not sufficiently characterized. Inflammasomes are cytosolic multi-protein complexes that react to intracellular stress to initiate inflammation. Our studies indicate that *Nlrp3* is required for neuroinflammation nigral cell loss resulting from chronic systemic rotenone exposure in mice and that *Nlrp3* expression is elevated in the midbrain in tissues obtained from PD patients. Our in vivo and in vitro studies are consistent with the reports of others indicating that microglia are a prominent cell-of-origin for inflammasome activity in the central nervous system. To further explore the function of *Nlrp3* in microglia, we exposed $Nlrp3^{-/-}$ mice to MPTP and analyzed these mice 30 days post-exposure; following a time period when inflammatory activity has been reported to impact overall neuronal cell loss. One month following MPTP exposure we conducted behavioral studies, serologic assays, and performed unbiased stereological analysis of neurons and glial cells in post-mortem brain tissues. Serologic analysis identified *Nlrp3*-dependent changes in the inflammatory cytokine profile resulting from MPTP exposure. We observed consistent nigral cell loss in WT mice and increased sparing of nigral neurons in $Nlrp3^{-/-}$ mice exposed to MPTP. While we readily observed elevated numbers of aggravated microglia in WT mice exposed to MPTP 30 days post-treatment, we did not observe such changes in identically treated $Nlrp3^{-/-}$ mice. Analyzing primary microglia in vitro, we observed that $Nlrp3^{-/-}$ microglia

were resistant to activation resulting from exposure to LPS and nigericin manifest as a reduction in the expression of IL6, iNOS, TNFα, and IL-1β. Notably, in LPS-primed microglial treated with nigericin, we observed an *Nlrp3*-dependent elevation of TNFα transcript compared with LPS alone. This finding is reminiscent of recent reports of transcriptional modulation by Nlrp3 in T_h2 cells. In support of transcriptional regulation of TNFα by Nlrp3, we have observed Nlrp3 protein only in nuclear extracts obtained from microglia primed with LPS and then stimulated with nigercirin. These studies complement our previous studies and reports by others further supporting a role for *Nlrp3* in PD-associated neuroinflammation and suggest that Nlrp3 plays a role in the transcriptional regulation of TNFα.

Disclosures: E.M. Martinez: None. **A.L. Young:** None. **K. von Herrmann:** None. **M.C. Havrda:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.24/K18

Topic: C.03. Parkinson’s Disease

Support: VA RX001613-01
AU PSRP00075

Title: Niacin attenuates inflammatory cytokine upregulation mediated through gpr109a

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Abstract: Neuroinflammation is central in Parkinson’s disease (PD) pathology. Microglia derived inflammatory cytokines are known to be involved in progressive degeneration of substantia nigra (SN) neurons. We have demonstrated up-regulation of anti-inflammatory receptor GPR109A in blood (PD patients) as well as in SN (post-mortem PD patient samples). This may be a part of body’s defense mechanism. Niacin (vitamin B3) acts on GPR109A to reduce the inflammation in PD. To understand the cellular mechanisms involved in the anti-inflammatory action of niacin we utilize here lipopolysaccharide (LPS) induced inflammatory cascade in Raw267.4 cells. These cells are macrophages that resemble microglial lineage. LPS is known to trigger inflammatory cytokines production such as IL1-beta, IL-6 and TNF-alpha via NF-kB pathway. NF-kB is the transcription factor and the translocation of its p65 unit to nucleus is an essential step in the inflammatory cascade. Here we demonstrate inhibition of pNF-kB

translocation by niacin in Raw267.4 cells via GPR109A. However in the absence of GPR109A, niacin failed to block the translocation of pNF-kB and the subsequent production of inflammatory cytokines in Raw267.4 cells. This anti-inflammatory action of niacin via GPR109A might be beneficial in PD to alleviate motor and non-motor symptoms.

Disclosures: B. Giri: None. **E. Bradley:** None. **B. Baban:** None. **J. Morgan:** None. **R. Chong:** None. **C. Wakade:** None.

Poster

207. Parkinson's Disease: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 207.25/L1

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01NS101958

Title: Defining the role of dj-1 in pathogenesis using cell-specific gene expression quantification and electrophysiology

Authors: *S. BOAS[1,2], A. BOHANNON[3], J. J. HABLITZ[4], M. S. GOLDBERG[5], R. M. COWELL[2,6]
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Abstract: The absence or altered expression of the protein DJ-1 has been associated with several neurological disorders including Parkinson Disease and Amyotrophic Lateral Sclerosis. Though many potential functions have been proposed, there is limited knowledge of the functional consequences of its deficiency in vivo. Given the heterogeneity of cell types in the brain, understanding how DJ-1 is differentially expressed within specific cell types is pivotal in understanding how certain populations are vulnerable to DJ-1 deficiency and how DJ-1 deficiency leads to disease. In order to investigate DJ-1 in a cell-specific fashion, we utilized RNAscope, an in situ hybridization technique, to quantify expression of DJ-1 in multiple cell types throughout the mouse brain. As previously demonstrated, there was widespread expression of DJ-1 transcript in the brain; however, expression levels varied between cell types. Interestingly, DJ-1 expression was enriched in parvalbumin-expressing interneurons (PV-INs). PV-INs are fast-spiking inhibitory neurons that synchronize excitatory neuronal networks by rhythmic inhibition. We used whole-cell patch-clamp electrophysiology in order to determine how the loss of DJ-1 affects cortical PV-IN modulation of pyramidal neurons in layer V, the main layer for descending motor output. We found that PV-INs from DJ-1 null animals had a

significantly more depolarized resting membrane potential. Layer V pyramidal neurons from null animals had both decreased frequency and amplitude of action potential-independent spontaneous inhibitory postsynaptic currents (iPSCs). When action potentials were not blocked with tetrodotoxin, the frequency of inhibitory events was still decreased, but the amplitude of events was increased compared to control iPSCs. When we looked at the distribution of these events based on amplitude, we found that there were significantly more relatively small and large events, but fewer moderate events in the null animals. Further work is needed to determine if this DJ-1-dependent disruption of inhibition could affect the role of PV-INs in their synchronization of excitatory networks, and if this may have broader impacts in the pathology of neurodegenerative diseases.

Disclosures: S. Boas: None. **A. Bohannon:** None. **J.J. Hablitz:** None. **M.S. Goldberg:** None. **R.M. Cowell:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.01/L2

Topic: C.06. Neuromuscular Diseases

Support: ERC

Title: miR126-5p down-regulation facilitates axon degeneration and NMJ disruption via a non-cell-autonomous mechanism in ALS

Authors: *R. MAIMON, E. PERLSON
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Abstract: Abstract
Axon degeneration and disruption of neuromuscular junctions (NMJs) are key events in Amyotrophic Lateral Sclerosis (ALS) pathology. Although the disease's etiology is not fully understood, it is thought to involve a non-cell-autonomous mechanism and alterations in RNA metabolism. Here, we identified reduced levels of miR-126-5p in pre-symptomatic ALS male mice models, and an increase in its targets: axon destabilizing type-3 Semaphorins and their co-receptor Neuropilins. Utilizing compartmentalized *in vitro* co-cultures, we demonstrated that myocytes expressing diverse ALS-causing mutations promote axon degeneration and NMJ dysfunction, which were inhibited by applying Neuropilin1 (NRP1) blocking antibody. Finally, overexpressing miR126-5p is sufficient to transiently rescue axon degeneration and NMJ disruption both *in vitro* and *in vivo*. Thus, we demonstrate a novel mechanism underlying ALS pathology, in which alterations in miR126-5p facilitate a non-cell-autonomous mechanism of motor neuron degeneration in ALS.

Significance Statement
In spite of some progress, currently no effective treatment is available for ALS. We suggest a novel regulatory role for miR126-5p in ALS and demonstrate for the first time a mechanism by which alterations in miR126-5p contribute to axon degeneration and NMJ disruption observed in ALS. We show that miR126-5p is altered in ALS models and that it can modulate Sema3 and NRP protein expression. Furthermore, NRP1 elevations in motor neurons and muscle secretion of Sema3A contribute to axon degeneration and NMJ disruption in ALS. Finally, overexpressing miR126-5p is sufficient to transiently rescue NMJ disruption and axon degeneration both *in vitro* and *in vivo.*

Disclosures: R. Maimon: None. **E. Perlson:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.02/L3

Topic: C.06. Neuromuscular Diseases

Support: Department of Defense Therapeutic Idea Award
ALS Association

Title: Liposome-mediated uptake of H-ferritin improves outcomes in the $SOD1^{G93A}$mouse model of amyotrophic lateral sclerosis

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Abstract: The misregulation of iron and subsequent oxidative stress are features shared consistently between humans with Amyotrophic Lateral Sclerosis (ALS) and in animal models of the disease. The iron sequestration protein H-ferritin has ferroxidase activity and limits the toxic potential of iron, making it an attractive therapy to pursue in ALS. One of the disadvantages of most systemically-delivered treatments for neurological diseases is that they exert their biological effects not only at their target sites but also at peripheral tissue and cells. This often results in dilution of the agent below therapeutic levels to the target tissue; a way to increase efficacy and reduce the amount of agent administered is to utilize liposomal drug carriers. The objective of this work is to determine if infusion of liposome-encapsulated iron-poor H-ferritin has neurotrophic properties in a murine model of ALS. Liposomes that were directed to microglia by the presence of surface-conjugated lipopolysaccharide (LPS) molecule as well as those lacking a targeting moiety were used. Artificial spinal fluid (aCSF) infusion served as a

surgical and vehicle control. At 90 days of age, mice with the $SOD1^{G93A}$ mutation underwent surgery allow for continuous infusion into the lateral ventricle. Disease onset was assessed by performance on the rotarod apparatus, and endpoint was determined by the inability of the animal to right itself. Our intervention with H-ferritin encapsulated with liposomes not targeted to a specific cell-type resulted in a significant 18 day delay in disease onset as compared to the aCSF-infused control group (median values). Liposomes containing H-ferritin directed to microglia with LPS did not have a positive influence on disease onset. A significant extension in lifespan occurred in mice treated with H-ferritin encapsulated by non-targeted liposomes, resulting in a 14.5 day extension of survival as compared to aCSF-infused $SOD1^{G93A}$ mice (median values). Specific delivery of H-ferritin to microglia was of limited benefit in extending lifespan. A plausible explanation for this outcome is over-stimulation of microglia by accessing them through the TL4 receptor. Our intervention in the animal model is of particular relevance to the clinical population because our intervention occurs at the peri-symptomatic stage of the disease; this would correlate to the time in which human patients would begin to notice symptoms and seek treatment in the clinic. Therefore, our therapy may be of greater clinical benefit than those compounds tested while animals are asymptomatic.

Disclosures: A.M. Snyder: None. **A.B. Madhankumar:** None. **E.B. Neely:** None. **O.D. Mrowczynski:** None. **E. Rizk:** None. **O.M. Hess:** None. **Z. Simmons:** None. **J.R. Connor:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.03/L4

Topic: C.06. Neuromuscular Diseases

Title: Preclinical study on the therapeutic potential of a novel EhpA4 blocking peptide for the treatment of ALS

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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease in which upper and lower motor neurons die off, leading to paralysis and eventually death within a few years after diagnosis. The variability in disease onset and progression among patients can partly be explained by genetic modifying factors. The EphA4 receptor tyrosine kinase was recently discovered by our lab to be such a disease modifier for ALS. Indeed, administration of KYL

peptide, a selective EphA4 blocking peptide, directly in the brain of ALS rats resulted in a modest increase in disease survival. Modification of the cyclic peptide 'APY' has led to the generation of 'APYd3', a highly specific, stable and potent antagonist for the EphA4 receptor. In this study, we aim to explore the therapeutic potential of this improved EphA4 antagonist in a mouse model of ALS. For continuous administration of the APYd3 peptide in the brain of $SOD1^{G93A\ +/-}$ mice, a model for ALS, an Alzet osmotic minipump was attached with a catheter to an intracerebroventricular cannula. Female mice were treated from 60 day of age until they died. The KYL peptide was used as a positive control while artificial cerebrospinal fluid (aCSF) and an inactive variant of APYd3 served as negative controls. Mice were evaluated three times per week by the rotarod and hanging wire tests. Disease onset was determined according to two different definitions: (1) reduction of rotarod performance by 50% compared to the maximum performance or (2) impossibility to perform the hanging wire test for at least 60 seconds. End stage was defined as the time when the mouse could no longer turn back on its paws within 20 seconds after placing it on its back. In this study, we were able to show that the APYd3 peptide is stable and fully active inside the osmotic pumps for at least 28 days. Moreover, intracerebroventricular infusion with 1 mM peptide resulted in detectable levels in the mouse brain. Although preliminary results suggest no difference between treatment groups in disease onset or survival (n=14), an increase in group size is needed before drawing final conclusions about the effects of this dose of peptide.

Disclosures: S. Smolders: None. **L. Rué:** None. **M.M. Gomez-Soler:** None. **E.B. Pasquale:** None. **P. Van Damme:** None. **R. Lemmens:** None. **W. Robberecht:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.04/L5

Topic: C.06. Neuromuscular Diseases

Support: JSPS KAKENHI Grant 17K09747
Japan ALS Association

Title: Target therapy for ALS with RNA aptamers -rescue of ALS phenotype resulting from loss of motor neurons with TDP-43 pathology in ALS model mice

Authors: *M. AKAMATSU[1], T. YAMASHITA[1], S. TERAMOTO[1], Z. HUANG[2], L. NIU[2], S. KWAK[1]
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Abstract: In the motor neurons of the vast majority of sporadic ALS patients, the expression of an RNA editing enzyme called ADAR2 is reduced, resulting in abnormal expression of glutamine/arginine (Q/R) site-unedited GluA2, a subunit of the AMPA receptor. AMPA receptors that contain the unedited GluA2 are highly Ca^{2+}-permeable, and an increase in Ca^{2+} influx in motor neurons results in activation of Ca^{2+}-dependent protease calpain in the cytoplasm, thereby causing TDP-43 pathology in the ADAR2-lacking motor neurons of both ALS patients and AR2 mice, a conditional ADAR2 knockout mouse model. Thus, normalization of the exaggerated Ca^{2+} influx mediated through abnormally expressed AMPA receptors is a potential therapeutic strategy for sporadic ALS, since toxic build-up of Ca^{2+} in the motor neurons leads to cell death. We previously reported that perampanel, a selective non-competitive AMPA receptor antagonist, robustly prevented the progressive motor dysfunctions and loss of motor neurons with TDP-43 pathology in the AR2 mice (Akamatsu M et al, Sci Rep. 2016). However, perampanel has a significant sedative side effect. Here we report our study of the efficacy and safety of AMPA receptor-specific RNA aptamers or RNA inhibitors on the ALS phenotype of the AR2 mice. RNA aptamers are a new group of potential ALS drug candidates, due to their high potency, selectivity and low immunogenicity. An RNA aptamer (FN1040) was continuously delivered to the cerebroventricule through an indwelling catheter that was connected to an Alzet osmotic pump. Two-week administration of the aptamer has significantly rescued the number and normalized the size of choline acetyltransferase (ChAT)-positive motor neurons in the spinal cord of AR2 mice. No sedation has been observed in the mice. Furthermore, a long-term infusion of the aptamer has blocked the progression of motor dysfunction, normalized TDP-43 mislocalization, and prevented the death of motor neurons. Our preliminary data have thus far shown a robust neuroprotective outcome on this ALS mouse model and suggest that use of AMPA receptor aptamers is a potentially new therapeutic approach for ALS.

Disclosures: M. Akamatsu: None. **T. Yamashita:** None. **S. Teramoto:** None. **Z. Huang:** None. **L. Niu:** None. **S. Kwak:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.05/L6

Topic: C.06. Neuromuscular Diseases

Title: A combination of acamprosate and baclofen (PXT864) as a potential new therapy for amyotrophic lacteral sclerosis

Authors: *L. BOUSSICAULT, J. LAFFAIRE, P. RINAUDO, S. NABIROTCHKIN, N. CHOLET, R. HAJJ, D. COHEN
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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating and fatal disease characterized by degeneration of upper and lower motoneurons leading to muscle weakness and paralysis. Currently there is no neuroprotective therapy impacting disease course and patients die on average within three years after disease onset. The only approved treatments for ALS are Riluzole and Edaravone, but their efficacy turned out to be very poor and short lasting, highlighting the urgent need for new innovative therapies. We previously demonstrated the ability of a combination therapy (PXT864) consisting of two repurposed drugs at low doses – acamprosate and baclofen – to synergistically restore a normal cellular and behavioral activity in Alzheimer and Parkinson disease models. Due to the overall overlap between genetic, molecular and cellular characteristics of these neurodegenerative diseases (i.e. GABAergic and Glutamatergic imbalance), we argued that this combination could be also effective for ALS. To this end, we first studied the effect of PXT864 in primary neuron-muscle co-cultures intoxicated by glutamate, as neuromuscular junction (NMJ) alterations play a crucial role in the progression of ALS. PXT864 was able to preserve synergistically and significantly NMJ area and number, as well as motoneurons neurite integrity against glutamate excitotoxicity as measured by NMJ and neurite specific markers. Importantly, PXT864 added to riluzole significantly improved riluzole protective effect against glutamate-induced damages on all endpoints. We next assessed PXT864 activity in primary cultures of motoneurons derived from SOD1 rats. ALS motoneurons presented severe maturation defects that were significantly improved by PXT864 combination. PXT864 was also able to protect SOD1 motoneurons and their neurites when intoxicated by glutamate, mimicking the excitotoxicity observed in ALS. Interestingly, when PXT864 was associated to riluzole, motoneurons protection was even improved. Glutamate or β-Amyloid intoxication induced an accumulation of TDP-43 protein in the cytoplasm, a hallmark of ALS. PXT864 completely prevented TDP-43 accumulation in SOD1 motoneurons and did not exhibit any negative interaction with riluzole on this endpoint. These results demonstrate the potential value of PXT864 alone or in combination to riluzole as a promising therapeutic strategy for the treatment of this severe and deadly disease.

Disclosures: L. Boussicault: A. Employment/Salary (full or part-time):; Pharnext. **J. Laffaire:** A. Employment/Salary (full or part-time):; Pharnext. **P. Rinaudo:** A. Employment/Salary (full or part-time):; Pharnext. **S. Nabirotchkin:** A. Employment/Salary (full or part-time):; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext. **N. Cholet:** A. Employment/Salary (full or part-time):; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext. **R. Hajj:** A. Employment/Salary (full or part-time):; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext. **D. Cohen:** A. Employment/Salary (full or part-time):; Pharnext. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pharnext.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.06/L7

Topic: C.06. Neuromuscular Diseases

Support: KAKENHI JP16K10787
JST PRESTO JPMJPR178C

Title: Potential of bi-directional brain machine interface using neural recording and optogenetic neuromodulation

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Abstract: A brain-machine interface (BMI) is a device, which interfaces directly with brain to control an external efforter (e.g. a robotic arm or computer). Position or touch sense is important for clinical applications of the BMI because ideal prosthetic limbs should be perceived as natural extensions of the users' bodies. We have started to design a cortical modulator using optogenetics - a new method for the manipulation of neurons to dial in potential sensory input in a bi-directional manner. Optogenetics technique reduces most of the key problems associated with electrical brain stimulation: there is no associated electrical artifact to interfere with the electrophysiological recordings, nor any tissue damage from the current injection. It also allows for precise control of the spatial pattern of stimulation. Here we report data from initial bench testing and implantation for the ECoG with LED in both the rat and non-human primate. The initial results suggest that the new ECoG array can be successfully translated from rodents to accommodate the technological challenges associated with successfully interfacing with the non-human primate brain.

Disclosures: F. Yoshida: None. **M. Hirata:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.07/L8

Topic: C.06. Neuromuscular Diseases

Support: ALSA 17-IIP-343
DoD Award nr. W81XWH-17-1-0036

Title: MRI/PET traceable microglia-targeted nanovectors: A theranostic platform for tracking and modulating neuroinflammation in amyotrophic lateral sclerosis

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Abstract: Activation and proliferation of microglia at sites of neuronal demise in the central nervous system (CNS) represents a pathological hallmark shared by both sporadic (sALS) and familial Amyotrophic Lateral Sclerosis (fALS). Increasing evidences point to skewing of microglia phenotype in favor of a neuroprotective, pro-regenerative environment/milieu as potential therapeutic strategy to slow down neuronal degeneration and improve disease outcome in ALS. We developed and characterized a novel pharmacological platform based on nanoparticles (NPs) composed of polymeric materials that can be functionalized with receptor-selective ligands to achieve specific targeting of activated microglia in ALS. To improve the potential clinical translability of these NPs, we exploited well-known ligands of the 18 kDa translocator protein (TSPO), already validated for use as PET tracers in the clinical setting (i.e. PK11195 and PBR28) to track microglia activation and neuroinflammation in ALS and several other neurodegenerative diseases. We demonstrated that these NPs target up to 30-50% of the microglia in the brain and spinal cord upon lumbar intrathecal injection. Covalent functionalization of the NPs surface with precursors of PK11195 and PBR-28 determined a TSPO-dependent uptake in microglia cell lines and did not affect specific binding to human TSPO (as demonstrated by microscale thermophoresis). Finally we demonstrated that the new NP platform developed in this project is suitable for loading and releasing small molecules or as non-viral gene delivery tool, by testing in vitro the capability to interfere with two well known molecular players involved in ALS pathology, i.e. upregulation of NADPH oxidase (NOX2) and of miR155. We are currently running a proof-of-concept preclinical study in the transgenic SOD1.G93A rodent models of ALS, to validate this NPs platform in terms of selectivity of uptake and MRI/PET traceability in the areas affected by CNS demise, and overall potential therapeutic efficacy. As compared to the commonly used gene therapy viral vectors, overall the NPs developed in this project represent a very attracting pharmacological platform, due to several advantages: i) no risk of pre-existing immunogenicity; ii) no risk of virulence or vector-related pathogenicity; iii) the possibility to combine gene delivery with release of therapeutic small molecules and iv) the possibility of tracking NPs by non-invasive approaches such as

MRI/PET. Overall this may pave the way to innovative theranostic approaches to improve ALS therapy.

Disclosures: M. Peviani: None. **R. Auriemma:** None. **U. Capasso Palmiero:** None. **M. Sponchioni:** None. **J. Molina Estevez:** None. **T. Mathews:** None. **S. Gatti:** None. **L. Politi:** None. **D. Moscatelli:** None. **A. Biffi:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.08/L9

Topic: C.06. Neuromuscular Diseases

Support: Target ALS ILC Award

Title: High-throughput screens in yeast for modifiers of TDP-43, FUS and C9orf72 toxicity identify diverse chemical lead series

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Abstract: Yeast models have proven to be an efficient method to screen for both genes of interest and small molecule modulators against toxic misfolded proteins in neurodegenerative diseases such as ALS. Yeast strains expressing TDP-43, FUS and one of the C9orf72 dipeptide repeat proteins (PR_{50}) were constructed in a drug-pump deletion background. All strains showed a toxic phenotype which was used as the end-point to screen for compounds that could antagonize this toxicity. The strains were screened against a set of 500K diverse compounds using a high-content flow cytometry assay. Unique series of compounds were identified as actives against all three proteins. We then confirmed activity in the same strains using optical density as an alternative read-out. Representative compounds were then further characterized in a TDP-43 *C.elegans* locomotion assay, a mouse NSC-34 (hTDP-43) cell line assay and in rodent primary neurons expressing hTDP-43 using a robotic microscopy assay. Several diverse lead series have emerged from this effort and target deconvolution strategies are underway in parallel

with concomitant screening of new analogs. Several putative targets have been identified from this approach. We will discuss the overall strategies and methods used.

Disclosures: D.G. Brown: A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. **C. Bardelle:** A. Employment/Salary (full or part-time):; AstraZeneca. **D. Murray:** A. Employment/Salary (full or part-time):; AstraZeneca. **L. Leach:** A. Employment/Salary (full or part-time):; AstraZeneca. **C. Stacey:** A. Employment/Salary (full or part-time):; AstraZeneca. **I. Feierberg:** A. Employment/Salary (full or part-time):; AstraZeneca. **K. Mack:** None. **A. Ford:** None. **E. Barbieri:** None. **K. Yee:** None. **R.R. Cupo:** None. **A. Javaherian:** None. **M. Aikio:** None. **N. Castello:** None. **S. Moss:** None. **A.D. Gitler:** None. **S. Finkbeiner:** None. **J. Shorter:** None. **H.J. Wobst:** A. Employment/Salary (full or part-time):; AstraZenenca. **N.J. Brandon:** A. Employment/Salary (full or part-time):; AstraZeneca.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.09/L10

Topic: C.06. Neuromuscular Diseases

Title: Pharmacodynamics of antisense oligonucleotides in the CNS of rodents and primates following central administration

Authors: *P. JAFAR-NEJAD, B. POWERS, A. SORIANO, J. MATSON, B. DEBROSSE-SERRA, P. NARAYANAN, C. MAZUR, E. E. SWAYZE, F. RIGO
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Abstract: Antisense oligonucleotide (ASO)-based therapeutics hold much promise for the treatment of neurodegenerative diseases, as demonstrated by the profound clinical benefit conferred by SPRINRAZA. To stop the production of proteins, chemically modified DNA containing ASOs bind to their complementary target RNAs and direct their catalytic degradation through the action of RNase H. The chemical characteristics of ASOs (6-7K molecular weight, highly charged molecules) results in a general lack of blood brain barrier penetration upon systemic administration. Thus, for CNS applications ASOs need to be delivery directly to the central nervous system (CNS) via intrathecal (IT) dosing. However, difficulties with delivering drugs to the brain by IT dosing have been noted due to large caudal to rostral drug concentration gradients. Here we investigated the distribution and activity of an RNase H ASO that targets MALAT1 RNA in the CNS of rodents and non-human primates (NHPs) after CNS administration. The ASO was administered at increasing doses to adult mice and rats by intracerebroventricular (ICV) and IT injections, respectively. Two weeks post injection, CNS tissues were analyzed for ASO distribution by ELISA and IHC, and RNA expression by qPCR

and ISH. We also administered ASO to cynomolgus monkeys by IT bolus injections at 25 mg on days 1, 14 and 28 and the tissue was collected 2 weeks after the last dose for ASO distribution and RNA expression. Central administration of the ASO in rodents resulted in widespread distribution of ASO and a dose-dependent reduction of Malat1 RNA in all CNS regions. Despite the larger CNS volume of cynomolgus monkeys, we also observed broad ASO distribution and target RNA reduction throughout the CNS This includes deep brain regions such as hippocampus, thalamus, amygdala, striatum and brain stem. In rodents and non-human primates, we also evaluated the activity of the ASO in the four major CNS cell types by dual ISH with a MALAT1 probe for ASO activity and a second probe to identify the cell type. This analysis showed robust ASO activity in neurons, oligodendrocytes, microglia and astrocytes throughout the CNS. Here we show that IT administration results in ASO distribution throughout the CNS regardless of CNS volume and robust activity in all the major CNS cell types. ASO technology is a versatile and powerful platform for CNS research that can be readily translated into clinical therapies.

Disclosures: P. Jafar-Nejad: A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **B. Powers:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **A. Soriano:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **J. Matson:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **B. DeBrosse-Serra:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **P. Narayanan:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **C. Mazur:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **E.E. Swayze:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. **F. Rigo:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.10/L11

Topic: C.06. Neuromuscular Diseases

Support: ALSA FOUNDATION

Title: A potent treatment effect after spinal subpial adeno-associated virus (AAV9) shRNA-SOD1 delivery in adults ALS $SOD1^{G37R}$mice

Authors: *M. BRAVO HERNANDEZ[1], T. TAKADORO[1], O. PLATOSHYN[1], S. MARSALA[1], S. DA CRUZ[2], B. K. KASPAR[4,5], D. W. CLEVELAND[2,3], M. MARSALA[1]
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Abstract: Background: Mutations in superoxide dismutase 1 (SOD1) are linked to familial amyotrophic lateral sclerosis (ALS) characterized by a progressive loss of α-motoneurons and resulting loss of motor-ambulatory and respiratory function leading to dead. Up today, there is no effective treatment for this devastating disease. Recent studies have shown that systemic delivery of AAV9_ShRNA_SOD1 slow disease progression, delay disease onset and extend survival once delivered in young ALS $SOD1^{G37R}$ mice. We have recently developed a subpial vector delivery technique and have demonstrated a potent trans-spinal transgene expression in adult rodents (mice, rat) and pig. Our current study was designed to study the SOD1 silencing effect and resulting treatment potency after subpial of AAV9_ShRNA_SOD1 delivery in adult pre-symptomatic ALS $SOD1^{G37R}$ mice. Methods: $SOD1^{G37R}$ mice or wild-type controls (150 days of age) were divided in 4 groups as follow: 1) Subpial cervical and lumbar AAV9_ShRNA_SOD1 delivery in $SOD1^{G37R}$ mice (n=17), 2) Sham surgery in $SOD1^{G37R}$ mice (n=15), 3) Positive control - no surgery ($SOD1^{G37R}$ mice) (n=5), and, 4) negative control-no surgery (n=12). After treatment the body weight, grip test and open field motor performance was monitored in 7 days intervals. On day of sacrifice (i.e. end stage time point) muscle fibrillation was recorded and spinal cord tissue harvested. The level of SOD1 silencing and neuroprotective effect was assessed by Q-PCR, immunofluorescence (neuronal and glial markers) and in situ hybridization. Results: If compared to sham-controls, animals receiving subpial injection of AAV9_ShRNA_SOD1 showed highly significant: i) delay in disease onset (343 vs 272 days) ii) delay at reaching disease end stage (493 vs 389 days), iii) improvement in grip strength, and, iv) improvement in open field motor performance. The IHC and FISH confirmed a potent (over 90%) mutated SOD1 silencing effect as assessed by decrease in SOD1 mRNA and protein with a maximum effect at 6-8 weeks. This silencing persists for minimum of 48 weeks after treatment. No detectable side effect resulting from subpial AAV9 delivery was seen. Conclusion: These data demonstrate a highly potent therapeutic effect after spinal subpial delivery of AAV9_ShRNA_SOD1. This treatment effect can be achieved even if the treatment is initiated in adult animals. Excellent safety profile in both small and large preclinical animal models (pig, non-human primates) of subpial AAV9 delivery warrant an accelerated transition of this treatment technology to human patients for treatment of inherited SOD1 mutation-linked ALS.

Disclosures: M. Bravo Hernandez: None. **T. Takadoro:** None. **O. Platoshyn:** None. **S. Marsala:** None. **S. Da Cruz:** None. **B.K. Kaspar:** A. Employment/Salary (full or part-time):; AVEXIS, INC.. **D.W. Cleveland:** None. **M. Marsala:** Other; CO-FOUNDER OF NEURGAIN TECHNOLOGIES.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.11/L12

Topic: C.06. Neuromuscular Diseases

Support: FAPESP (2013/16168-8)

Title: Human mesenchymal stem cell therapy delays progression of the disease and increases motoneuron survival in SOD1^{G93A} transgenic mice

Authors: *G. CHIAROTTO[1,2], M. V. DE CASTRO[1], A. S. S. DUARTE[1], A. C. M. LUZO[1], A. L. R. OLIVEIRA[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the selective and progressive loss of motoneurons in the spinal cord, brain stem, and motor cortex. Although the hallmark of ALS is the motoneuron degeneration, it is a non- autonomous disease with the active participation of astrocytes, microglia and T cells. Such nonneuronal cells act as protagonists of neuroinflammation, one of the main and most evident pathogenic mechanism involved in the disease progression. Pharmacological treatment with riluzole is not curative and has little effect on the prolongation of patient survival. Thus, the development of new therapeutic strategies is of utmost importance. In addition to pharmacological therapies, the use of stem cells has been heavily investigated, seeking immunomodulatory and neuroprotective effects. The objective of this study was to verify if human mesenchymal stem cells (hMSCs) from adipose tissue present therapeutic potential in SOD1^{G93A} transgenic mice. The treatment was carried out in the asymptomatic phase of the disease (10^{th} week) by a single systemic application of hMSC ($1x10^5$ cells). The animals were sacrificed at the 14th week (initial stage of symptoms) and at the end stage (ES) of the disease. The lumbar spinal cord of the animals was dissected out and processed for Nissl staining (evaluation of neuronal survival), and transmission electron microscopy (TEM) for the ultrastructural study of the alpha motoneurons at the ES of disease. Behavioral analyzes considering the onset of disease and its progression, neurological score, body weight, and motor control (rotarod test), started on the 10th week and were performed every three days until the ES of the disease. The results revealed that treatment with hMSC promoted greater neuronal survival (44%) when compared to animals of the vehicle group. However, such effect was not evidenced in the ES of the disease. TEM showed better ultrastructural preservation of the ventral horn in animals treated with hMSC. These results corroborate with the behavior data showing that hMSC delayed motor deficit and reduced the weight loss when compared to vehicle animals. Also, cell therapy delayed the course of the disease and significantly improved survival of sick animals by 15-days. Overall, our results indicate that treatment with hMSC has beneficial effects, enhancing neuronal survival, and promoting a less degenerative neuronal microenvironment. Thus, it may be considered as a promising therapy to improve quality of life and to extend the lifespan of ALS patients.

Disclosures: G. Chiarotto: None. **M.V. De Castro:** None. **A.S.S. Duarte:** None. **A.C.M. Luzo:** None. **A.L.R. Oliveira:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.12/L13

Topic: C.06. Neuromuscular Diseases

Title: Drug-like small molecules targeting catalytic multi-protein complexes that correct mislocalization of TDP-43 in ALS-FTD

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Abstract: Background: Multi-protein complex (MPC) "assembly machines" that are normally hard to detect by conventional proteomics due to their transience/lability appear to be a critical weak link in many diseases, including ALS. We have identified small molecules that target and correct aberrant MPC putative assembly machines involved in the pathophysiology of ALS.
Methods: We developed three assays. The first allows us to image nucleocytoplasmic mislocalization of proteins implicated in ALS-FTD, from patient-derived fibroblasts. The second allows us to image oxidative stress-dependent TDP-43 aggregation in stress granules. Drug resin affinity chromatography (DRAC) followed by mass spectrometry (MS-MS) provided a third biochemical assay to identify the MPC drug targets. Human transgenic TDP-43 *C.elegans* was used to corroborate the cellular and biochemical findings.
Results: One class of compound corrects mislocalization by returning TDP-43 to the nucleus. Other compound classes prevent cytoplasmically localized TDP-43 from aggregating in stress granules. DRAC analysis reveals distinct subsets of the ALS protein interactome involved in each of the three chemotypes explored to date. These compounds are active in vivo and rescue *C.elegans* transgenic from swimming-induced motor paralysis (SWIP), and prevent the motor neuron degeneration responsible for SWIP.
Conclusions: Assembly modulation is a novel and productive approach to ALS therapeutics. TDP-43 aggregates appear to be the downstream consequences of assembly events whose aberration triggers ALS. DRAC has allowed identification of the protein components of assembly machines – and shown these novel drug targets to be composed of proteins previously identified as part of the ALS disease interactome – but not previously known to be transiently together as an MPC. Our lead compound has excellent brain exposure, good pharmacokinetic properties, and is safe and well-tolerated in mice and rats. We believe this will be a treatment specifically targeting the causative molecular events leading to ALS.

Disclosures: S. Selvarajah: None. **S. Sahu:** None. **A. Moreira:** None. **N. DeYarman:** None. **D. Goldsmith:** None. **C. Maios:** None. **S.V. Trossbach:** None. **V. Bader:** None. **K. Paulvannan:** None. **V. Asundi:** None. **D. Dey:** None. **D. Solas:** None. **A. Parker:** None. **C. Korth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Prosetta Biosciences Inc. **V. Lingappa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Prosetta Biosciences Inc.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.13/L14

Topic: C.06. Neuromuscular Diseases

Support: The National Key R&D Program of China (No. 2016YFA0501902)
The National Natural Science Foundation of China (No. 31471017 and No. 81671254)

Title: Activation of the MEK/ERK pathway by TDP-43 induces the innate immune responses and contributes to ALS pathogenesis

Authors: *X. DENG[1,2], Z. WANG[1], X. SUN[1,2], S. QIU[1], Y. DUAN[1,2], G. DUAN[1], A. DU[1], Y. FANG[1,2]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a rapid progression neurodegenerative disease characterized by motor neuron degeneration and loss. Mutations in the gene encoding TAR DNA binding protein 43 (TDP-43) can cause ALS, and TDP-43-containing cytoplasmic inclusions are a pathologic hallmark of ALS. However, the underlying mechanism of TDP-43-induced neurodegeneration remains unclear. Using a previously established *Drosophila* model of ALS (Kim et al., 2014), we conducted a targeted screen of kinases that modifies TDP-43 neurotoxicity. In the screen, we found that knockdown of *Downstream of raf1* (*Dsor1*), the *Drosophila* homologue of MAPK kinase (MEK), significantly suppressed the TDP-43-induced photoreceptor cell neurodegeneration, age-dependent climbing deficit, and shortened lifespan. Further, we showed that the protein abundance, phosphorylation levels or subcellular distribution of TDP-43 was not affected by downregulation of *Dsor1*. These data indicate that the modifying effect of *Dsor1*/MEK is not due to an alteration of TDP-43 *per se*. Instead, it is possible that TDP-43 affects the MAPK pathway, which may be involved in the disease pathogenesis. Indeed, we found that in TDP-43 flies, the phosphorylation level of rolled (rl), the downstream target of the Dsor1/MEK and the homologue of the mammalian extracellular signal-regulated kinase (ERK), was significantly elevated, suggesting that TDP-43 activates the MEK/ERK pathway.

Furthermore, we demonstrated that activation of MEK/ERK pathway by overexpression of activated *rl* in fly neurons led to neurodegeneration, whereas suppression of the MEK/ERK pathway by knockdown of *rl* significantly ameliorated the degenerative phenotypes of the TDP-43 flies. Our most recent data suggested that TDP-43-mediated activation of the MEK/ERK pathway induced innate immune responses in the fly model. Most encouragingly, we discovered that an FDA-approved MEK inhibitor for treatment of some cancers significantly reduced TDP-43-induced immune responses and neurodegeneration, and extended the lifespan of the fly model. Together, these findings indicate that TDP-43 induced dysfunction of innate immunity by abnormal MEK/ERK activation may directly contribute to ALS and MEK inhibitors that mitigate this process may represent a novel therapeutic approach.

Disclosures: X. Deng: None. **Z. wang:** None. **X. sun:** None. **S. qiu:** None. **Y. duan:** None. **G. duan:** None. **A. du:** None. **Y. fang:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.14/L15

Topic: C.06. Neuromuscular Diseases

Support: ALS Association
NINDS
Department of Defense
CIRM

Title: Development of novel small molecule autophagy inducers for treatment of ALS

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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects motor neurons. It results in paralysis and loss of control of vital functions, such as speech, swallowing and breathing, leading to premature death. Life expectancy of ALS patients averages 2–5 years from diagnosis. Mutations in a number of genes including SOD1, TDP43, and FUS can cause familial ALS. Furthermore, mislocalization and aggregation of wildtype TDP43 has been observed in motor neurons from nearly all sporadic ALS patients. It has been suggested that in ALS and other neurodegenerative diseases, misfolded proteins cause cellular dysfunction that leads to neurodegeneration. Autophagy is a cellular mechanism by which misfolded proteins, toxic protein aggregates, and injured organelles are directed to the lysosome to be degraded and recycled as nutrients to the cell. Therefore drugs that can induce autophagy in neurons could be beneficial for ALS and neurodegenerative diseases in general. We

have invented a novel automated robotic microscopy and single-cell longitudinal imaging platform to investigate neurodegeneration in iPSC-derived motor neurons from ALS patients. We utilized our imaging system to create HTS-amenable patient iPSC-derived cellular models for ALS and test libraries of novel small molecules with therapeutic potential. We designed a series of novel small molecule autophagy inducers based on a previously discovered pharmacophore and carried out structure-activity relationship studies to identify lead compounds that can induce autophagy in neurons and rescue neurodegeneration in patient-derived cellular models of ALS. These molecules are blood brain penetrant and could be developed as therapeutics for ALS and other neurodegenerative diseases. This work was supported by NINDS, CIRM, ALS Association, and Department of Defense.

Disclosures: **A. Javaherian:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Caspian Therapeutics Inc. **N. Castello:** None. **M. Chan:** None. **A. Baral:** None. **S. Finkbeiner:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Caspian Therapeutics Inc.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.15/L16

Topic: C.06. Neuromuscular Diseases

Support: Shire Pharmaceuticals Contract

Title: A novel therapeutic approach to treat the neuromuscular weakness caused by Spinal Muscular Atrophy

Authors: *K. S. OJALA, Y. LI, M. LIANG, P. WIPF, S. MERINEY
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Abstract: Spinal Muscular Atrophy (SMA) is the most common genetic cause of infant and childhood death. A null genetic mutation in the SMN1 gene causes ubiquitously low levels of Survival of the Motor Neuron (SMN) protein critical during activity-dependent neuromuscular development. Low SMN expression causes neuromuscular pathology, severely reduced synaptic transmission, and leads to neuromuscular denervation and subsequent α-motoneuron degeneration. The gradual loss of motoneurons results in muscular paralysis and culminates in early death due to respiratory failure. The only FDA-approved approach to treat SMA is to use antisense oligonucleotides (ASOs) to target a paralogous gene, SMN2, to increase protein expression. While SMA pathology is improved by centrally administered ASO treatment, evidence suggests that ASOs have limited peripheral penetration, and thus provide suboptimal

benefit to neuromuscular junctions during the critical period of development. This incomplete rescue of the neuromuscular system will require long-term maintenance to ameliorate the progressive functional decline beyond childhood (after the requirement for high SMN expression in motoneurons is over). Furthermore, many SMA patients lack access to ASO therapy due to medical costs, treatment availability, and immune rejection. New treatments for SMA should complement current treatment by targeting withstanding deficits via an SMN2-independent strategy. We have evaluated a novel treatment using a calcium channel agonist, GV-58, in combination with a potassium channel blocker, 3,4-DAP. In ex vivo recordings from SMNdelta7 model mouse synapses, GV-58 plus DAP can increase the magnitude of transmitter released following action potential activity. Furthermore, we have shown that acute in vivo administration of GV-58 + DAP to PD8-10 SMNdelta7 mouse pups increases grip strength compared to healthy littermates. Our novel treatment might be used in conjunction with current ASO therapy, or as a stand-alone strategy to improve neuromuscular function in patients requiring SMN-independent approaches to treat weakness.

Disclosures: K.S. Ojala: 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.; Shire Pharmaceuticals. **Y. Li:** 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.; Shire Pharmaceuticals. **M. Liang:** 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.; Shire Pharmaceuticals. **P. Wipf:** 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.; Shire Pharmaceuticals. **S. Meriney:** 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.; Shire Pharmaceuticals.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.16/L17

Topic: C.06. Neuromuscular Diseases

Title: Intrathecal AAV9-SOD1-shRNA administration for amyotrophic lateral sclerosis

Authors: *G. M. THOMSEN[1], S. B. LIKHITE[2], S. CORCORAN[2], A. KASPAR[1], K. FOUST[1], L. BRAUN[1], K. C. MEYER[2], B. K. KASPAR[1]
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is an adult-onset neurodegenerative disease, characterized by loss of motor neurons, progressive paralysis and death. Dominant mutations in the superoxide dismutase 1 (*SOD1*) gene are among the most frequent causes of inherited ALS. Previously, we evaluated gene replacement therapy utilizing adeno-associated virus serotype 9 (AAV9), a vector that efficiently crosses the blood brain barrier, carrying a GFP reporter to deliver a short hairpin RNA (shRNA) downregulating SOD1. This vector significantly improved disease outcome in ALS mouse models. The treatment was well-tolerated, but the presence of a foreign transgene and regulatory elements excluded a direct application of this vector in human clinical trials. We therefore developed an AAV9-SOD1-shRNA vector, AVXS-301, designed for use in clinical trials. We determined that AVXS-301 is efficient in reducing SOD1 levels both in vitro and in vivo. ICV administration in $SOD1^{G93A}$ mice at postnatal day 1 resulted in therapeutic benefit nearly twice of that achieved with the previous GFP-containing construct. We have now reported one of the longest survival extensions achieved in the most severe ALS mouse model with one single cerebrospinal fluid (CSF) administration of AVXS-301. In preparation for future application in human clinical trials, we have administered AAV9-SOD1-shRNA to both young (one-year-old Cynomolgus macaque) and adult (10-year-old Rhesus monkey) non-human primates and have shown that this is both safe and effective in knocking down SOD1 in the central nervous system (CNS). These studies are critical for determining a safe and effective dose that can be successfully translated in clinical trials for ALS patients.

Disclosures: G.M. Thomsen: A. Employment/Salary (full or part-time):; AveXis, Inc.. **S.B. Likhite:** None. **S. Corcoran:** None. **A. Kaspar:** None. **K. Foust:** A. Employment/Salary (full or part-time):; AveXis, Inc.. **L. Braun:** None. **K.C. Meyer:** None. **B.K. Kaspar:** A. Employment/Salary (full or part-time):; AveXis, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AveXis, Inc.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.17/L18

Topic: C.06. Neuromuscular Diseases

Support: NIH HL093056
T32HL094294

Title: Novel small molecules promote axon outgrowth over CSPGs

Authors: *M. R. BLAKE[1], R. GARDNER[1], H. JIN[2], M. S. COHEN[3], B. A. HABECKER[4]
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Abstract: Neurons are unable to regenerate following many types of injury including spinal cord injury and myocardial infarction (MI). A component of the extracellular matrix, chondroitin sulfate proteoglycans (CSPG), prevents reinnervation of the damaged site. While CSPGs can be degraded enzymatically by bacterial chondroitinase ABC to promote nerve regeneration, enzymatic approaches are limited for human use. The CSPG receptor, protein tyrosine phosphatase σ (PTPσ), has been targeted to promote nerve regeneration after spinal cord injury and MI. In those studies, targeting PTPσ yielded promising recovery of motor function after spinal injury and protection against arrhythmias after myocardial infarction. To date, there are no small molecules that can restore nerve growth by modulating CSPG signaling. We have generated novel small molecules, HJ-01 and HJ-02, which restore sympathetic axon growth over CSPGs in vitro. Trk receptors are substrates for PTPσ, and activation of TrkB with brain derived neurotrophic factor (BDNF) leads to an increase in downstream-phosphorylated ERK1/2 kinases. Addition of PTPσ to TrkB expressing human embryonic kidney (HEK), however, decreases BDNF-stimulated ERK1/2 phosphorylation. HJ-01 and HJ-02 both restored BDNF-stimulated ERK1/2 phosphorylation in the presence of PTPσ. These results suggest that HJ-01 and HJ-02 prevent negative regulation of TrkB by PTPσ. Similarly, addition of HJ-02 prevents CSPG mediated modulation of collapsin response mediator protein 2 (CRMP2) phosphorylation in sympathetic neurons. In a mouse model of MI, both compounds promoted sympathetic reinnervation of the cardiac scar and, surprisingly, restored cardiac function as measured by echocardiography. Taken together our results suggest that these novel small molecules could prove therapeutically useful in promoting nerve regeneration over CSPGs.

Disclosures: M.R. Blake: None. **R. Gardner:** None. **H. Jin:** None. **M.S. Cohen:** None. **B.A. Habecker:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.18/M1

Topic: C.06. Neuromuscular Diseases

Title: Evaluating HDAC6 as therapeutic target for Amyotrophic Lateral Sclerosis by antisense-mediated inhibition in the adult mouse CNS

Authors: *K. LING[1], L. SUN[2], Y. LUO[2], M. ZHANG[2], A. MCCAMPBELL[2], F. RIGO[1]
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Abstract: Genetic ablation of *Hdac6* has been shown to delay disease progression and increase survival in the $SOD1^{G93A}$ mouse model of Amyotrophic Lateral Sclerosis (ALS). To evaluate the therapeutic potential of HDAC6 inhibition in ALS, we developed antisense oligonucleotides (ASOs) that specifically target *Hdac6* and investigated whether CNS-directed HDAC6 reduction was sufficient to mitigate disease phenotypes in $SOD1^{G93A}$ mice. Intracerebroventricular injection of HDAC6-ASO in adult mice robustly reduced HDAC6 expression in brain and spinal cord. HDAC6 reduction also resulted in an increase in acetylation of a known HDAC6 substrate α-tubulin suggesting efficient target engagement. However, ASO-mediated HDAC6 reduction it did not improve compound muscle action potential or survival of $SOD1^{G93A}$ mouse model of ALS. These findings suggest that HDAC6 inhibition in the adult mouse CNS is not sufficient as a therapeutic approach for SOD1-ALS.

Disclosures: K. Ling: A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals, Inc. **L. Sun:** A. Employment/Salary (full or part-time):; Biogen. **Y. Luo:** A. Employment/Salary (full or part-time):; Biogen. **M. Zhang:** A. Employment/Salary (full or part-time):; Biogen. **A. McCampbell:** A. Employment/Salary (full or part-time):; Biogen. **F. Rigo:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals, Inc..

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.19/M2

Topic: C.06. Neuromuscular Diseases

Support: ALSA Milton Safenowitz Postdoctoral Fellowship

Title: Retinoid activating nanoparticles increase lifespan and reduces neurodegeneration in the $SOD1^{G93A}$ mouse model of ALS

Authors: *D. X. MEDINA, E. P. CHUNG, C. TEAGUE, R. SIRIANNI, R. P. BOWSER
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Abstract: Retinoic acid (RA) has been established to have important roles in both neuronal development and normal nervous system function. Recent evidence has shown that changes in the RA signaling pathway are correlated with ALS pathology and other neurodegenerative disorders. In this study, we sought to examine the neuroprotective role of retinoic acid (RA) signaling in amyotrophic lateral sclerosis (ALS). We hypothesized that activation of retinoid signaling will reduce disease progression in $SOD1^{G93A}$ transgenic mouse model of ALS.

Specifically, we investigated the therapeutic value of targeted retinoid activation via the RA receptor β (RARβ). To address this question, we utilized adapalene, an FDA approved RARβ agonist, which our lab had previously found to be neuroprotective in cultured motor neurons. Currently adapalene is used clinically as a topical treatment for dermatological disorders, however, due to its hydrophobicity, and rapid clearance rates, delivery of this drug to the nervous system is a major challenge for assessing its therapeutic value. To address this, we engineered adapalene loaded polymeric nanoparticles (Adap-NPs) composed of poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) to achieve delivery to the CNS. Adap-NPs were administered to $SOD1^{G93A}$ transgenic mice via lateral tail vein injections 3x a week starting at 61 days of age. Motor function was measured weekly using different motor tasks, (e.g. rotarod) during treatment to determine treatment effect on disease progression. Treatment effect on survival, disease onset and progression were measured. Markers of neurodegeneration and inflammation in the spinal cord were also measured to determine the effect of Adap-NPs on ALS-like pathology. We found that chronic administration of Adap-NPs resulted in a significant increase in average lifespan in transgenic mice and delayed disease progression (Gehan-Breslow-Wilcoxon test $p=0.03$; $p=0.04$, respectively). This increase was associated with significantly improved motor performance in multiple motor tasks, and reduction of roughly 50% in spinal motor neuron loss in transgenic mice ($p<0.05$). These data provide supporting evidence for targeting the retinoic acid signaling pathway as a therapeutic approach for ALS. In addition, this study also highlights value of utilizing nanomedicine approaches to improve the delivery of drug candidates.

Disclosures: D.X. Medina: None. **E.P. Chung:** None. **C. Teague:** None. **R. Sirianni:** None. **R.P. Bowser:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.20/M3

Topic: C.06. Neuromuscular Diseases

Support: NS097080

Title: ALS drug discovery via high-throughput phenotypic screening using iPSC-derived human motor neurons

Authors: M. HENDRICKSON[1], J. KOUZNETSOVA[2], W. ZHENG[2], *Z.-W. DU[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease primarily affecting motor neurons. Over the past two decades, over 70 candidate drugs were identified

from studies with model animals and immortalized human cell lines expressing disease-causing mutations. Unfortunately, there are only two drugs approved to treat the condition, neither of switch increases patient survival by more than a few months. This sobering reality highlights the urgent need for new therapeutic development for ALS. However, new and more relevant cell culture are needed to reduce the attrition rate. One such approach is the use of neurons differentiated from patient induced pluripotent stem cells (iPSCs), which present new opportunities for modeling disease processes and screening drug libraries. We have developed technology to produce very large quantities of highly enriched human neurons from patient iPSCs and to greatly accelerate their maturation. We subsequently developed a high-throughput screening (HTS) system using human motor neurons derived from individuals with amyotrophic lateral sclerosis (ALS). Using genome editing techniques on the iPSC line, the reporter nanoluciferase (Nluc) was fused to endogenous neurofilament light chain (NFL). The assay was adapted to meet HTS requirements, including: large batch sizes, 1536-well format, minimal well-to-well variation, short-term culture, plating by automated dispenser, and low reagent volumes. Applying a quantitative HTS approach, we screened the LOPAC, NPC, and MIPE libraries (>6,000 compounds) in a dose dependent manner and show a hit rate of ~0.5%. One of these hits increase the NFL level by ~60% with no observed toxicity and is currently undergoing further investigation.

Disclosures: M. Hendrickson: A. Employment/Salary (full or part-time):; BrainXell, Inc.. **J. Kouznetsova:** None. **W. Zheng:** None. **Z. Du:** A. Employment/Salary (full or part-time):; BrainXell, Inc..

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.21/M4

Topic: C.06. Neuromuscular Diseases

Title: Apilimod rescues C9orf72 repeat expansion-induced phenotypes *in vivo*

Authors: *K. A. STAATS[1], C. SEAH[2], Y. WANG[5], M. CHATEAU[3], N. KOUTSODENDRIS[2], D. KIM[2], A. SAHIMI[2], P. CANNON[3], B. V. ZLOKOVIC[6], J. ICHIDA[4]
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a rare devastating progressive paralysis with no cure. Frontal Temporal Dementia (FTD) is the second most frequent form of dementia after Alzheimer's disease, for which also no cure is known. The main known cause of these diseases is

a hexanucleotide repeat expansion (HRE) in *C9orf72*. It is predicted that the repeat expansion contributes to neurodegeneration by both a loss of function (decreased transcription of the *C9orf72* gene) and gain of function (e.g. dipeptide repeat protein production). Recently, apilimod, a PIKfyve kinase inhibitor, was identified able to rescue neurodegeneration, in a drug screen performed at the Ichida lab on induced motor neurons (iMNs) from ALS patients harboring the C9orf72 HRE. Here, we show effects of the *C9orf72* HRE and the therapeutic potential of apilimod on these effects *in vivo*. We show that a haploinsufficiency of C9orf72 in mouse motor neurons leads to a decrease in early endosomes and lysosomes, which are both increased after treatment with apilimod. Additionally, we show that glutamate receptors are increased in hippocampal neurons of *C9orf72* knockout mice, and that this increase induces a vulnerability to excitotoxic insults. Apilimod treatment decreases both the levels of glutamate receptors in hippocampal neurons as well as decreases the vulnerability of these cells to an excitotoxic insult *in vivo*. To conclude, we show that apilimod also addresses the gain-of-function pathology induced by the *C9orf72* HRE by decreasing the number of dipeptide repeat proteins in hippocampal neurons *in vivo*. In summary, our data showed a neuroprotective effect of the FDA approved compound, apilimod, in *in vivo* mouse models of *C9orf72* HRE-induced ALS and FTD.

Disclosures: K.A. Staats: None. **C. Seah:** None. **Y. Wang:** None. **M. Chateau:** None. **N. Koutsodendris:** None. **D. Kim:** None. **A. Sahimi:** None. **P. Cannon:** None. **B.V. Zlokovic:** None. **J. Ichida:** Other; Co-founder of AcuraStem.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.22/M5

Topic: C.06. Neuromuscular Diseases

Title: Graphene based biomarker platform for amyotrophic lateral sclerosis

Authors: *A. SEKSENYAN[1,2], B. KEISHAM[3], S. DENYER[2], P. KHEIRKHAH[2], G. D. ARNONE[2], P. AVALOS[4], A. D. BHIMANI[2], C. SVENDSEN[4], V. BERRY[3], A. I. MEHTA[2]
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Abstract: Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease, characterized by rapid loss of upper and lower motor neurons resulting in patient death from respiratory failure within 3-5 years of initial symptom onset. Although at least 30 genes of major effect have been reported, the pathobiology of ALS is not well understood. Compounding this is the lack of a reliable laboratory test which can accurately diagnose and monitor the

progression of this rapidly deteriorating disease. This barrier has created a severe road-block for researchers trying to develop novel therapeutics and clinicians initiating treatments. Therefore, alongside identification of etiologies and therapeutics, development of a diagnostic and prognostic biomarker is a foremost research priority. Herein, we report the use of graphene, a sensitive nanomaterial, in combination with Raman spectroscopy to identify specific signals in the cerebrospinal fluids (CSF) of ALS patients which can be used to develop a diagnostic biomarker. Graphene, a 2-dimensional sheet with a honeycomb lattice comprised of sp^2 hybridized carbon atoms, possesses an ultrasensitive surface which can detect even a single molecule attachment. The phononic properties of graphene are influenced by the dipole potential of any biomaterial attached on its surface. When graphene is interfaced with a molecule, the dipole of the interfaced molecule induces an electric field on graphene thereby modifying its carrier concentration. This alteration affects the vibrational energies of graphene which can be mapped using Raman spectroscopy. Using CSF from ALS patients, we demonstrate that the second-order overtone of in-plane phonon vibration energies (2D) of interfaced graphene can be sensitively modified by the components in the CSF. The n-doping mechanism employed by our platform is disease specific and was able to distinguish ALS from other neurodegenerative diseases, including other motor neuron diseases and multiple sclerosis (MS). Moreover, by using the rat $SOD1^{G93A}$ model of ALS, we were able to monitor the progression of the disease by our graphene biomarker platform. These results establish for the first time, to our knowledge, the use of graphene to study human CSF and demonstrate changes in its phononic properties that can be utilized for studying neurodegenerative diseases and biomarker development.

Disclosures: A. Seksenyan: None. **B. Keisham:** None. **S. Denyer:** None. **P. Kheirkhah:** None. **G.D. Arnone:** None. **P. Avalos:** None. **A.D. Bhimani:** None. **C. Svendsen:** None. **V. Berry:** None. **A.I. Mehta:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.23/M6

Topic: C.06. Neuromuscular Diseases

Support: NIH 1R01NS097679

Title: Mitochondria as axonal calpastatin-conveyors to prevent programed neuromuscular synaptic elimination

Authors: *X. WANG
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Abstract: Skeletal muscles undergo atrophy in response to diseases and aging. Here we report that mitofusin 2 (Mfn2), a protein mainly located in the mitochondrial outer membrane, functions as a dominant suppressor of neuromuscular synaptic loss to preserve skeletal muscles in disease and during aging. Mfn2 is reduced in spinal cords of a mouse model of motor neuron disease (transgenic $SOD1^{G93A}$ mice) and aged mice. Through preserving neuromuscular synapses, the forced expression of Mfn2 in motor neurons is sufficient to prevent skeletal muscle wasting in both $SOD1^{G93A}$ and aged mice. By contrast, deletion of Mfn2 in motor neurons produces neuromuscular synaptic dysfunction and skeletal muscle atrophy in wild type mice. Neuromuscular synaptic loss after sciatic nerve transection can also be alleviated by upregulation of Mfn2 in motor neurons. Mfn2 coexists with calpastatin, an endogenous specific inhibitor of the calpain system crucial for nerve terminal protein degradation and synaptic function, largely in mitochondria-associated membranes (MAMs), and regulates the levels of calpastatin in motor axons via an active axonal transport mechanism dependent on mitochondrial trafficking. Genetic inactivation of calpastatin abolishes Mfn2-mediated protection of neuromuscular synapses. Our results suggest that Mfn2 is a potential key component of a novel and heretofore unrecognized mechanism of cytoplasmic protein transport and proteolysis control. By selectively targeting calpastatin-enriched MAMs to nerve terminals to inhibit the localized protein degradation, Mfn2 may play a general role in preserving neuromuscular synapses in disease, during aging and upon nerve injury, and serve as a common therapeutic target for skeletal muscle atrophy.

Disclosures: X. Wang: None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.24/M7

Topic: C.06. Neuromuscular Diseases

Support: NIH grant R01NS093491
NIH grant R01CA161056
NIH grant P30MH075673

Title: Dendrimer conjugated GCPII inhibitor improves motor deficits in the $SOD1^{G93A}$ mouse

Authors: *C. TALLON[1], A. SHARMA[2], Z. ZHANG[2], A. G. THOMAS[5], C. ROJAS[6], S. P. KAMBHAMPATI[2], R. SHARMA[2], K. LIAW[3], S. KANNAN[4], R. M. KANNAN[2], B. SLUSHER[1]
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Univ. Sch. of Med., Baltimore, MD; [6]Johns Hopkins Drug Discovery, Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Glutaminate carboxypeptidase II (GCPII) is metalloenzyme that catalyzes the hydrolysis of N-acetyl aspartylglutamate to glutamate (Glu) and N-acetylaspartate. Basal GCPII activity is low in mocroglia, however, under stimulation or pathological conditions, GCPII activity is upregulated leading to excess Glu. Excess glutamate receptor activation leads to glutamate excitotoxicity which has been associated with several neurodegenerative diseases, such as ALS. Consequently, inhibiting GCPII is an attractive target for intervention. Our group and others have shown that blocking GCPII activity in ALS mouse models improves motor neuron cell survival. Even though many classes of GCPII inhibitors have been synthesized, they have issues related to poor oral availability, instability and limited brain penetration, hampering their development as CNS therapeutics. To combat this, we conjugated a potent GCPII inhibitor, 2-PMPA, onto a hydroxyl PAMAM dendrimer (D-2PMPA) which has been previously shown to selectively penetrate the brain under conditions of inflammation and specifically target activated microglia and astrocytes. We verified that the D-2PMPA was able to get into $SOD1^{G93A}$ C57Bl/6 mouse brains using Cy5 labeled dendrimer and observed overlapping staining of the Cy5 signal with microglia in both the brain and spinal cord as early as 8 weeks of age, indicating localization with microglia. We then initiated a therapeutic trial of twice weekly 20mg/kg IP injections of D-2PMPA or dendrimer alone beginning at 12-13 weeks of age in both male and female SOD1 mice. Motor function was monitored every other week over 8 weeks for males and 10 weeks for females by measuring rotarod and grip strength performance. We observed a statistically significant improvement in the grip strength of the male mice following 2 weeks of treatment that persisted until 6 weeks of treatment ($p<0.05$) with a positive trend at 8 weeks ($p=0.09$). With the females, we observed a significant preservation of grip strength after 10 weeks of D-2-PMPA treatment versus dendrimer alone ($p<0.01$). Importantly, none of the mice showed overt signs of toxicity or weight loss. Current efforts are focused on increasing study power and histology to determine muscle innervation and motor neuron survival during treatment. Our results demonstrate that utilizing dendrimer mediated targeting of 2-PMPA is able to not only enter the brain and spinal cord of $SOD1^{G93A}$ mice but that it also produces positive effects on grip strength, even nearing the final stages of the disease. If translated, this could provide patients with prolonged muscle strength and therefore the possibility of longer independence.

Disclosures: C. Tallon: None. **A. Sharma:** None. **Z. Zhang:** None. **A.G. Thomas:** None. **C. Rojas:** None. **S.P. Kambhampati:** None. **R. Sharma:** None. **K. Liaw:** None. **S. Kannan:** None. **R.M. Kannan:** None. **B. Slusher:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.25/M8

Topic: C.06. Neuromuscular Diseases

Support: Prize4life
The Pape-Adams
RGK Foundation

Title: The molecular tweezer, CLR01, inhibits SOD1 aggregation *in vitro* and in the G93A-SOD1 mouse model of ALS

Authors: *R. MALIK[1], H. MENG[1], C. FONTANILLA[1], C. I. CORRALES[1], N. SEPANJ[1], S. R. ATLASI[1], F.-G. KLÄRNER[4], T. SCHRADER[4], M. WIEDAU-PAZOS[1], G. BITAN[1,2,3]
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Abstract: Introduction: Mutations in Cu-Zn Superoxide Dismutase (SOD1) cause 15-20% of familial amyotrophic lateral sclerosis (fALS) cases. The amino-acid substitutions caused by these mutations destabilize the protein's structure leading to its self-assembly into toxic oligomers and aggregates hypothesized to cause the motor neuron degeneration in affected patients with fALS. Currently, disease-modifying therapy is not available for ALS. Molecular tweezers (MTs) are broad-spectrum inhibitors of the self-assembly and toxicity of amyloid proteins. They disrupt key hydrophobic and electrostatic interactions, thus preventing the formation of toxic oligomers and aggregates. Objectives: 1) To determine the effect of the molecular tweezer, CLR01 on the aggregation of ALS-related forms of SOD1 in vitro. 2) To test CLR01 in the G93A-SOD1 mouse model. Specifically, we asked if CLR01 could inhibit SOD1 aggregation in the mice and whether such inhibition would improve motor function, delay disease onset, delay mortality, and/or affect the survival of neuronal cells in the spinal cord. Methodology: Recombinant SOD1 variants were incubated in the absence or presence of CLR01 and monitored by ThT fluorescence and electron microscopy. G93A-SOD1 mice were treated by daily subcutaneous injection of 0, 0.5, or 5 mg/kg CLR01 starting at a pre-symptomatic stage at 50 days of age until meeting criteria for euthanasia. Animal behavior and motor function were tested. Spinal cords were analyzed by immunohistochemistry. Results: CLR01 inhibited the aggregation of WT and disease-associated variants of SOD1 in vitro. The aggregation of all variants was inhibited completely at a 5-fold molar excess of CLR01. Treated mice did not show improved motor function. A small decrease in disease duration was found in the 0.5 mg/kg group, ~23% in males and ~37% in females (p= 0.0427). In contrast, the high dose group did not differ significantly from vehicle-treated mice. Misfolded SOD1, measured by the misfolded-SOD1-specific antibody 10C12 was reduced significantly in both treatment groups, demonstrating target engagement. The data demonstrate that CLR01 can inhibit SOD1 misfolding and aggregation both in vitro and in vivo, yet additional studies are needed to determine the therapeutic potential of this approach.

Disclosures: R. Malik: None. **H. Meng:** None. **C. Fontanilla:** None. **C.I. Corrales:** None. **N. Sepanj:** None. **S.R. Atlasi:** None. **F. Klärner:** None. **T. Schrader:** None. **M. Wiedau-Pazos:** None. **G. Bitan:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.26/M9

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01NS079339
MDA Grant 254860

Title: Pharmacological inhibition of BACE1 enhances peripheral nerve regeneration in ALS disease model

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Abstract: Amyotrophic Lateral Sclerosis (ALS), the most common degenerative disease of motor neurons in adults, is characterized by progressive dying back of motor axons and death of motor neurons eventually leading to muscle wasting and death. In the peripheral nervous system, intact axons close to neuromuscular junctions (NMJ's) vacated in the disease process can sprout in attempt to innervate the vacant NMJ. Adaptive sprouting is seen both in ALS patients and the SOD1 mouse, albeit limited, and is quickly overtaken by the disease course. An agent that enhances outgrowth and promotes sprouting of peripheral nerves could potentially slow the progression of ALS symptoms.

Our lab discovered that when Beta-site APP Cleaving Enzyme (BACE1), is inhibited, the rate of axonal regeneration is significantly improved. BACE1 is an aspartyl protease best known for its role in cleavage of amyloid precursor protein (APP) of Alzheimer's Disease (AD). Our previously published work suggests an inverse relationship between BACE1 levels and regeneration in the peripheral nervous system. Therefore, we are exploring the possibility of identifying pharmacological inhibition of BACE1 as a means to improve the quality of life for patients with motor neuron diseases with dying-back axonopathy, such as ALS. Using the $SOD1^{G93A}$ mouse, we are examining the cutaneous maximus muscle (CMM), which is innervated by axons from the lateral thoracic nerve (LTN). We previously characterized the degeneration of the LTN-CMM system in SOD1 mice and found that it is an ideal system for testing drug efficacy at early disease stages. The CMM is an appealing muscle in which to study motor degeneration in ALS because it only contains type II neuromuscular synapses innervated by pure fast-fatigable alpha-motor axons, which are the most vulnerable to degeneration. It is innervated by a single motor nerve, the LTN, which allows for space-time resolution from caudal degeneration to rostral degeneration.

After starting treatment at 1 month of age, we observed that 1-2 months steady supply of oral

BACE1 inhibitor decreases the extent of denervation and enhances axo-terminal sprouting in SOD1 mice. Our preliminary data suggest mice treated with inhibitor for an extended time (3 months) have increased innervation compared to vehicle treated controls. We are also investigating if inhibitor treatment during the disease course (starting treatment at 2-3 months) can increase reinnervation and sprouting. Since in-depth safety and pharmacokinetics data have already been obtained from AD clinical trials, we anticipate that BACE1 inhibition may be a viable option for extending the retention of motor function in patients with ALS.

Disclosures: K.L. Marshall: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck. **C. Tallon:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck. **M.E. Kennedy:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck. **M.H. Farah:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.27/M10

Topic: C.06. Neuromuscular Diseases

Title: *In vivo* pharmacological blockade of mGlu5 receptors by the negative allosteric modulator CTEP ameliorates the disease progression in the SOD1^{G93A} mouse model of amyotrophic lateral sclerosis

Authors: *C. USAI[1], M. MILANESE[2,3], T. BONIFACINO[2], C. TORAZZA[2], F. PROVENZANO[2], S. RAVERA[2], C. REBOSIO[2], M. BALBI[2], G. BONANNO[2,3]
[1]Natl. Rese Council, Genova, Italy; [2]Dept. of Pharmacy, Unit of Pharmacol. and Toxicology, [3]Ctr. of Excellence for Biomed. Res., Univ. of Genova, Genova, Italy

Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by loss of motor neurons (MNs). Although the etiology is not completely understood and has been ascribed to numerous causes, one major reason for MNs death is glutamate (Glu)-mediated excitotoxicity. At present there is no effective cure for ALS; thus, focused drug therapies are definitely needed. In this scenario, Group I metabotropic glutamate receptors (mGluR1 and mGluR5) represent potential targets for intervention, since they are actively involved in the regulation of cellular processes altered in ALS. We have previously demonstrated that activation of presynaptic mGluR1 and mGluR5 autoreceptors by the mixed mGluR1/5 agonist (S)-3,5-Dihydroxyphenylglycine (DHPG) resulted in the stimulation of Glu release in the spinal cord of WT and *SOD1^{G93A}* mice, which involved both mGluRs. While DHPG was active at micro-molar concentrations in WT mice, it was much more potent in *SOD1^{G93A}* mice, being operative at nanomolar concentrations, an effect mainly involving mGluR5 (PMID: 22634363). More

recently, we have shown that knocking-down mGluR1 (PMID: 24361555) or mGluR5 (PMID: 29656361) in *SOD1*^{G93A} mice significantly delays the disease onset, prolongs survival and ameliorates the clinical progression of ALS. Based on these results, we investigated here the effect of the pharmacological blockade of mGluR5 in SOD1^{G93A} mice administering 2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1H-imidazol-4-yl)ethynyl)pyridine (CTEP), an orally bioavailable, mGluR5 negative allosteric modulator (NAM), at the doses of 2 mg/kg every 48h or 4 mg/kg every 24h by gavage, starting at the early symptomatic stage of the disease (90 days of life). Clinical onset, survival probability, progression of the disease, and disease cellular hallmarks were analyzed in drug-treated vs. vehicle-treated SOD1^{G93A} mice. CTEP produced a dose dependent amelioration of clinical facets. The lower dose only barely produced positive pharmacological effects; the higher dose significantly postponed the disease onset, increased survival probability and improved motor abilities in treated mice. These effects were more prominent in female than in male SOD1^{G93A} mice. Thus, the pharmacological blockade of mGluR5 has a significant impact *in-vivo* on ALS clinical outcome. In conclusion, our previous and present results suggest that mGluR5 may represent a promising target in ALS and the pharmacological data here presented provide a rationale for the possible use of CTEP or other mGluR5 NAMs, already under clinical study, for the cure.

Disclosures: C. Usai: None. **M. Milanese:** None. **T. Bonifacino:** None. **C. Torazza:** None. **F. Provenzano:** None. **S. Ravera:** None. **C. Rebosio:** None. **M. Balbi:** None. **G. Bonanno:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.28/M11

Topic: C.06. Neuromuscular Diseases

Support: ALS Association
MeiraGTx

Title: More expansive gene transfer to the rat CNS: AAV PHP.EB vector dose-response and comparison to AAV PHP.B

Authors: R. D. DAYTON, M. S. GRAMES, *R. L. KLEIN
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Abstract: Abstract
Engineered recombinant adeno-associated virus (AAV) vectors have advanced the transduction of neurons in the CNS on an expansive, wide-scale basis since the papers first using AAV9 for this purpose. Wide-scale CNS expression could be relevant to gene therapy as well as be indispensable for basic studies such as disease-modeling and functional studies. For example, the

wide-scale gene transfer approach could expedite hypothesis testing in vivo relative to the generation of germ-line transgenic mice for all of the genes of interest. Wide-scale gene transfer is more efficient in neonatal subjects than in adults, so improving upon gene transfer efficiency in adults is an important goal. Here we characterized the relatively novel engineered AAV PHP.EB vector for expansive gene transfer in the CNS of adult rats at three doses over a one log range. The dose-response data were consistent; expression levels can be controlled in a reproducible manner in the rat from moderate to robust levels. Within the CNS, the AAV PHP.EB derived expression was neuron-selective to neuron-specific, while outside the CNS, organs such as the liver and heart were transduced by the parenteral gene delivery. Though we demonstrated graded expression levels, only the high dose, 1.2 x 10e14 vector genomes/kg, yielded efficient expression in spinal cord motor neurons of the adult rat, so this vector dose would be required for models of spinal cord motor neuron disease. The neuronal expression in the rat CNS was greater with AAV PHP.EB than the previous engineered vector AAV PHP.B. AAV PHP.EB is thus one of the most efficient AAV vectors in the field for CNS gene transfer.

Disclosures: R.D. Dayton: None. **M.S. Grames:** None. **R.L. Klein:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.29/M12

Topic: C.06. Neuromuscular Diseases

Title: An *in vivo* screening platform for ALS targets using ALS rodent models

Authors: *L. SUN[1,2], G. TOMASSY[3], Y. LUO[3], M. ZHANG[3], J. AMACKER[3], Y. CHEN[3], S. SU[3], A. MCCAMPBELL[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease characterized by degeneration of upper and lower motor neurons in the brain and spinal cord. ~10% of patients with ALS are defined as having familial ALS (fALS), which is typically inherited as a highly penetrant, dominant trait. The remaining 90% of cases are classified as sporadic (sALS) because they lack a clear family history, although this term does not preclude a genetic contribution in these cases. Searching for effective therapies for ALS remains a challenging quest for several reasons. First, no good sALS animal model and only a few good fALS models are available. Second, ALS-relevant disease phenotypes/endpoints in animal models are often slow-manifesting, which slows down process of efficacy evaluation. Third, the delivery of therapeutic modalities to the brain and spinal cord remains difficult. Here we report an in vivo screening platform for ALS targets using rodent models. We established appropriate delivery methods for exploratory therapies of different modalities. We also identified several

disease-relevant functional endpoints to evaluate the efficacy of the exploratory therapies. Importantly, these functional endpoints can be measured at early stage of the disease, even before the onset of visible motor deficits, dramatically reducing the length of in vivo studies. Using this platform, we tested several ALS therapies and validated the efficacy of BIIB067 IONIS-SOD-1_{Rx}, which is now in phase I clinical trial.

Disclosures: L. Sun: None. **G. Tomassy:** None. **Y. Luo:** None. **M. Zhang:** None. **J. Amacker:** None. **Y. Chen:** None. **S. Su:** None. **A. McCampbell:** None.

Poster

208. Therapeutic Developments in ALS

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 208.30/M13

Topic: C.06. Neuromuscular Diseases

Title: Neuromuscular synapse preservation with MuSK #13 agonist antibody does not lead to functional benefits in the $SOD1^{G93A}$mouse model of ALS

Authors: *S. L. DOMINGUEZ[1], A. SENGUPTA-GHOSH[1], Z. JIANG[1], T. EARR[1], J. IMPERIO[1], L. XIE[2], K. BARCK[2], J. EASTHAM-ANDERSON[3], H. CAI[4], G. AYALON[1], R. CARANO[2], A. EASTON[1]
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Abstract: Synapse loss at the neuromuscular junction (NMJ) is one of the major pathological phenotypes that occur in patients with amyotrophic lateral sclerosis (ALS), as well as in animal models of ALS, specifically in $SOD1^{G93A}$ mice. It has been hypothesized that NMJ loss may occur upstream of motor neuron death. In turn, protection of the NMJ may delay motor neuron death through an as yet unknown retrograde signaling and delay disease progression. To test this hypothesis, we treated $SOD1^{G93A}$ mice with an agonist antibody to MuSK, a receptor tyrosine kinase involved in maintaining muscle synapses, and measured: 1) preservation of synapses in the diaphragm and 2) benefits on diaphragm function and respiration. We used three different methods to assess diaphragm and lung function across the course of disease (Phrenic nerve compound muscle action potentials (PhMN CMAP), plethysomography and MicroCT). We found that anti-MuSK treatment preserved diaphragm NMJs compared with control treated mice, but found no delay in the functional decline. While $SOD1^{G93A}$ mice showed significantly reduced diaphragm CMAP by 10 weeks of age and respiratory deficits between 18 -22 weeks of age, chronic anti-MuSK treatment, beginning at 6 wks of age, had no effect on any of these measures. Moreover, there were no treatment effects on weight loss, ALS disease progression (paralysis), motor neuron loss (specifically in C3-5), or overall survival. These data suggest that preservation

of the neuromuscular junction in the diaphragm via MuSK activation is not sufficient to protect $SOD1^{G93A}$ mice from spinal motor neuron loss, respiratory deficits, and ultimately survival.

Disclosures: S.L. Dominguez: A. Employment/Salary (full or part-time):; full time, Genentech. **A. Sengupta-Ghosh:** A. Employment/Salary (full or part-time):; full time, Genentech. **Z. Jiang:** A. Employment/Salary (full or part-time):; full time, Genentech. **T. Earr:** A. Employment/Salary (full or part-time):; full time, Genentech. **J. Imperio:** A. Employment/Salary (full or part-time):; full time, Genentech. **L. Xie:** A. Employment/Salary (full or part-time):; full time, Genentech. **K. Barck:** A. Employment/Salary (full or part-time):; full time, Genentech. **J. Eastham-Anderson:** A. Employment/Salary (full or part-time):; full time, Genentech. **H. Cai:** A. Employment/Salary (full or part-time):; full time, Genentech. **G. Ayalon:** A. Employment/Salary (full or part-time):; full time, Genentech. **R. Carano:** A. Employment/Salary (full or part-time):; full time, Genentech. **A. Easton:** A. Employment/Salary (full or part-time):; full time, Genentech.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.01/M14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant NS 043205
King's College London Graduate School International Studentship

Title: Early onset gait abnormalities and novel sites of CNS pathology in a mouse model of CLN1 disease

Authors: H. R. NELVAGAL[1,3,4], C. SHYNG[2], M. S. SANDS[2], *J. D. COOPER[1,3,4]
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Abstract: The neuronal ceroid lipofuscinoses (NCLs) are a group of progressive childhood neurodegenerative lysosomal storage disorders. Each is caused by a mutation in a different gene and all forms are fatal. Infantile NCL (INCL, CLN1 disease) is an early onset and rapidly progressing form of NCL. It is caused by mutations in the *CLN1* gene, which codes for the lysosomal enzyme palmitoyl protein thioesterase-1 (PPT1). While the brain was always thought to be the main locus of pathology in humans and Ppt1-deficient ($Ppt1^{-/-}$) mice, significant spinal pathology that contributes to clinical outcome has recently been described in CLN1 disease. In this study, we characterized changes in the gait of $Ppt1^{-/-}$ mice using a semi-automated gait

analysis system, which revealed unexpectedly early abnormalities including a period of hypermotility. This occured at a time when the mice were otherwise asymptomatic, and was followed by a progressive overall loss of motor function. Analyzing pathology in the brainstem and spinal cord revealed characteristic and profound neuroinflammation and neuron loss, which occured before similar events started in either the brain or cerebellum, but corresponded to the progression of gait abnormalities. There was also novel evidence for post-natal developmental deficits and pronounced white matter pathology in the spinal cord, as well as significant pathology in other regions of the sensorimotor pathways. We also explored progressive changes in the expression of markers for pain in the spinal cord to explain the early period of hypermotility. Taken together, the observed progressive gait abnormalities in *Ppt1*$^{-/-}$ mice and pathological changes in these largely unexplored regions of the CNS may help explain the limited success of previous brain-directed therapies for CLN1 disease. They also fundamentally change our understanding of the progression and site-specific disease pathogenesis in CLN1 disease. This will greatly impact the timing and targeting of future therapeutic approaches for the NCLs.

Disclosures: H.R. Nelvagal: None. **C. Shyng:** None. **M.S. Sands:** None. **J.D. Cooper:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.02/M15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: BMBF GO-Bio

Title: Targeting autopaghy in ALS by BiAgil - A specific TGFßRII LNA-ASO

Authors: *S. KUESPERT[1], R. HEYDN[1], S. PETERS[1], E. ZITZELSPERGER[1], T.-H. BRUUN[1], L. J. AIGNER[2], U. BOGDAHN[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a multifactorial neurodegenerative lethal disorder with no effective treatment so far. The current molecular genetic campaign is increasingly elucidating the molecular pathogenesis of this fatal disease. A critical process in the pathogenesis of numerous neurodegenerating disorders including ALS is an autophagy dysfunction. Dyslocalization and cytoplasmic aggregation of proteins indicate defects in protein trafficking and may correlate to severity of disease progression. Analysis of post mortem tissue from sporadic ALS but also familiar ALS patients provide evidence for accumulation of toxic

aggregates. An emerging target for mediating a homeostatic protein dysfunction represents the Transforming Growth Factor-ß (TGF-ß) system. Previous studies demonstrate enhanced TGF-ß ligand concentrations within plasma, Cerebrospinal Fluid (CSF), but also spinal cord samples of ALS patients. This growth factor is also involved in mediating autophagic activities either directly or by indirect effects. Taken together, a reduced TGF-ß-signaling might represent an interesting target to modulate dysfunction in autophagy. A novel LNA antisense-oligonucleotide "BiAgil" targeting the TGF-ßRII contributes to an improved clearance of protein aggregates by inhibiting TGF-ß signaling. Therefore, neuronal precursor cells (ReNcell CX cells) were treated with pathological levels of TGF-ß following BiAgil application. Factors important in autophagy like e.g. p62, mTor, Ulk-1, Atg7, PI3K were analyzed by quantitative real-time RT-PCR, immunoblotting and immunocytochemistry.Results indicate that blocking cellular TGF-ß signaling by BiAgil leads to an improved clearance of toxic aggregates by boosting autophagy in neuronal precursor cells (ReNcell CX cells). Thus, BiAgil seems to be a promising candidate for a treatment approach in ALS.

Disclosures: R. Heydn: None. **S. Peters:** None. **E. Zitzelsperger:** None. **T. Bruun:** None. **L.J. Aigner:** None. **U. Bogdahn:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.03/M16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: SFB CRC 128 - B06

Title: Connexin 32-deficient mice show increased susceptibility to induced autoimmune neuro-inflammation: An effect mediated by the intrinsic disinhibition of cortical neurons?

Authors: *M. CERINA[1], P. HUNDEHEGE[1], J. VOGT[1], A. M. HERRMANN[1], S. EICHLER[1], S. AUFMKOLK[3], T. BUDDE[2], E. SPECKMANN[2], K. GÖBEL[1], N. MELZER[1], S. G. MEUTH[1]
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Abstract: The interdependency between inflammation and neurodegeneration is a crucial point for understanding the pathophysiological mechanism of many diseases, including multiple sclerosis (MS). Recent evidence supports the hypothesis that activation of immune cells and their infiltration into the central nervous system (CNS) alter neuronal network activity in MS patients and in some animal models. However, at the same time, numerous and recent evidence support

also the hypothesis that the CNS requires the interactions with the immune system for a correct functioning. Here, we aim to understand the dynamics of such mechanisms.
Transgenic mice lacking the gap junction protein Connexin32 ($Cx32^{-/-}$), known to be characterized by an intrinsic impaired inhibitory system and wild types (WT), were immunized to induce an experimental autoimmune encephalomyelitis (EAE) in the CNS. Then, consequences of inflammation were investigated on well-known and structured cortico-thalamic networks by performing functional assays in vitro and in vivo. Neuronal activity was shown to be altered in $Cx32^{-/-}$ animals compared to WT: brain fluorescence maps of activity show abnormal spatio-temporal patterns of activation and propagation in response to electrical stimulation of cortical neuronal networks. Novel object recognition tests indicated that both short- and long-term memory were impaired compared to WT controls. Interestingly, inducing EAE in $Cx32^{-/-}$ led to a worsening of the disease course in comparison to controls at late stages of the disease. The latter is generally associated to neurodegenerative - rather than inflammatory mechanisms. This conclusion would be corroborated by unaltered levels of CNS inflammation markers and behavioral phenotype upon immunization. Taken together, our findings would suggest that the intrinsic disinhibition of cortical neurons of $Cx32^{-/-}$ mice may be responsible for cognitive impairments and increased susceptibility to inflammatory attacks, which in a reciprocal manner, might further impact on neuronal activity and neurodegeneration.

Disclosures: M. Cerina: None. **P. Hundehege:** None. **J. Vogt:** None. **A.M. Herrmann:** None. **S. Eichler:** None. **S. Aufmkolk:** None. **T. Budde:** None. **E. Speckmann:** None. **K. Göbel:** None. **N. Melzer:** None. **S.G. Meuth:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.04/M17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Regulation of muscleblind-like 2 reduction in neurodegeneration

Authors: *L.-H. WANG[1,2], G.-S. WANG[1,2]
[1]Inst. of Biomed. Sciences, Academia Sinica, Taipei, Taiwan; [2]Taiwan Intl. Grad. Program in Interdisciplinary Neuroscience, Natl. Yang-Ming Univ. and Academia Sinica, Taipei, Taiwan

Abstract: The Muscleblind-like (MBNL) protein family plays an important role in the regulation of developmental alternative splicing, polyadenylation transitions and in the pathogenesis of myotonic dystrophy type 1 (DM1). DM1 is the most common cause of adult-onset muscular dystrophy. Brain involvement in DM1 includes mental retardation, attention deficit and hyperactivity disorder, excessive daytime sleepiness and psychiatric disorders. Decline in

cognitive function with age is a common feature of adult-onset DM1. The genetic basis of DM1 is an expansion of CTG trinucleotide repeats in the 3' untranslated region of Dystrophia Myotonica Protein Kinase (DMPK) gene. Mutant DMPK mRNA binds and sequesters MBNL proteins, resulting in their loss-of-function. In vitro characterization of MBNL family members revealed that different MBNL members exhibit distinct susceptibility to expanded CUG RNA and affinity to the splicing pre-mRNAs. Whether MBNL members differentially respond to expanded CUG RNA in vivo remains elusive. We generated a mouse model for postnatal expression of expanded CUG RNA in the brain that recapitulates DM1 brain features, including misregulated alternative splicing and neurodegeneration. We showed that reduced MBNL1 cytoplasmic content is an early event response to expanded CUG RNA, whereas reduced MBNL2 expression associated aberrant MBNL2-regulated alternative splicing was a relatively late event. We then further investigate the causal mechanism of neurodegeneration associated MBNL2 reduction. We also determine whether the temporal expression pattern of MBNL2 is correlated with its role in controlling developmental regulated alternative splicing.

Disclosures: L. Wang: None. **G. Wang:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.05/M18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: ATM is activated by ATP depletion and modulates mitochondrial function through NRF1

Authors: *H. CHOW[1,2], A. CHENG[1], X. SONG[1], M. SWERDEL[3], R. P. HART[3], K. HERRUP[1]
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Abstract: Cerebellar atrophy, a prominent symptom of ataxia telangiectasia (A-T), is closely associated with altered expression of TCA cycle and oxidative phosphorylation genes. A-T is caused by mutations in the ATM gene, and we find that ATM-deficient neurons have reduced oxidative phosphorylation capacity. They cannot increase ATP production in response to neuronal activity because they cannot activate nuclear respiratory factor-1 (NRF1), a transcription factor that regulates dozens of nuclear-encoded mitochondrial genes. Reduced ATP levels induce oxidative activation of ATM, which then phosphorylates NRF1 at T259. Phosphorylated NRF1 homo-dimerizes, translocates to the nucleus and drives mitochondrial gene expression. Modelling data suggest that the link to ataxia is through the high energy needs of Purkinje cell activity. In the context of ATM deficiency, these needs make Purkinje cells

uniquely vulnerable to mitochondrial dysfunction and cell death. Our findings identify ATM as a guardian of mitochondrial output as well as genomic integrity.

Disclosures: H. Chow: None. **A. Cheng:** None. **X. Song:** None. **M. Swerdel:** None. **R.P. Hart:** None. **K. Herrup:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.06/N1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: H2020-MSCA-IF-2014-658352
H2020-MSCA-COFUND-2014-665919
JCI-2015-24576
RyC-2012-11873
ERC-2014-StG-638106
SAF2014-57981P

Title: Unraveling neuronal pathology driving Leigh syndrome

Authors: *I. BOLEA[1], A. GELLA[1], E. SANZ[1], P. PRADA[1], P. MACHUCA[1], F. K. KALUME[2], A. QUINTANA[1]
[1]Inst. de Neurociències. UAB, Bellaterra, Spain; [2]Ctr. for Integrative Brain Res., Seattle Children's, Seattle, WA

Abstract: Dysfunctions of the mitochondrial energy-generating machinery cause a series of progressive, untreatable and usually fatal diseases collectively known as mitochondrial disease (MD). High energy-requiring organs such as the brain are especially affected, leading to developmental delay, ataxia, respiratory failure, hypotonia, seizures and premature death. While only discrete neuronal populations are susceptible, their molecular identity and their contribution to the disease remain unknown. Mice lacking the mitochondrial Complex I subunit *Ndufs4 (*Ndufs4KO mice*)*, recapitulate the classical signs of Leigh Syndrome (LS), the most common presentation of MD, with predominant CNS affectation. Here, we identify the critical role of two genetically-defined neuronal populations driving the fatal phenotype in Ndufs4KO. Selective inactivation of *Ndufs4* in *Vglut2*-expressing glutamatergic neurons (cKO^{Vglut2} mice) causes brainstem inflammation, motor and respiratory deficits and early death. On the other hand, *Ndufs4* deletion in *Gad2*-expressing GABAergic neurons (cKO^{Gad2} mice) leads to basal ganglia inflammation without motor or respiratory involvement, but accompanied by severe epileptic seizures that precede a premature death. These results provide novel insight in the cell type-

specific contribution to LS pathology and open new avenues to understand the underlying cellular mechanisms of mitochondrial disease.

Disclosures: I. Bolea: None. **A. Gella:** None. **E. Sanz:** None. **P. Prada:** None. **P. Machuca:** None. **F.K. Kalume:** None. **A. Quintana:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.07/N2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Canadian Institutes of Health Research (CIHR)
Fonds de recherche du Québec – Santé (FRQS)

Title: Early neuronal pathogenesis and dysfunction by the activation of AMP-activated protein kinase - Mammalian target of rapamycin pathway

Authors: *N. A. BELFORTE, J. L. CUEVA VARGAS, A. DI POLO
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Abstract: Purpose: Metabolic stress has been proposed to contribute to neuronal damage in glaucoma, but the mechanism driving this response is not understood. The adenosine monophosphate-activated protein kinase (AMPK) is a master regulator of energy homeostasis that becomes active at the onset of energy stress. AMPK is a potent inhibitor of the mammalian target of rapamycin complex 1 (mTORC1), which we showed is essential for the maintenance of retinal ganglion cell (RGC) dendrites, synapses, and survival. Here, we tested the hypothesis that AMPK is an early mediator of metabolic stress in glaucoma. Methods: Unilateral elevation of intraocular pressure was induced by injection of magnetic microbeads into the anterior chamber of mice expressing yellow fluorescent protein in RGCs. Inhibition of AMPK was achieved by administration of siRNA or compound C. RGC dendritic trees were 3D-reconstructed and analyzed with Imaris (Bitplane), and survival was assessed by counting Brn3a or RBPMS-labeled soma and axons in the optic nerve. RGC function was examined by quantification of anterograde axonal transport after intraocular administration of cholera toxin β-subunit. Retinas from glaucoma patients were analyzed for expression of active AMPK. Results: Ocular hypertension triggered rapid upregulation of AMPK activity in RGCs concomitant with loss of mTORC1 function. AMPK inhibition with compound C or siRNA effectively restored mTORC1 activity and promoted an increase in total dendritic length, surface and complexity relative to control retinas. Attenuation of AMPK activity led to robust RGC soma and axon survival. For example, 95% of RGCs (2983 ± 258 RGCs/mm^2, mean ± S.E.M.) survived with compound C

compared to 77% in vehicle-treated eyes (2430 ± 233 RGCs/ mm^2) (ANOVA, $p<0.001$) at three weeks after glaucoma induction (n=8-10/group). Importantly, blockade of AMPK activity effectively restored anterograde axonal transport. Lastly, RGC-specific upregulation of AMPK activity was detected in human glaucomatous retinas relative to age-matched controls (n=11-15/group). Conclusions: Metabolic stress in glaucoma involves AMPK activation and mTORC1 inhibition promoting early RGC dendritic pathology, dysfunction and neurodegeneration.

Disclosures: J.L. Cueva Vargas: None. **A. Di Polo:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.08/N3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACyT Grant No. 575264
CONACyT Grant No.252808

Title: Chronic olanzapine administration attenuates memory alteration and neuronal abnormalities in prefrontal cortex and nucleus accumbens induced by animal model of schizophrenia in the rat

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Abstract: Olanzapine (OLZ) is an atypical antipsychotic widely used in the treatment of Schizophrenia (SCHZ), however its mechanism of action has not been fully described yet. Besides the neonatal ventral hippocampal lesion (nVHL) has emerged as a model of schizophrenia-related behavior in the rat. These rats exhibit behavioral changes that manifest mainly after puberty. Together with the behavioral alterations, neural morphological changes have been reported in this model. We recently demonstrated that nVHL animals exhibit dendritic atrophy and spine loss in the Prefrontal Cortex (PFC) and Nucleus Accumbens (Nacc). This study aimed to determine whether OLZ treatment (0.25 mg/kg/day for 21 days) was capable of reducing PFC and Nacc neuronal alterations observed in nVHL rats. We evaluated Novel Object Recognition in these animals. The morphological evaluation included examination of dendrites using the Golgi-Cox procedure.

Golgi-Cox staining revealed that nVHL induced dendritic retraction and spine loss in PFC pyramidal neurons and Medium Spine Neurons in Nacc. Interestingly, repeated OLZ treatment ameliorated dendritic pathology and neuronal loss in the PFC and Nacc of the nVHL rats. Our data show that OLZ may foster recovery of PFC and Nacc damage in post-pubertal nVHL rats and suggests that the use of neuroleptic agents for the management of some schizophrenia-related symptoms may help to understand the PFC and Nacc alterations pathways in these disorders (Supported by: CONACyT grants (No. 575264) to HTB and (No.252808) to GF).

Disclosures: R.A. Vazquez: None. **D.J. Apam-Castillejos:** None. **G. Flores:** None. **H. Tendilla:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.09/N4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Improving the translatability of stem cell research through the intersections of xenofree and reproducibility protocol development

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Abstract: Despite the great promise of stem cell research, the introduction of xenogenic (animal-origin) materials continues to contaminate and severely limit their neuroscientific and clinical applicability. Specifically, the use of xenogenic materials in induced pluripotent stem cell (iPSC) and support media introduces a range of negative research and ethical factors including: (1) increased variability in model systems (2) limitations to predictive value to human physiology (3) risk of transfer of pathogens (4) animal suffering and (5) delays and/or failing regulatory requirements in clinical applications. In order to address these concerns our group has established the Xeno Free (XF) Initiative [http://www.xenofree.org]. A main goal of the XF Initiative is to create an open resource for scientists to develop and adopt research approaches that are free of animal-derived reagents and media as well as provide an online community for xenofree stem cell research. In the process of establishing the toolkit, our initial examination of over 100 peer-reviewed publications using xenofree methods, issues of standardization for the online protocols became an increasing concern. Related issues of reproducibility and how to assess the validity of the methods used in research also arose. Here we describe how the process of developing this repository and online community has met with -- and is working to overcome -- such real-world issues, including: [i] documentation and accessibility to automated techniques

(ii) cataloguing xenofree media, materials and vendors (iii) developing common nomenclature and formats in a large diverse research field (iii) protocol versioning, (iv) preserving knowledge against loss of institutional and laboratory memory due to ad hoc laboratory practices and researcher migration. We also analyzed the roadmaps and outputs of other research resource projects and examined best practices in similar efforts to remove materials of animal-origin (e.g., fetal-bovine-serum-free studies). To further help refine the development of our xenofree stem cell toolkit, we also drew as inspiration methods used by on-line tech communities and industry sectors (e.g., open software development, online marketplaces). In creating this XF stem cell research resource we have discovered that such open collaborative efforts not only have the intended effects of improving translational relevance of studies, but also have the potential to help inform reproducibility issues more broadly in neuroscience as well as other research domains.

Disclosures: A. Lam: None. **F. Li:** None. **E.L. Ohayon:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.10/N5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FP7 GA ERC-2012-SyG_318987–ToPAG

Title: Aggregation of artificial β-sheet proteins causes lysosomal dysfunction in neurons

Authors: *A. MISHRA[1], T. SCHÄFER[2], N. RAIMUNDO[3], R. KLEIN[1], W. BAUMEISTER[2], I. DUDANOVA[1], R. FERNÁNDEZ-BUSNADIEGO[2]
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Abstract: Protein aggregates in neurodegenerative diseases exert toxicity through different mechanisms including the loss of native function of the misfolded protein and the toxic gain of function. Therefore, in conjunction with efforts to decipher the physiological role of disease proteins, it is crucial to study the poorly understood toxic gain of function effects that contribute to disease etiology. In this study, we analyzed cortical neurons expressing artificial aggregating β-sheet proteins (β-proteins) that accumulate into toxic aggregates to understand common mechanisms that lead to neuronal dysfunction and neurodegeneration. Using correlative cryo-electron tomography, we observed that β-proteins aggregate into large, irregular inclusions. Neurons harboring β-protein aggregates showed alterations in lysosomal morphology. Moreover,

autolysosomal function was impaired, as demonstrated by dysregulation of autophagosomal markers and reduction in cathepsin proteolytic activity. Thus, aggregation per se may underlie the autolysosomal defects observed in many neurodegenerative diseases. Of note, an interactome screen identified AP-3 μ1, a subunit of the AP-3 complex that is involved in protein trafficking from the Golgi apparatus to lysosomes, as the strongest interactor of β-proteins in neurons (poster by Riera Tur, et al.). We showed that AP-3 μ1 colocalizes with β-protein aggregates, and β-protein toxicity in cortical neurons was partially rescued by AP-3 μ1 overexpression. Thus, AP-3 μ1 sequestration may be a critical determinant of lysosomal dysfunction and β-protein toxicity in neurons. Interestingly, AP-3 μ1 was also sequestered by mutant huntingtin exon1 inclusion bodies suggesting relevance of our findings for aggregation of natural disease-causing proteins.

Disclosures: A. Mishra: None. **T. Schäfer:** None. **N. Raimundo:** None. **R. Klein:** None. **W. Baumeister:** None. **I. Dudanova:** None. **R. Fernández-Busnadiego:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.11/N6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Mass spectrometry imaging (MSI) identifies region-specific changes in the cerebral pattern of lipid distribution in a mouse model of Niemann-Pick-disease type C1 (NPC1)

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Abstract: NPC1 is a rare autosomal-recessive lipid transport and storage disorder affecting peripheral tissues as well as the brain, where progressive dysmyelination and neurodegeneration occurs along with strong accumulation of gangliosides GM2 and GM3. Histological studies revealed a distinct degeneration of the corpus callosum and Purkinje cells, but detailed information on affected functional regions is still lacking. We used heterozygous inbreeding pairs of NPC1 mice (BALB/cNctr-Npc1m1N/J) to generate *NPC1−/−* and control wild type mice. Male and female 60-70 day old *NPC1−/−* and control mice (n=10) were anesthetized with

pentobarbital and decapitated, in agreement with European guidelines (2010/63/EU) and approved by the governmental Ethics Committee (study 7221.3-1-01-011/16). The brains were dissected, frozen in isopentane (-40°C) and 10 µm sections cut in a cryostat. Matrix assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) was used for lipid analysis. Adjacent sections were coated with 2, 5-dihydroxybenzoic acid (DHB) and analyzed in positive and negative ion mode using a MALDI LTQ-Orbitrap XL mass spectrometer at 100 µm lateral resolution, followed by cytoarchitectonic staining and evaluation. SCiLS Lab MVS, version 2018, was used to identify discriminative peaks and generate MS images. Lipids were assigned from LIPID MAPS (http://www.lipidmaps.org) based on the high accuracy mass measurement (5 ppm mass tolerance). In agreement with previous data, GM2 (d18:1/18:0) and GM3 (d36:1) levels were significantly increased in multiple regions in *NPC1−/−* brains, including cerebral cortex. However, the highest levels occurred in amygdala (amy), followed by olfactory bulb (ob), hippocampus (CA3) and slight increases in retrosplenial cortex (RS), thalamus (Th) and cerebellar cortex (Cb/gm). In addition, we found significant region-specific accumulation of ganglioside GM1(d38:1) and phosphoinositol (PI 36:4), with highest levels for GM1 in RS, Th, and Cb/gm and for PI (36:4) in RS, Th, Ob, piriform cortex (Pc) and corpus callosum (CC). Sulfatides (ST), such as ST (d18:1/24:1) levels were significantly reduced in CC, Th, Amy, Rs Pc, CA3 and internal capsule but remained stable in cerebellar white mater. This indicates a wider range of cerebral lipid changes in brains of *NPC1−/−* mice which allows a functionally analysis of behavioral tests, provides indications for new therapeutic interventions related to new target lipids and opens new avenues for a targeted analysis of pathology-related connectivity changes at the macro- and microscale using new techniques such as polarized light imaging both in animal models and in humans.

Disclosures: H. Bidmon: None. **E. Gonzalez de San Roman:** None. **M. Witt:** None. **A. Wree:** None. **K. Amunts:** None. **P.F. Huesgen:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.12/N7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MRC MR/N004582/1
Parkinson's UK G-1602

Title: Wallerian degeneration: From mice, flies and fish to people

Authors: *M. P. COLEMAN[1], A. LORETO[2], P. HUPPKE[3], E. WEGENER[3], C. ANGELETTI[4], X. YANG[2], G. ORSOMANDO[4], J. GILLEY[2]

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Abstract: The Wallerian degeneration of injured axons is regulated by a pathway that involves PHR1, NMNAT2, SARM1 and Axed and is largely conserved between mammals, *Drosophila* and fish. Animal and cell culture models show that physical injury is just one way to initiate this pathway. Others include apoptotic death of the soma, genetic or toxic axonal transport impairment, protein synthesis inhibition, mitochondrial uncoupling and specific knockdown or deletion of NMNAT2. Consequently, models of diseases involving these mechanisms can be alleviated, such as Parkinson's disease, peripheral neuropathy, glaucoma, motor neuron disease, traumatic brain injury and ischemia. Most strikingly, specific activation of the Wallerian pathway by NMNAT2 deletion causes a fatal nerve growth phenotype that is permanently rescued when SARM1 is also deleted.
While these studies indicate widespread therapeutic potential, the limitation of animal and cellular models means there is still uncertainty about which specific human diseases involve the Wallerian pathway. Here, we report the first human gene mutations involving Wallerian pathway genes and their association with rare axonal disorders. By profiling additional coding variants of NMNAT2 and SARM1 we are testing their scope to influence axon vulnerability in the human population. We show that low NMNAT2 expression level also causes axon vulnerability in mice that is likely to be more pronounced in longer human axons. We conclude that Wallerian pathway activation causes one or more rare human disorders and suggest that additional variation in coding sequence and expression level is a likely disease modifier of common human neurodegenerative diseases. As drugs blocking Wallerian degeneration are developed, this will help to show where they can be most effective.

Disclosures: M.P. Coleman: None. **A. Loreto:** None. **P. Huppke:** None. **E. Wegener:** None. **C. Angeletti:** None. **X. Yang:** None. **G. Orsomando:** None. **J. Gilley:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.13/N8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: miRNA let7i inhibits the progesterone-induced protection against oxidative stress in both glial and neuronal cells

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Abstract: Previously, our laboratory reported that Pgrmc1 is a critical mediator of progesterone-induced BDNF release from astrocytes, which in turn, is necessary to elicit downstream signaling events that are vital for cell viability. Given this critical role that Pgrmc1 plays in mediating progesterone's protective effects, we wanted to explore what regulates Pgrmc1. In silico analysis revealed that Pgrmc1 can be regulated by the microRNA, Let7i. As such, we hypothesized that Let7i decreases Pgrmc1, thereby limiting the protective efficacy of progesterone. Our data revealed that transfection of C6 astrocytes and differentiated SH-SY5Y cells with a let7i mimic decreased the expression of Pgrmc1 mRNA and protein levels. Furthermore, transfection with the let7i mimic also disrupted the protective efficacy of progesterone against H_2O_2-induced oxidative stress. Interestingly, we discovered that H_2O_2 itself resulted in an increase in let7i expression in both C6 and SH-SY5Y cell lines. These data support the potential role of let7i as a negative regulator of progesterone-induced cytoprotection, and consequently, provide insight into the possibility that inhibition of let7i expression may be a strategy to facilitate progesterone's protective efficacy, especially against insults/ diseases in which oxidative stress plays a role (e.g., stroke, traumatic brain injury, and such neurodegenerative diseases such as Alzheimer's disease). Moreover, variation in the extent of overexpression of let7i could also help explain the variability of response to progesterone.

Disclosures: S. Kim: None. **M. Singh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.14/N9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: *In vitro* characterization of the unfolded protein response as a mechanism of neurodegeneration

Authors: *A. J. SANTIAGO-LOPEZ[1,3,4], A. F. NAZZARI[1], K. BERGLUND[2], C.-A. N. GUTEKUNST[1], R. E. GROSS[1]
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Abstract: Background: Chronic activation of the unfolded protein response in the ER (UPR^{ER}) has been identified in various models of neurodegenerative diseases including in Parkinson's Disease (PD). Tunicamycin, a *N*-glycosylation inhibitor and well-known pharmacological inducer of UPR^{ER}, has been recently proposed as a "neurotoxin" that induces parkisonian-like features that include dopaminergic cell death and endogenous alpha-synuclein aggregation. One prominent neuropathological feature of PD is the loss of synaptic connections in the nigrostriatal

pathway due to severe axonal degeneration and neuritic dystrophy. Herein, we sought to investigate whether activation of the UPR^{ER} would induce morphological changes indicative of a neurodegenerative phenotype. **Methods:** We conducted quantitative immunofluorescence analysis of primary cortical neurons treated with 5-$\mu g \cdot mL^{-1}$ of tunicamycin over a period of 24 hr. Using semi-automated image analysis, we quantified the effects of tunicamycin on neurite morphology and classical markers of the UPR^{ER}. **Results:** Our preliminary results indicate that exposure of primary neurons to tunicamycin for at least 24 hr results in an overall reduced morphological complexity as evidenced by a decrease in neurite length, neurite branching, and terminal end-points, compared to vehicle-treated controls. These observations coincide with the expression of CCAAT-enhancer-binding protein homologous protein (CHOP), a downstream product of the PERK/ATF4 arm of the UPR^{ER}, and an indicator of apoptosis. We further examined potential regulators of the neuronal cytoskeleton and found increased levels of Ser3-phosphorylated actin-modulating protein cofilin-1 in neurons undergoing UPR^{ER} compared to untreated cultures. We are currently expanding our investigation to characterize the role of PERK/ATF4 signaling in orchestrating these events and evaluating whether alpha-synuclein pathology induces a similar reorganization of the neuronal cytoskeleton. **Conclusion:** Our preliminary results provide additional evidence to support the use of sustained activation of UPR^{ER} as a simplified model of neurodegeneration and for the modulation of the UPR^{ER} as a therapeutic approach in neurodegenerative diseases.

Disclosures: A.J. Santiago-Lopez: None. **A.F. Nazzari:** None. **K. Berglund:** None. **C.N. Gutekunst:** None. **R.E. Gross:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.15/N10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant HL140182
NIH Grant NS102495
NIH Grant HL66299
NIH Grant HL135003
NIH Grant HL60024

Title: Pseudomonas aeruginosa induced endothelial amyloids impair mouse learning

Authors: *M. T. LIN, Y. XU, X. ZHA, R. BALCZON, T. STEVENS
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Abstract: Critically ill patients who develop hospital-acquired pneumonia are at increased risk of cognitive decline. However, the mechanisms underlying cognitive dysfunction are unknown. *Pseudomonas aeruginosa* is a gram-negative bacterium that causes nosocomial pneumonia. *Pseudomonas aeruginosa* directly induces cytotoxic lung endothelial amyloid and oligomeric tau production and release via its type 3 secretion system and injection of exoenzymes. Lung infection with these organisms results in amyloid accumulation in the cerebrospinal fluid of critically ill patients. Here, we report that the stereotaxic intracerebral injection of *Pseudomonas aeruginosa* infection-induced, endothelium-derived amyloids affect mouse locomotive behavior and impair performance in novel object recognition and water maze tasks. Moreover, such neurocognitive impairment is dependent upon the type 3 secretion system of *Pseudomonas aeruginosa* and can be alleviated by immunoneutralization with the A11 antibody, a pan antibody selective for amyloids. Immunoneutralization with the T22 antibody, which is selective for tau oligomers, only partially reversed mouse performance in learning-and-memory tasks. Thus, depending upon their capability to disrupt the blood-brain barrier, endothelium-derived amyloids may be a plausible mechanism that could elicit neurocognitive deficit in patients who contract nosocomial *Pseudomonas aeruginosa* pneumonia.
Supported by NIH grans: HL140182 (to M.T.L.), NS102495 (to X.M.Z.), HL66299 (to T.S. and R.B.), HL135003 (to T.S. and R.B.), and HL60024 (to T.S.)

Disclosures: M.T. Lin: None. **Y. Xu:** None. **X. Zha:** None. **R. Balczon:** None. **T. Stevens:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.16/N11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS-NIH R01 NS088645
MDA 294842

Title: Loss of nuclear TDP-43 is linked to DNA double-strand break repair defects in neurons

Authors: *J. MITRA[1,2], E. N. GUERRERO[2], P. M. HEGDE[2], V. M. VASQUEZ[2], H. WANG[2], M. L. HEGDE[2]
[1]Houston, TX; [2]Radiation Oncology & Neurolog. Insitute, Houston Methodist Res. Inst., Houston, TX

Abstract: Tar DNA binding protein, 43KDa (TDP-43) is a multi-functional RNA/DNA binding protein, essential for cell survival. TDP-43 proteinopathy mediated by its nuclear clearance is a

hallmark of progressive motor neurodegeneration disorders including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Mutations in TDP-43 has been accounted for 5 - 10% of the familial patients as well as 90 - 95% in sporadic ALS in the United States. Studies have revealed TDP-43's role in multiple cellular processing for neural functioning mostly related to RNA metabolism, but its DNA binding role has remained enigmatic till date. Here, we show for the first time that TDP-43's nuclear depletion in motor neurons lead to accumulation of DNA double-strand breaks (DSBs) as analyzed by significant increase in DSB-specific marker proteins' (γH2AX, p-53BP1, p-ATM) foci formation. Furthermore, endogenous TDP-43 co-IP as well proximity ligation assay (PLA) confirmed enhanced interaction of TDP-43 with classical non-homologous end joining (NHEJ) pathway-associated proteins (DNA-PKcs, Ku70, XRCC4/LigaseIV complex and polymerase λ) in addition to DDR proteins (γH2AX, p-53BP1, p-ATM). Genetic and biochemical analyses revealed that loss of TDP-43 and/or its nuclear clearance sensitizes neuronal cells to undergo apoptosis combined with persistent accumulation of nuclear genome damage. Nuclear loss of TDP-43 has been found to be mechanistically linked to impairment of chromatin recruitment of critical DDR and DSBR proteins and compromised DSB ligation efficiency. In summary, exploration of novel and crucial events of motor neuronal cell death through DNA damage could be important therapeutic interventions in TDP-43-linked neurodegenerative diseases.

Disclosures: J. Mitra: None. **E.N. Guerrero:** None. **P.M. Hegde:** None. **V.M. Vasquez:** None. **H. Wang:** None. **M.L. Hegde:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.17/N12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The effect of the circadian cycle on the glymphatic system

Authors: *X. CAI[1], J. QIAO[2], I. HARDING[3], P. P. KULKARNI[4], C. F. FERRIS[5]
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Abstract: The glymphatic system is a newly discovered waste clearance system in the brain that removes harmful metabolites including amyloid-β and tau, which are associated with various neurodegenerative conditions including Alzheimer's, Parkinson's and Huntington's disease, in addition to chronic traumatic encephalopathy. Similarly, while the circadian system helps maintain brain homeostasis, dysfunction in circadian rhythms can also contribute to the

pathogenesis of neurodegenerative diseases. However, the exact relationship between the circadian system and glymphatic function remains under characterized. In this study, contrast kinematic MRI experiments on fully awake rats were performed during either the dark or light phase using ICV injection of gadobenate dimeglumine (MultiHance ®) contrast agent. The glymphatic system of twelve Sprague Dawley male rats on regular (n=6) or reversed (n=6) 12/12 light/dark cycles was imaged using a T1-weighted MR sequence. Data were collected throughout both light and dark phases to investigate the influence of diurnal oscillations on long-term glymphatic dynamics. Rats were also imaged 24 hrs after contrast administration. Glymphatic system transport was assessed in fully segmented brain regions using an atlas developed in-house by evaluating changes in signal intensity compared to baseline. Clustering analysis was also applied to quantify the influx and efflux of contrast agent in the glymphatic pathway and peripheral brain areas. In the olfactory bulb, where CSF is drained into the peripheral lymphatic system, rats displayed shorter times to maximum contrast and faster clearance rates during light cycle than rats in the dark cycle in the awake state. These data suggest that in addition to sleep/wake cycle state, circadian rhythms are crucial for proper glymphatic system function. Furthermore, these data also suggest that inadequate sleep and altered circadian rhythms, alone or combined, may negatively affect the glymphatic system, thus leading to the development of neurodegenerative disease.

Disclosures: X. Cai: None. **J. Qiao:** None. **I. Harding:** None. **P.P. Kulkarni:** None. **C.F. Ferris:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.18/O1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DOD
RBP
NEI P30

Title: Effect of KLF9 phosphorylation on chromatin binding, transcriptome expression, and axon regeneration

Authors: *A. MADAAN[1], S. SHAH[2], M. NAHMOU[1], E. CAMERON[2], J. L. GOLDBERG[2]
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Abstract: Krüppel-like factors (KLFs), a family of zinc-finger transcription factors, regulate the developmental decrease in intrinsic axon growth ability in CNS neurons including retinal

ganglion cells (RGCs). KLF9 is critical in neural cell differentiation and suppresses neurite growth in embryonic and postnatal RGCs, hippocampal and cortical neurons; knocking down KLF9 promotes long-distance optic nerve regeneration. We have previously demonstrated that KLF9 interaction with JNK3 regulates KLF9's ability to suppress neurite growth, and that two novel phosphorylation sites, serines S106 and S110, were both imperative in modulating KLF9's ability to suppress neurite growth in vitro and regeneration in vivo. Phospho-null KLF9 S106/110A substitutions abolished wild-type KLF9's growth-suppressive effect; whereas phospho-mimic KLF9 S106/110E substitution potentiated KLF9's suppressive effect on RGCs. Little is known about genomic targets or mechanism of action of KLF9, especially that of KLF9 mutants in RGCs. We assessed the transcriptomes by RNA-sequencing and the genomic binding sites by chromatin-immunoprecipitation (ChIP) of these KLF9 phospho-mimic and phospho-null constructs in embryonic hippocampal neurons and RGCs with affinity-tagged constructs packaged into adeno-associated viral (AAV). Understanding how differential binding of these KLF9 transcription factor mutants is expected to shed light on basic mechanisms of action of phosphorylation of transcription factors, generate new candidate target genes for promoting axon regeneration, and contribute to therapeutic approaches for CNS injury and degenerative disease.

Disclosures: A. Madaan: None. **S. Shah:** None. **M. nahmou:** None. **E. Cameron:** None. **J.L. Goldberg:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.19/O2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The neuronal mitochondrial metabolite NAA regulates energy metabolism in oligodendrocytes through epigenetic mechanisms

Authors: *N. K. SINGHAL[1], K. ALKHAYER[1], S. STERNBACH[1], A. E. WEAVER[1], P. BANNERMAN[2], T. BURN[2], H. HUANG[3], L. SHRIVER[3], F. GUO[2], D. E. PLEASURE[2], R. CLEMENTS[1], E. J. FREEMAN[1], J. MCDONOUGH[1]
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Abstract: N-acetylaspartate (NAA) is synthesized in neurons by the enzyme N-acetyltransferase-8-like (NAT8L) and broken down in oligodendrocytes by aspartoacylase (ASPA) into acetate and aspartate. NAA has been found to be decreased in multiple sclerosis (MS) postmortem cortex, but the significance of reduced NAA to MS pathology is not clear. Deletion of the NAT8L gene results in a depletion of the neuronal mitochondrial metabolite

NAA. These NAT8L knock out mice have defects in myelin including reductions in several myelin lipids and less compact myelin. We have hypothesized that neuronal derived NAA regulates energy production in oligodendrocytes by modulation in the levels of histone H3 methylation. To test this hypothesis, we measured levels of metabolites of intermediary metabolism in primary cultures of oligodendrocytes treated with NAA. We found increased levels of α-ketoglutarate, which has been reported to regulate histone demethylase activity of the KDM5 family of demethylases. Consistent with this, NAA treatment of oligodendrocytes resulted in reduced levels of tri methylation of histone H3 on lysine 4 (H3K4me3) which is involved in cellular growth and energetics, indicating that NAA catabolism in oligodendrocytes activates KDM5 demethylases. Furthermore, we also found a decrease in the oxygen consumption rate in NAA treated oligodendrocytes indicating inhibition of aerobic respiration. This inhibition was blocked by treatment with CPI-455, an inhibitor of the KDM5 histone demethylases that demethylates H3K4me3. We also observed that NAA treatment was associated with increases in the expression of genes involved in sulfatide and sphingomyelin synthesis and a decrease in electron transport chain complex expression. These data suggest that neuronal-derived NAA signals through epigenetic mechanisms in oligodendrocytes to regulate their metabolism.

Disclosures: N.K. Singhal: None. **K. Alkhayer:** None. **S. Sternbach:** None. **A.E. Weaver:** None. **P. Bannerman:** None. **T. Burn:** None. **H. Huang:** None. **L. Shriver:** None. **F. Guo:** None. **D.E. Pleasure:** None. **R. Clements:** None. **E.J. Freeman:** None. **J. McDonough:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.20/O3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2016M3C7A1913844

Title: Administration of amiloride, inhibitor of acid-sensing ion channels (ASICs), reduces hypoglycemia-induced hippocampal neuronal death

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Abstract: Diabetic patients experience various degrees of hypoglycemic symptoms as a result of attempting tight control of blood glucose. If hypoglycemia becomes repetitive or severe hypoglycemia (blood glucose level falls below ~3.5mM) occurs, it can lead to unconsciousness,

seizure or death. Our lab has previously shown that hypoglycemia and subsequent glucose reperfusion causes brain damage through cascading neuronal death pathways. Of particular concern, excessive zinc accumulation in the cells reliably leads to neuronal death after hypoglycemia. Also, when the mitochondria have too little glucose due to hypoglycemia, they attempt to produce enough ATP via alternative metabolic pathways; however, this process produces lactate accumulation which leads to lactic acidosis. Acid-sensing ion channels (ASICs) acts as an important role in central neuronal system and are involved in many physiological processes and pathologic conditions. The primary role of ASICs is to sense decreased levels of extracellular pH and promote a neuronal response. Under pathological conditions such as inflammation, ischemia or hypoxia, rapid acidification activate ASCs both on pre-and postsynaptic neurons. Activation of ASCIs causes increased permeability to Na^+ and Ca^{2+} influx, which can act as secondary messengers in cell signaling, causing cell apoptosis, and tissue injury in the cell under pathological conditions. Therefore, aberrant expression and activation of ASICs contributes to apoptosis, autophagy, and the progression of diverse neurodegenerative diseases. Amiloride, a diuretic agent known to block Na^+/H^+, Na^+/Ca^{2+} exchangers, inhibits ASICs activated by acidosis. We hypothesize that excessive zinc accumulates via activated ASICs under hypoglycemic conditions and thus triggers neuronal death processes. Therefore, we investigated whether amiloride may reduce zinc accumulation and hippocampal neuronal death by inhibiting ASICs after hypoglycemia. To evaluate this, we used an insulin-induced hypoglycemia animal model and injected amiloride (10mg/kg, *i.v*, 1 time) immediately after hypoglycemia. We conducted Fluoro Jade-B (FJB) staining to detect degenerating neurons in the hippocampus at 7days after hypoglycemia. As a result, amiloride treatment reduced neuronal death compared to the vehicle treated group. Therefore, the present study suggests that amiloride may be used as a highly promising therapeutic tool to prevent hypoglycemia-induced neuronal death.
Key word: Hypoglycemia, Zinc accumulation, Acidosis, ASICs, Amiloride, Oxidative stress, Neuron death

Disclosures: A. Kho: None. **T. Chung:** None. **S. Suh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.21/O4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2016M3C7A1913844

Title: The effects of dichloroacetic acid (DCA) on neuronal cell death induced by pilocarpine-induced seizure

Authors: *S. LEE[1], B. CHOI[1], M. LEE[2], H. SONG[2], H. CHOI[2], J. PARK[3], M. SOHN[4], S. SUH[1]
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Abstract: Epileptic seizure is a transient symptom of abnormal brain activity that can interrupt normal brain function and if recurrent and severe it can cause neuronal cell death and cognitive impairments. Previous studies have shown a significant decrease in ATP levels after seizure, which is a contributing factor in seizure-induced neuronal death. Dichloroacetic acid (DCA) has been shown to prevent mitochondrial apoptosis in cancer cells. DCA is also known to be involved in ATP production by activating pyruvate dehydrogenase (PDH), a gatekeeper of glucose oxidation, as a PDHK (pyruvate dehydrogenase kinase) inhibitor. Based on these previous studies, we tested our hypothesis that treatment with DCA after seizure may have a therapeutic effect by increasing the proportion of pyruvate converted to adenosine triphosphate (ATP). Seizure was induced by intraperitoneal (ip) injection of pilocarpine (25 mg / kg) in adult male rats. DCA (100 mg / kg) was injected once daily into the intraperitoneal space for 3 days or 1 week after seizure. Neuronal death and oxidative stress were assessed at 3 days or 1 week after seizure to determine if DCA increased neuronal survival and reduced oxidative damage in the hippocampus. 4HNE and Fluoro-Jade-B were used to evaluate oxidative stress and neuronal cell death, respectively. In the present study, we found that when DCA treated for 1-week seizure-induced hippocampal neuronal cell death was reduced compared to the vehicle-treated group. Thus, the present study demonstrates that treatment with DCA may have therapeutic potential on seizure-induced neuronal death and cognitive impairments.

Disclosures: S. Lee: None. **B. Choi:** None. **M. Lee:** None. **H. Song:** None. **H. Choi:** None. **J. Park:** None. **M. Sohn:** None. **S. Suh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.22/O5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-5017M3C7A1028937

Title: 2'-5' oligoadenylate synthetase-like 1(OASL1) deficiency aggravates neuronal death after traumatic brain injury

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Abstract: Traumatic brain injury (TBI), also known as intracranial injury, occurs when the brain is damaged by physical force. When traumatic brain injury occurs, primary injury (physical brain deformation) is produced. This primary injury produces secondary injuries such as BBB disruption, oxidative injury and inflammatory response. Recently, it has been reported that the type-1 interferon related inflammatory response is associated with CNS disorders. The *Oasl1* gene is known to negatively regulate interferon regulator 7 (IRF7) expression associated with the expression of interferon. Deletion of the *Oasl1* gene has been reported to increase the expression of type-1 IFN. Thus, our hypothesis is that the induction of TBI in *Oasl1*-deficient mice will result in increase of type 1 interferon expression and thereby aggravates neuronal death processes after TBI. TBI was induced using a controlled cortical injury device (2.0 mm lateral to the midline and 1.0 mm to the bregma). Brain samples were obtained at 24 hours after TBI and histological evaluation was performed for detecting brain injury. Fluoro-Jade B staining was performed to confirm presence of degenerating neurons. We found an increased number of degenerating neurons in *Oasl1* knockout mice. We also conducted Iba1 staining to assess the activity of microglia. The activity of microglia was increased in the *Oasl1* knockout mice. We also performed CD16/32 (M1 type) staining to identify the phenotype of activated microglia. We found that activated microglia were mainly M1 type. The present study found that *Oasl1* gene deletion increased the number of degenerating neurons and the activity of M1 phenotype microglia after TBI. Therefore, this study suggests that increased IFN-1 by deletion of *Oasl1* gene aggravates neuronal death after TBI.

Disclosures: J. Jeong: None. **B. Choi:** None. **M. Lee:** None. **S. Suh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.23/O6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2016M3C7A1913844

Title: Carvacrol attenuates hippocampal neuron death after global cerebral ischemia via inhibition of transient receptor potential melastatin 7

Authors: *D. HONG[1], K.-H. PARK[2], S. SUH[1]
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Abstract: When blood flow into the brain is blocked, cerebral ischemic symptoms quickly appear and neurons undergo a number of complex degeneration pathways. Vesicular zinc is released into synaptic cleft and then translocates into the cytoplasm, which leads to reactive oxygen species (ROS) production and neurodegeneration. For the last two decades, evidence supporting the concept of zinc-induced neuronal death has been introduced and several intervention strategies have been investigated. However, no effective intervention techniques have demonstrated except for using zinc chelators. Carvacrol inhibits transient receptor potential melastatin 7 (TRPM7), which regulates the homeostasis of extracellular metal ions, such as calcium, magnesium and zinc. TRPM7 siRNA or knockdown has shown neuroprotective effects after stroke. Carvacrol can block the influx of zinc via TRPM7 channels into the intraneuronal space. Therefore, in the present study we tested whether carvacrol show any neuroprotective effects after global cerebral ischemia (GCI) through blocking zinc influx. To test our hypothesis, we used eight week old male Sprague-Dawley rats, and a GCI model was induced by bilateral common carotid artery occlusion (CCAO) accompanied by blood withdrawal from the femoral artery. Ischemic duration was set for a 7-minute EEG isoelectric period. Whether carvacrol treatment shows a neuroprotective effect, various histological evaluation techniques were performed. Carvacrol (50mg/kg) was injected into the intraperitoneal space once per day for 7 days after the onset of GCI. The present study found that administration of carvacrol significantly decreased the number of degenerating neurons, microglial activation, oxidative damage and zinc translocation after GCI via downregulation of TRPM7 channels. These findings suggest that carvacrol, the TRPM7 inhibitor, may have therapeutic potential after GCI by reducing intracellular zinc translocation.

Disclosures: D. Hong: None. **K. Park:** None. **S. Suh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.24/O7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2017M3C7A1028937

Title: Amiloride reduces hippocampal neuron death after transient cerebral ischemia

Authors: *B. KANG, B. CHOI, S. SUH
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Abstract: Acidosis in the brain plays an important role in neuronal injury and is a common feature of neurological diseases including ischemia, traumatic brain injury, epileptic seizure and hypoglycemia. It has been reported that the acid-sensing ion channel (ASICs) is known to be one key mediator of acidosis-induced neuronal injury and activation of ASICs contributes to acidosis-mediated ischemic brain injury. In this study, we sought to evaluate the hypothesis that blocking ASICs with amiloride attenuates hippocampal neuronal death and zinc accumulation following transient cerebral ischemia (TCI). C57BL/6J male mice (aged 2-3 months) were subjected to TCI by bilateral common carotid artery (CCA) occlusion for 30 minutes, blood flow was restored and amiloride (10 mg/kg, *i.p.*) was immediately injected after TCI. Neuronal death and zinc accumulation were assessed by Fluoro-Jade B (FJB) and N-(6-methoxy-8-quinolyl)-para-toluenesulfonamide (TSQ) staining, respectively, in brains harvested 24 hours after TCI. We found that TCI induced by bilateral CCA occlusion gave rise to considerable neuronal death and zinc accumulation in the hippocampus. The number of FJB-positive neurons was remarkably lower in the amiloride-treated group than in the vehicle-treated group in the subiculum, CA1, CA2, CA3 and dentate gyrus. In addition, TSQ staining also showed that amiloride treatment strongly reduced zinc accumulation in the same hippocampal areas. The present study demonstrates that amiloride attenuates TCI-induced neuronal injury by blockage of intracellular zinc accumulation. Therefore, this study suggests that amiloride may have high therapeutic potential for prevention of TCI-induced neuronal death.

Disclosures: B. Kang: None. **B. Choi:** None. **S. Suh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.25/O8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2017M3C7A1028937

Title: Effects of amiloride, acid-sensing ion channels (ASICs) inhibitor, in hippocampal neuronal death after pilocarpine-induced seizure

Authors: *D. KANG[1], B. CHOI[1], M. LEE[2], H. CHOI[2], H. SONG[2], S. SUH[1]
[1]Physiol., Hallym Univ., Chuncheon, Korea, Republic of; [2]Neurology, Hallym University, Col. of Med., Chuncheon, Korea, Republic of

Abstract: Epileptic seizure arises due to the presence of excessive, uncontrolled neuronal activity in the brain. If severe epilepsy continues without intervention, it leads to zinc release, oxidative stress, neuronal death and cognitive impairment. Amiloride is known as acid-sensing ion channels (ASICs) inhibitor. ASICs are localized to the cellular membrane and are regulated by the concentration of extracellular protons (H^+) in the brain. When epileptic seizures occur, ASICs are activated by binding increased H^+, and subsequently multiple species of cations, including Na^+ and Ca^{2+}, enter into the neurons, which promotes mechanisms leading to neuronal cell death. In addition, zinc is released excessively from the presynaptic terminals after seizure. However, the relationship between ASICs and zinc toxicity has not been established. In the present study, we hypothesize that seizure-induced zinc translocation into postsynaptic neuron may occur via ASICs, followed by excessive zinc accumulation, which may cause neuronal death. To test our hypothesis, we used a pilocarpine-induced seizure animal model and administrated amiloride (10mg/kg, *i.p,* 1 time) at 2 hours after seizure. After 1 week, we performed fluoro-Jade B (FJB) staining and Neuronal Nuclei (NeuN) staining to confirm any protective effects of amiloride on seizure-induced neuronal death in the hippocampus. N-(6-methoxy-8-quinolyl)-para-toluene sulfonamide (TSQ) staining was also performed to determine the concentration of free zinc. Here we found that amiloride decreased the degree of hippocampal neuronal death and the number of TSQ positive neurons are reduced compared to the vehicle treated group after seizure. Therefore, the present study suggests that administration of amiloride can be used as a useful therapeutic method to prevent neuronal death and cognitive impairment after seizure.

Disclosures: D. Kang: None. **B. Choi:** None. **M. Lee:** None. **H. Choi:** None. **H. Song:** None. **S. Suh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.26/O9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2017R1C1B1004226

Title: Sildenafil aggravates traumatic brain injury-induced neuronal death through nitric oxide and zinc pathways

Authors: *B. CHOI, J. JEONG, S. SUH
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Abstract: Sildenafil, a type 5 phosphodiesterase isoenzyme (PDE5) inhibitor, is a vasoactive agent used to treat male erectile dysfunction thorough enhancement of the nitric oxide (NO)-mediated pathway. NO is known to be involved in Zn^{2+} homeostasis. It has been reported that NO-mediated Zn^{2+} release from intracellular storage can trigger neuronal death and NO production induces vesicular Zn^{2+} release, which in turn activates NADPH oxidase and PARP-1 after brain insult. In the present study, we sought to evaluate the hypothesis that increasing NO production with pre-treatment of sildenafil induces further intracellular Zn^{2+} release, leading to excessive Zn^{2+} accumulation in neurons and thereby causing neuronal death following traumatic brain injury (TBI). C57BL/6J male mice (aged 3-5 months) were given sildenafil (10 mg/kg, p.o.) and then subjected to a controlled cortical impact (CCI) injury over the parietal cortex at 30 minutes after sildenafil treatment. Neuronal death and Zn^{2+} accumulation were assessed by Fluoro-Jade B (FJB) and N-(6-methoxy-8-quinolyl)-para-toluenesulfonamide (TSQ) staining, respectively, in brains harvested 24 hours after TBI. We found that TBI induced by CCI injury gave rise to neuronal death and Zn^{2+} accumulation in the ipsilateral hippocampus. However, the number of FJB-positive neurons was remarkably greater in the sildenafil-treated group than in the vehicle-treated group in the CA1 and dentate gyrus of ipsilateral hippocampus. In addition, TSQ staining also showed that sildenafil treatment significantly increased the number of Zn^{2+} accumulated neurons in the same regions. The present study demonstrates that sildenafil aggravates TBI-induced neuronal death by enhancement of the NO- and Zn^{2+}-induced neuronal death pathway. Therefore, the present study suggests that pre-treatment of sildenafil may not have neuroprotective effects but aggravates neuronal death after TBI.

Disclosures: B. Choi: None. **J. Jeong:** None. **S. Suh:** None.

Poster

209. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurodegeneration I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 209.27/O10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: JSPS Grant 17K11114
JSPS Grant 26462329
JSPS Grant 15K20031

Title: Declines in protein quality control and external insults promote cognitive dysfunction

Authors: *T. AOE[1], H. JIN[2], H. KOKUBUN[2], M. KOMITA[3]
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Abstract: (Background) Most neurodegenerative diseases are sporadic and develop with age. Degenerative neural tissues often contain intra- and extracellular protein aggregates, suggesting that the proteostasis network that combats protein misfolding could be dysfunctional in the setting of neurodegenerative disease. Binding immunoglobulin protein (BiP) is an endoplasmic reticulum (ER) chaperone that is crucial for protein folding and modulating the adaptive response in early secretory pathways. The interaction between BiP and unfolded proteins is mediated by the substrate-binding domain and nucleotide-binding domain with ATPase activity, facilitating protein folding and maturation. BiP also has a recovery motif at the carboxyl terminus. The aim of this study is to examine cognitive function in model mice with an impaired proteostasis network by expressing a mutant form of BiP lacking the recovery motif. We also investigated if impairments were exacerbated by exposure to environmental insults like inhaled anesthetics on cognitive function. (Method) We examined cognitive function by performing eight-arm radial maze testing of heterozygous knock-in mice expressing a mutant BiP and assessed the additional impact of general anesthesia in the context of proteostasis dysfunction. Testing on 8 days in mice with or without anesthetic exposure was performed 10 weeks, 6 months, and 1 year after birth. Animal movements were recorded and evaluated later. (Results) Long-term observations revealed that age-related cognitive decline occurred earlier in mutant BiP mice compared to wild-type littermates. An accumulation of ubiquitinated proteins was observed in the mutant brain and spinal cord by immunohistochemistry, indicating a failure of the proteostasis network due to insufficient BiP function. Notably, exposure to inhalational anesthetics exacerbated cognitive impairment in mutant mice. (Conclusion) These results suggest that proteostasis network impairment may contribute to age-related neurodegeneration, and this is worsened by external insults.

Disclosures: T. Aoe: None. **H. Jin:** None. **H. Kokubun:** None. **M. Komita:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.01/O11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Congressionally Directed Medical Research Programs (CDMRP)
Medical College of Georgia Foundation, Augusta University

Title: Axonal transport targets for reversing the adverse effects of neurotoxin exposure

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Abstract: The chemicals known as organophosphates (OPs) have a wide array of uses in industrial and agricultural settings as pesticides, but they have also been associated with a variety of adverse health effects in humans and other non-target organisms. While their acute toxicity is associated with inhibition of cholinesterase enzymes, this mechanism is inadequate to explain the long-term adverse effects of OPs. Previous research in our laboratory indicated that repeated OP exposures can lead to deficits in axonal transport (AXT), an important observation since AXT is an essential process in neurons that is responsible for the movement of a variety of important macromolecules to and from a neuron's cell body. Methods to rescue (or attenuate) AXT deficits resulting from OP exposures may thus represent an important therapeutic strategy to combat the negative effects of OPs. In the studies described here, we initially analyzed post mortem brains from OP-exposed rats to identify targets that might contribute to OP-related deficits in AXT. While multiple targets were evaluated including post-translational modifications of structural proteins that affect AXT through the regulation of microtubule dynamics and stability (e.g., Tau phosphorylation, tubulin acetylation), our most notable observations were alterations in the activation of protein kinases. Specifically, in the hippocampus of rats repeatedly exposed to the OP, diisopropylfluorophosphate (DFP), transient increases in ERK phosphorylation and transient decreases in AKT phosphorylation were observed, while persistent decreases in GSKIIIβ phosphorylation were observed. In subsequent live cell imaging studies in vitro, DFP-induced impairments in AXT were attenuated with the GSKIIIβ inhibitor, lithium chloride. These results thus suggest that targeting a signaling kinase known to regulate AXT may be a rational therapeutic approach to attenuate or reverse OP-related adverse neurological effects.

Disclosures: S.X. Naughton: None. **Z. Wei:** None. **G. Wu:** None. **A.V. Terry:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.02/O12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: L'Institut Servier
Medical College of Georgia Foundation, Augusta University

Title: Axonal transport targets for age-related neurodegenerative diseases

Authors: *A. V. TERRY, JR[1], W. BECK[1], P. CALLAHAN[1], P.-C. LIN[2], S. NAUGHTON[1]
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Abstract: Axonal transport (AXT) is an essential process in neurons that is responsible for the movement of a variety of important macromolecules to and from a neuron's cell body. Moreover,

impairments in AXT have been implicated in the pathology of several age-related neurological illnesses (e.g., Alzheimer's disease, Parkinson's disease). Notably, some evidence suggests that deficits in AXT occur prior to the onset of overt neuropathology. Accordingly, methods to rescue (or attenuate) AXT deficits in these illnesses is an emerging therapeutic strategy to modify disease outcome. In the studies described here, we initially evaluated several compounds that target microtubule stability (Epothilone D, Pregnenolone, Parthenolide, and Nicodazole) in vitro for their ability to attenuate deficits in AXT induced by soluble Aβ oligomers, which are known to play a key role in the neuropathology of AD. Live cell imaging methods were used for the analysis of AXT of membrane bound organelles (MBOs) in rat primary cortical neurons that contained the amyloid precursor protein (APP) tagged with the fluorescent marker GFP. Depending on concentration, each compound evaluated showed some ability to attenuate the negative effects of Aβ on AXT. In the second (in vivo) phase of our studies, we used a manganese-enhanced magnetic resonance imaging (MEMRI) method for measuring AXT in living mice in real time in olfactory neurons, to 1) evaluate the effects of age on axonal transport and 2) to evaluate of the effects of chronic administration of Epothilone D on axonal transport in aged mice. In the age comparisons, AXT rates were clearly higher in young versus aged (wild type) mice. In addition, in aged mice, Epothilone D, was associated with an increase in the axonal transport rate versus vehicle-treated subjects. Collectively, these results suggest that compounds that target microtubule stability offer a viable treatment strategy for treating age-related neurological disorders where axonal transport is impaired.

Disclosures: A.V. Terry: None. **W. Beck:** None. **P. Callahan:** None. **P. Lin:** None. **S. Naughton:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.03/O13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Air Force Office of Scientific Research (EOARD, London, UK), and Air Force Material Command, USAF, under grant number FA8655-05-1-3065;
Air Force Material Command, USAF Grant nr FA8655-05-1-3065
Swedish Medical Research Council (Nr 2710-HSS)
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Alzheimer's Association (IIRG-09- 132087),
The Indian Medical Research Council, New Delhi, Govt of India
The University Grants Commission, New Delhi, India

Title: Exacerbation of nicotine induced neurotoxicity in depression

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Abstract: We have shown earlier that nicotine neurotoxicity is exacerbated by hot and cold environment. However, nicotine intake and addiction could be influenced by several other factors e.g., hypertension or diabetes as shown earlier. Other factor could be depression. Depressed people they often find some solace in smoking that eventually leads to nicotine addiction and brain dysfunction. Since depression is one of the leading causes of concern in military personnel, in this investigation we explored the role of depression in nicotine-induced neurotoxicity. Our previous studies showed that nicotine exposure (9 mg/kg, s.c.) for one-week results in breakdown of the blood-brain barrier (BBB) to albumin and induce vasogenic edema formation and neuronal damages in several brain regions. Depressive illnesses alone are able to compromise BBB dysfunction causing slowly developing brain pathology in human populations. We used animal model of forced swimming (FS) to mimic depression like illnesses and examined additional nicotine exposure to understand neurotoxicity in this combination. For this purpose, naïve male rats (age 25 to 28 weeks) or nicotine-administered animals were subjected to FS individually in a pool of water (depth 18 cm, water temperature 30°C) for 30 min daily for one week. When the rats develop immobility, the water is stirred using a glass rod so that animals are forced to swim continuously for 30 min. On the 8th day, BBB permeability, edema formation and neuronal damages were examined. Our results showed that nicotine exposure did not influence the immobility pattern during 30 min FS daily as compared to naïve animals. However, the BBB breakdown to Evans blue albumin (EBA) was 2-to 4 fold higher in nicotine exposure in FS rats. These nicotine exposed FS rats also showed greater edema formation and higher neuronal injuries in identical brain areas as compared to naïve rats. Interestingly nicotine exposed rats after FS showed extension of neuronal injuries in the brain not seen in naïve nicotine exposes animals. Immunocytochemical analyses showed greater expression of heat shock protein 72 (HSP) in the areas showing neuronal injuries and BBB leakage in Nicotine exposed FS rats. Expression of HSP 72 (an inducible isoform of stress protein) suggests that enhanced cellular stress could be responsible for exacerbation of neurotoxicity in FS and nicotine exposed animals. Taken together our observations suggest that a combination of depression and nicotine exposure lead to widespread neuronal damages, not reported earlier. Whether nicotine exposure and FS combine could induce age-related neurotoxicity, a feature that is currently being examined in our laboratory.

Disclosures: S. Sharma: None. **A. Sharma:** None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **A. Nozari:** None. **A. Ozkizilcik:** None. **R. Patnaik:** None. **Z. Tian:** None. **H.S. Sharma:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.04/O14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Field Neurosciences Institute
John G. Kulhavi Professorship

Title: Solid lipid curcumin particles improve active avoidance performance and reduce mutant huntingtin aggregates in the YAC128 mouse model of Huntington's disease

Authors: *A. AL-GHARAIBEH[1,2], R. CULVER[1,2], S. HEILEMAN[1,2], D. STORY[1,2,3], K. SPELDE[1,2], N. MUHN[1,2], N. MUNRO[1,2], J. ROSSIGNOL[1,2,4], P. MAITI[1,2,3,5,6], G. DUNBAR[1,2,3,6]
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Abstract: Huntington’s disease (HD) is a genetic neurodegenerative disease characterized by motor, cognitive, and psychiatric symptoms. The main pathological features of the disease are neuronal loss, abnormal changes in dendrites and dendritic spines of medium spiny neurons (MSNs), and mutant huntingtin protein aggregation. Although the genetic cause has been identified, the exact pathway for the massive neuronal degeneration is not known. Curcumin, a natural polyphenol extracted from the plant *Curcuma longa*, which can cross blood brain barrier, is known as anti-oxidant, anti-inflammatory with aggregate-binding and neural- protective properties. The poor solubility, absorption and bioavailability of curcumin limits its potential clinical utility. To circumvent this shortcoming, solid lipid curcumin particles (SLCPs), which increase curcumin bioavailability, have been used. In this study, we tested the efficacy of SLCPs as a treatment for HD. For this purpose, we utilized YAC128 mice at 11 months of age and treated them every other day by oral gavage of 100 mg/kg of SLCPs for 8 weeks. We measured their performance on the accelerating rotarod for 8 weeks, and active avoidance during week 8. We then sacrificed the mice, extracted their brains and utilized them for Western blot analyses. Although no significant differences on the accelerating rotarod measures were observed, the latency for escape in the active avoidance test decreased significantly in HD mice treated with SLCPs, compared to HD controls. Our Western blot results revealed a decrease in mutant huntingtin aggregate (EM48) and increase in LC3B suggesting increase in mutant huntingtin clearance and activation of autophagy pathway. We also found that HD mice treated with SLCPs showed increases in brain derived neurotrophic factor (BDNF) and its receptor (TrkB), and

synaptophysin, when compared to HD controls, suggesting neuroprotection effect. Our results suggest that SLCPs can reduce the pathological changes in the brains of YAC128 HD mice, and provide a therapeutic strategy for treating HD.

Disclosures: A. Al-Gharaibeh: None. **R. Culver:** None. **S. Heileman:** None. **D. Story:** None. **K. Spelde:** None. **N. Muhn:** None. **N. Munro:** None. **J. Rossignol:** None. **P. Maiti:** None. **G. Dunbar:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.05/O15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Keck School of Medicine

Title: Epigallocatechin-3-gallate. a green tea polyphenol, decreases beta-amyloid uptake and neuronal cell death via binding to 67kDa laminin receptor

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Abstract: Previous studies have shown that β-amyloid enters neuronal cells, in part, either by binding directly to the 67kDa laminin receptor (67LR), a cell-surface-associated protein with a high affinity to β-amyloid, or by associating with prions that bind to the 67LR. This uptake may play an important role in mediating β-amyloid-induced neuronal toxicity. Previous studies have demonstrated that epigallocatechin-3-gallate (EGCG), an active ingredient of green tea polyphenol, can attenuate the neuronal toxicity caused by the β-amyloid peptide. Our previous research has shown that EGCG mediates its neuroprotective and neurotrophic actions by inducing intracellular signaling mediated by a direct binding of this polyphenol to 67LR. From these studies, we hypothesized that EGCG binds to 67LR, inhibiting the subsequent binding and uptake of β-amyloid, and thus preventing β-amyloid induced neurotoxicity. Neuroscreen-1 cells treated with a low concentration of green tea polyphenol mixture (0.1 μg/ml) or EGCG (100 nM) showed a decrease in the cellular uptake of fluorescent-labeled human β-amyloid peptide(1-42). A pretreatment with the same agents also protected neuronal cells from β-amyloid(25-35)-induced cell death, which was measured by the reduction of thiazolyl blue tetrazolium bromide. This EGCG-induced neuroprotection was mediated by the internalization of the 67LR and the subsequent increase of intracellular cAMP levels. Consistent with this possibility, neuronal cells treated with cAMP-elevating agents (forskolin and rolipram) were also protected from β-amyloid-induced cell death. Therefore, EGCG signaling via 67LR may even prevent the

neuronal toxicity caused by β-amyloid that entered into cells through 67LR-independent mechanisms. Conceivably, 67LR is an important neuroprotective receptor that may be targeted in the development of drugs to prevent β-amyloid-induced pathology, which can ultimately protect against Alzheimer's disease. <!--EndFragment-->

Disclosures: R. Gopalakrishna: None. **C. Le:** None. **C.Y. Lin:** None. **J. Jiang:** None. **N.R. Bhat:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.06/O16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Fondecyt (Chile) # 1130241

Title: Pharmacological modulation of P21-activated kinases (PAKs) in an *in vitro* neuronal model of Down's syndrome: A possible therapeutical target

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Abstract: Down Syndrome (DS), or trisomy 21 in humans, results from the presence of an extra copy of autosome 21. The most striking features are mental retardation and an early onset of Alzheimer's-like dementia. The CTb cell line, derived from the cerebral cortex of a trisomy 16 fetal mouse (Ts16), an animal model of DS, is a permanent *in vitro* model for the study of DS-related cell pathophysiology. Using this CTb line and establishing specific gene knockdown conditions for DS-related genes, we have defined neuronal impairments in the trisomic condition as compared with a control cerebral cortex cell line, named CNh, derived from a normal littermate. Deregulation of signaling pathways underlying neuronal development and function is present in DS-pathology. In this regard, the serine/threonine p21-activated kinases (PAKs) act on downstream effectors LIMK and cofilin, leading to reorganization of actin filaments, thus determining correct morphological development in terms of process emission and branching. A DS-related gene, *dscam*, which codes for the protein DSCAM (Down Syndrome Cell Adhesion Molecule) regulates PAKs activity via phosphorylation. We have previously shown that CTb cells overexpress DSCAM compared to CNh cells. Further, trisomic cells exhibited reduced process number and length compared to controls, and an increased F/G actin ratio. After

stimulation with the DSCAM agonist netrin, PAKs, LIMK and cofilin exhibited abnormally increased phosphorylation (2 fold) in CTb cells. DSCAM knockdown with siRNA transfection reverted these parameters to levels comparable to those of CNh cells. Hence, PAKs appeared as an interesting pharmacological target. We have now evaluated the effect of PAKs inhibitors IPA-3 and FRAX486 in CTb cells. In vitro toxicity studies revealed therapeutic index values (calculated as LD50/IC50) for IPA-3 of 7.56 and 9.88 in CNh and CTb cells, respectively (n=4 experiments). FRAX486 values were 581.3 and 772.2, for CNh and CTb cells, respectively (n=9 experiments). Hence, we decided FRAX486 was a better candidate. After 3 days differentiation, CTb cells treated with this inhibitor exhibited an increase in process length, compared to untreated cells (15,03 ± 10.6 µm untreated vs. 19.1 ± 14.4 µm treated. n= 385, 315. p=.00002). Values for CNh cells, both treated and untreated with FRAX486, did not differ statistically from those of treated CTb cells. Our work suggests that PAKs deregulation in the trisomic condition can be addressed pharmacologically. Such modulation can help recover an important neuronal function in DS, such as process emission.

Disclosures: M.B. Gaete: None. **R. Pérez-Nuñez:** None. **J. Barnier:** None. **A.M. Cárdenas:** None. **P.A. Caviedes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pablo Caviedes: Patent protection on CNh and CTb cells lines.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.07/P1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT
Margaretha af Ugglas Foundation
Olle Enqvist Foundation
Stohnes Foundation
Demensfonden
Old Servants Foundation
KI Young Scientist Grant

Title: Hypercholesterolemia and 27-hydroxycholesterol enhance S100A8 and RAGE expression in the brain: A link towards amyloid-beta accumulation

Authors: *R. LOERA-VALENCIA, M. ISMAIL, M. LODEIRO, P. MERINO-SERRAIS, S. MAIOLI, L. MATEOS, I. BJÖRKHEM, E. PUERTA, A. CEDAZO-MINGUEZ
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Abstract: Growing evidence suggest that alterations in cholesterol metabolism and in inflammatory responses have an important role in neurodegenerative disorders including Alzheimer´s disease (AD). Oxysterols are cholesterol metabolites proposed as regulators of cholesterol metabolism in the brain with multiple implications in memory function as well as in neurodegeneration. In this study, we report that high fat diet and excess 27-hydroxycholesterol (27-OH), a cholesterol metabolite passing from the circulation into the brain, induce the upregulation of the glial inflammatory mediator S100A8 as well as its receptor RAGE both in vivo and in vitro. S100A8 is observed as extracellular aggregates, similar to those previously reported in the hippocampi of amyloid-β (Aβ) overproducing mouse models. In addition, we found the 27-OH mediated increase in RAGE levels in vitro is mediated by RxRγ rather than by LXR or AT1 receptors, in a mechanism involving NF-κB activation. These results may indicate that the S100A8/RAGE increase in the brain is one of the mechanisms behind the association of high peripheral cholesterol and excessive 27-OH in the inflammation pathogenesis of AD.

Disclosures: R. Loera-Valencia: None. **M. Ismail:** None. **M. Lodeiro:** None. **P. Merino-Serrais:** None. **S. Maioli:** None. **L. Mateos:** None. **I. Björkhem:** None. **E. Puerta:** None. **A. Cedazo-Minguez:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.08/P2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01DA039821 (F.W.)
R01AA022082 (F.W.)
R21AA023648 (F.W.)
R21DA043030 (N.S.)

Title: Transdermal CBD protects against alcohol-induced cellular degeneration: Cell-type specific gene expression analysis

Authors: *A. LAQUE, O. KOZANIAN, G. WAGNER, T. KERR, G. DE NESS, N. SUTO, F. WEISS
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Abstract: Alcohol dependence is a chronic relapsing disorder of compulsive alcohol seeking and use. Cannabidiol- a major non-psychoactive component of *cannabis sativa*- has long received attention for its therapeutic potential against a variety of neuropsychiatric/degenerative disorders, including alcoholism. Previously, we identified a substantial benefit from transdermal-application of cannabidiol (tCBD) against alcohol relapse in rats. Though CBD demonstrates

clinical potential for various alcohol-related complications, little is known of the molecular mechanisms responsible for CBD's action. Here, we aim to identify key molecular targets altered by alcohol dependence (EtOH-Dep) and assess whether a tCBD treatment regimen could potentially reverse the harmful effects induced by chronic alcohol exposure. We employed a combined methodology of cell type-specific (fluorescent activated cell sorting (FACS)) gene expression profiling (RNA-Seq) of hippocampal neurons and astrocytes. Wistar rats were divided into four groups defined by 1. Vapor Exposure: EtOH-Dep (12hr/d EtOH Vapor; 12hr/d air) or Non-Dep (air) and 2.Treatment: tCBD 15mg/kg or VEH 0 mg/kg. Rats were housed in vapor chambers for 6 weeks while undergoing tCBD treatment (tCBD/VEH applied every 48hr). At 6 weeks rats were sacrificed, brains extracted, and hippocampi were collected for downstream FACS-> RNA-Seq application. The gene expression profiles of rats were compared based on treatment (VEH vs. tCBD) and Vapor Exposure (EtOH-Dep vs. Non-Dep). We found that EtOH-Dep significantly decreased the hippocampal astrocyte population but had no effect on neurons. Interestingly, astrocytes in EtOH-Dep rats treated with tCBD resembled that of Non-Dep rats. These finding suggests tCBD treatment elicits a protective effect against alcohol-induced hippocampal astrocyte degradation. Taken together, tCBD appears to serve as an effective therapeutic approach for treating symptoms against alcoholism and alcohol associated morbidities as 1. the ease of transdermal CBD gel application is translationally relevant in a clinical perspective, 2. tCBD exhibits substantial anti-relapsing effects against alcohol, 3. and tCBD offers protection against the cellular degradation resulting from chronic alcohol exposure. In order to improve medical strategies for combating alcoholism, it is important that we acquire a comprehensive understanding of the neurobiological underpinnings mediating CBD's therapeutic effects. The compelling results from this study, thus, prompt further cell-type specific investigation of different brain regions impacted by alcohol dependence.

Disclosures: A. Laque: None. **O. Kozanian:** None. **G. Wagner:** None. **T. Kerr:** None. **G. De Ness:** None. **N. Suto:** None. **F. Weiss:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.09/P3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: The role of BHMT in methionine metabolism in multiple sclerosis

Authors: *S. STERNBACH, N. SINGHAL, K. ALKHAYER, J. MCDONOUGH
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Abstract: Multiple sclerosis (MS) is characterized by neurological dysfunction and demyelination of the central nervous system. We have previously shown that betaine levels are

reduced in MS cortex and these levels are correlated with H3K4me3 levels. We have also shown that betaine regulates neuronal mitochondrial activity by modulating methionine metabolism intermediates and levels of H3K4me3 methylation in the cuprizone mouse model of MS. In this model, the SAM/SAH ratio is decreased, which leads to a decrease in histone 3 trimethylation on lysine 4 (H3K4me3), which functions to activate transcription of oxidative phosphorylation genes – the same genes that are downregulated in MS. Our lab hypothesizes that through betaine supplementation, BHMT locally contributes to SAM synthesis for histone methylation; however, the mechanism is unclear. Salt gradient fractionation and immunocytochemistry were performed to determine how tightly BHMT is bound to chromatin. Our data show that BHMT is present in the nucleus of primary rat neurons and mouse hippocampus, and tightly bound to chromatin through a ncRNA. These data suggest that changes in methionine metabolism may be linked to corresponding mitochondrial energetics, mediated by ncRNA.

Disclosures: S. Sternbach: None. **N. Singhal:** None. **K. Alkhayer:** None. **J. McDonough:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.10/P4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Targeting Keap1 as a therapeutic approach for neurodegenerative disease

Authors: *D. E. STROCHLIC[1], G. SRUBEK TOMASSY[1], S. SU[1], A. MCCURLEY[1], K. LING[2], B. LI[1], D. UJLA[1], K. RICHTER[1], L. SUN[1], Y. LUO[1], M. ZHANG[1], J. AMACKER[1], G. MARSH[1], L. JANDRESKI[1], F. RIGO[2], C. E. HENDERSON[1], A. MCCAMPBELL[1]
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Abstract: Extensive evidence implicates oxidative stress in the pathogenesis of neurodegenerative diseases. A promising strategy for neuroprotection is overexpression or activation of Nrf2, a master transcription factor that activates antioxidant and cytoprotection defense mechanisms. Overexpression has been shown to be neuroprotective in rodent models of neurological disease, including ALS and retinal degeneration, but ectopic expression of Nrf2 can be oncogenic. We therefore investigated whether knockdown of Keap1, a negative regulator of Nrf2, might confer similar neuroprotective benefits. Active and well-tolerated Keap1 antisense oligonucleotides (ASOs) were developed for use in mouse models of motoneuron and retinal disease, via intracerebroventricular and intravitreal injection, respectively. ASO delivery resulted in 60-80% knockdown of Keap1 transcript in target tissues, with a concomitant induction of Nrf2-target genes (e.g. Hmox1, Nqo1). In two genetic models of ALS (mice overexpressing mutant SOD1 or TDP-43), Keap1 ASOs were administered ~2 weeks prior to symptom onset.

Despite expected pharmacodynamic responses, ASO treatment had no effect on a panel of physiological, biochemical, behavioral, and anatomical measures. Similarly, Keap1 ASOs effectively modulated the Nrf2/Keap1 pathway in retina but were unable to protect retinal ganglion cells from death following optic nerve damage or protect photoreceptors from death in phosphodiesterase mutant mice (rd10 allele), a retinitis pigmentosa model. The lack of neuroprotection in four disease models might be explained by insufficient knockdown of Keap1 or by insufficient levels of Nrf2.

Disclosures: D.E. Strochlic: A. Employment/Salary (full or part-time):; Biogen. **G. Srubek Tomassy:** A. Employment/Salary (full or part-time):; biogen. **S. Su:** A. Employment/Salary (full or part-time):; biogen. **A. McCurley:** A. Employment/Salary (full or part-time):; biogen. **K. Ling:** A. Employment/Salary (full or part-time):; ionis. **B. Li:** A. Employment/Salary (full or part-time):; biogen. **D. Ujla:** A. Employment/Salary (full or part-time):; biogen. **K. Richter:** A. Employment/Salary (full or part-time):; biogen. **L. Sun:** A. Employment/Salary (full or part-time):; biogen. **Y. Luo:** A. Employment/Salary (full or part-time):; biogen. **M. Zhang:** A. Employment/Salary (full or part-time):; biogen. **J. Amacker:** A. Employment/Salary (full or part-time):; biogen. **G. Marsh:** A. Employment/Salary (full or part-time):; biogen. **L. Jandreski:** A. Employment/Salary (full or part-time):; biogen. **F. Rigo:** A. Employment/Salary (full or part-time):; Ionis. **C.E. Henderson:** A. Employment/Salary (full or part-time):; biogen. **A. McCampbell:** A. Employment/Salary (full or part-time):; biogen.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.11/P5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: SNRP: NIH U54NS083924
RCMI: NIH 8612md007583

Title: Comparison of the neuroprotective effects of two nicotinic ligands

Authors: V. A. ETEROVIC[1], H. R. ARIAS[2], D. PEREZ[1], O. LYKHMUS[3], K. USPENSKA[3], M. SKOK[3], *P. A. FERCHMIN[1]
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Abstract: 4R-cembranoid (4R) and 3-furan-2-yl-N-p-tolyl-acrylamide (PAM-2) are neuroprotective drugs that target the α7 nicotinic acetylcholine receptor (α7). However, while 4R is a non-competitive inhibitor of α7, PAM-2 is a positive allosteric modulator of this receptor. The objective of this work is to compare the neuroprotective activity of PAM-2 with that of 4R,

in rat hippocampal slice and in mice mitochondria. Recording of population spikes (PSs) in the CA1 area of rat acute hippocampal slices was used to assess the injury caused by NMDA application and neuroprotection by 4R and PAM-2. The 4R and PAM-2 were applied for one hour 30 min after NMDA. Initial PSs were recorded before NMDA application and the final PS at the end of the experimental treatment. Data were analyzed by Kruskal-Wallis ANOVA, followed by Dunn's test.
Neither PAM-2 nor 4R displayed activity in the absence of NMDA. Application of NMDA decreased the PS recovery to 30% of ACSF controls. PS recovery was significantly increased when NMDA was followed by the application of 10 μM 4R (82% $p<0.001$) or 10 μM PAM-2 (68%, $p<0.001$). These results confirmed that both 4R and PAM-2 are neuroprotective. The dose-response curve for 4R had two components, one with low efficacy (40-44% PS recovery) in the pM-nM range, and the second in the nM-μM range with minimum and max. activities of 39% and 76%, respectively, and EC_{50} = 97 nM and Hillslope = 5.9. PAM-2 dose-response curve had two components a high-affinity component (2.5-15.0 μM) with EC_{50} =5.1 μM and a low-affinity component (30-50 μM) with EC_{50} = 25 μM. Both components had a Hill coefficient>>1. The neuroprotective activity of 10 μM 4R (82%, $p<0.001$) was significantly decreased by simultaneous application with 2.5 μM PAM-2 (82% vs. 54%, $p<0.02$). Interestingly, PAM-2 was not protective at 2.5 μM. Also, the neuroprotection by10 μM 4R plus 10 μM PAM-2 were not significantly different from each of the drugs applied alone. In conclusion, significant PS recovery after NMDA was observed when applying PAM-2 and 4R. The fact that the positive effects of PAM-2 and 4R were not additive could be explained by competition of these two drugs at the α7 receptor.
In liver mitochondria, the activities of PAM-2 and 4R were determined obtained from WT and KO mice. PAM-2 attenuated Cyt c release in WT, but not α7-/- or α7/β2-/- mice mitochondria exposed to high Ca^{2+}, but not to H_2O_2 or wortmannin, whereas 4R activity was effective against Ca^{2+} and H_2O_2, but less against wortmannin. These results suggest that PAM-2 and 4R inhibit Cyt c release by different mechanisms.

Disclosures: V.A. Eterovic: None. **H.R. Arias:** None. **D. Perez:** None. **O. Lykhmus:** None. **K. Uspenska:** None. **M. Skok:** None. **P.A. Ferchmin:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.12/P6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: New role of serotonin receptor HTR1E in mediating neurotrophic effects of NF-α1/CPE through ERK signaling

Authors: *V. K. SHARMA, L. TOULABI, Y. XUYU, Y. P. LOH
Section on Cell. Neurobiology, Program on Developmental Neurosci., NICHD, Natl. Inst. of Hlth., Bethesda, MD

Abstract: Neurotrophic factor-α1/Carboxypeptidase E(NF-α1/CPE) is secreted by neurons and endocrine cells where it acts as a prohormone processing enzyme intracellularly and a neurotrophic factor, extracellularly. It has been shown that NF-α1/CPE can induce neural stem cell differentiation to astrocytes during neural development, and it can also protect hippocampal neurons from oxidative stress-induced cell death through ERK and AKT pathways. Based on these findings, we hypothesize that there should be NF-α1/CPE receptors at the cell membrane to regulate these functions. Ligand binding studies were performed in neuronal HT22 cell line using recombinant CPE labeled with ^{125}I. Specific binding was obtained which indicates that NF-α1/CPE work through a ligand-receptor complex. Next, a high throughput screening was performed for potential NF-α1/CPE receptors against a library of orphan GPCRs. 5-hydroxytryptamine receptor 1-E (5-HTR1E) showed a strong positive signal for NF-α1/CPE. Binding between NF-α1/CPE and HTR1E was supported by co-immunoprecipitation of NF-α1/CPE with HTR1E. Consistent with NF-α1/CPE's action to increase ERK/FGF2 signaling for neuroprotection, we found that the level of phosphorylated ERK 1/2 and FGF2 were significantly up-regulated when HTR1E expressing cells were treated extracellularly with CPE. This study has provided evidence for a novel role of HTR1E as a potential CPE receptor that can activate downstream ERK signaling to mediate various physiological functions.

Disclosures: V.K. Sharma: None. **L. Toulabi:** None. **Y. Xuyu:** None. **Y.P. Loh:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.13/P7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Colciencias Contrato No.616-2014

Title: *In vitro* effects on cerebral cell survival of ischemic preconditioning before the application of a lethal stimulus and its relationship with O-GlcNAc glycosylation

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Abstract: Ischemic tolerance has been described as a one of the most robust ways to give neuroprotection to cerebral cells. Among the described mechanisms involved in that response is the role of the mitochondria as a calcium regulator and regulation of different kinds of proteins such as IL1, Bcl-2 and HSP. On the other hand, O-GlcNAc glycosylation has been shown to increase cell survival when its levels are increased in response to a stressing stimulus. In the present work we evaluate if O-GlcNAc glycosylation is one of the mechanisms by which brain cells acquire ischemic tolerance. To evaluate the above mentioned, we conducted experiments in an *in vitro* model of cultured brain cells from newborn Wistar rats subjected to an ischemic preconditioning protocol via the application of non-lethal oxygen-glucose deprivation (OGD) before the application of a lethal OGD. Besides, we evaluated the effect of hexosamine biosynthetic pathway (HBP) inhibition by DON and Alloxan, compounds that can inhibit the Glutamine fructose-6-phosphate amidotransferase (GFAT) and the O-GlcNAc transferase (OGT) respectively, enzymes involved in this pathway. To assess whether an OGD stimulus can induce ischemic tolerance, brain cells were subjected to a non-lethal OGD of 15 minutes. At the end of this time and after one hour in normal conditions, cells were subjected to a lethal OGD of 120 minutes. Preliminary results indicate that the mortality rate is not reduced in the cells subjected to a non-lethal stimulus before the application of the lethal stimulus in comparison with the cells subjected only to the lethal stimulus. Besides, in the HBP inhibition with a mixture of DON and Alloxan the results were similar to the above mentioned. The results suggest that the preconditioning protocol applied did not induce ischemic tolerance acquisition, and do not allow us to confirm whether O-GlcNAC glycosylation is one of the mechanisms involved in ischemic tolerance acquisition in brain cells. These results are opposite to that previously reported in the conference Neuroscience 2017 in which we demonstrated in an *in vivo* model of ischemic preconditioning (IPC) that this protocol reduces the infarct size and increases the level of protein OGlcNAcylation, suggesting a possible participation of this protein modification in the neuroprotection generated. In consequence, we consider that we have to adjust several parameters of our *in vitro* model to be able to generate ischemic tolerance *in vitro*. For example, the non-lethal time chosen may be too long and could be triggering delayed death pathways and applying it just before the lethal stimulus may induce brain cells death.

Disclosures: C.F. Cardozo Hernandez: None. **E. Viveros:** None. **A. Vera:** None. **J. Gonzalez:** None. **L. Becerra:** None. **J. Rengifo:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.14/P8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant MH18501

Title: Neuroprotective roles of biliverdin reductase in the brain

Authors: *R. KOTHARI[1], C. VASAVDA[2], A. P. MALLA[1], R. TOKHUNTS[3], A. LIN[4], M. JI[2], R. XU[2], H. SAAVEDRA[2], A. M. SNOWMAN[2], C. RICCO[1], J. I. SBODIO[2], T. W. SEDLACK[2], B. D. PAUL[2], S. H. SNYDER[2]
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Abstract: Bilirubin is one of the most commonly measured metabolites in medicine, but its function in vivo is largely unknown. Some evidence suggests that bilirubin is an antioxidant. However, this has only been observed in vitro or with exogenous bilirubin, and it is controversial whether bilirubin exhibits significant antioxidant activity in vivo compared to the cell's battery of antioxidants. Using a novel genetic mutant mouse model that lacks the bilirubin biosynthetic enzyme, biliverdin reductase (BVR), we find that endogenous bilirubin is cytoprotective in multiple cell types.

BVR is a highly conserved enzyme in mammalian heme catabolism responsible for converting biliverdin to bilirubin. In addition to producing bilirubin, BVR also exhibits serine/threonine kinase activity that might play some roles in various signaling pathways in response to stress. In support of these reports, BVR-/- cells are hypersensitive to multiple oxidants, including the superoxide donor pyrogallol, hydrogen peroxide, and 4-hydroxynonenal. When challenged with oxidants, BVR-/- cells accumulate reactive oxygen species (ROS), as measured by dihydroethidium.

To assess where bilirubin may function in vivo, we first examined BVR expression in a variety of organs. BVR is widely distributed with notable variation. Despite being considered a neurotoxin that leads kernicterus and Crigler-Najjar, we were surprised to find that bilirubin is produced at a surprisingly high degree in the brain. When exposed to excitotoxic levels of the neurotransmitter N-Methyl-D-aspartate (NMDA), BVR-/- mice experience significantly larger lesions as assessed through histology.

Taken together, our results demonstrate a physiologic role for BVR and bilirubin in redox homeostasis and neuroprotection against oxidative and excitotoxic stress. The exact mechanism by which BVR/bilirubin exert neuroprotection is still hotly debated, and further investigation will yield insight into how to leverage heme catabolism's protective effects to treat oxidative diseases.

Disclosures: R. Kothari: None. **C. Vasavda:** None. **A.P. Malla:** None. **R. Tokhunts:** None. **A. Lin:** None. **M. Ji:** None. **R. Xu:** None. **H. Saavedra:** None. **A.M. Snowman:** None. **C. Ricco:** None. **J.I. Sbodio:** None. **T.W. Sedlack:** None. **B.D. Paul:** None. **S.H. Snyder:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.15/P9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neurotrophic, anti-apoptotic and neuroprotective multifunctional activities of NX210, a thrombospondin repeat derived peptide

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Abstract: Traumatic or degenerative disorders of the central nervous system (CNS) represent a major public health issue, as the consequences are currently irreversible with no treatment available.
NX210 is a patented peptide derived from the most conserved sequence of the thrombospondin repeats (TSRs) of the **SCO-spondin**, a naturally secreted protein highly conserved in vertebrates and expressed during neurogenesis. We demonstrated that NX210 carries multifunctional activities on neural cells: **neurotrophic (A)**, **anti-apoptotic (B)** and **neuroprotective (C)** properties.
A) We showed on different cellular models that NX210 is able to induce cell extension and to increase **neurite outgrowth**. In addition to *in vitro* results, *in vivo* efficacy studies have been performed in rat models of spinal cord injury (SCI) demonstrating axonal regrowth stimulation and functional recovery improvement. Briefly, in the first model (aspiration of dorsal funiculi) 80% of NX210-treated rats displayed a sharp fiber regrowth (neurofilament immunostaining) *vs*. a minor regrowth in 1 control rat. In the second model (contusion with the NYU impactor), NX210 treatment improved functional recovery with a dose-dependent effect as compared to the vehicle (60% of NX210-treated rats having a BBB score ≥ 14 *vs* 17% control).
B) Preliminary results also unveil NX210 **anti-apoptotic activities.** This additional property was demonstrated both *in vitro* and *in vivo*, with 1) the abolition of TRAIL-induced apoptosis in hippocampal primary cell cultures; and 2) *in vivo* anti-apoptotic effect (caspase-3 labelling) on olfactory neurons in a model of axotomy.
C) Finally, NX210 reveals strong **anti-oxidative properties**, as demonstrated in multiple neuronal oxidative stress models and on different cell types, from B104 neuroblastoma cell line to primary rodent neurons. For example, cell viability of rat B104 neuroblastoma cells was determined after culture in presence of H_2O_2 (to induce oxidative stress), with NX210 applied either with a 24h pre-treatment or in co-treatment. In pre-treatment, NX210 displayed strong neuroprotection, with up to 85% cell viability at 190 µM *vs* 34% with H_2O_2 alone. In co-treatment NX210 demonstrated very high neuroprotection too, with significant enhancement of cell viability in a dose dependent manner (up to 94% at 380 µM *vs* 13% for H_2O_2 alone).

In conclusion, by combining antioxidant, anti-apoptotic and neuroregenerative actions, NX210 can be a potent multi-targeting candidate to treat traumatic and degenerative CNS diseases. NX210 safety studies have shown no relevant side effects in rats and dogs, and a phase I clinical trial (tolerance) is currently starting in Europe.

Disclosures: **N. Delétage:** A. Employment/Salary (full or part-time):; Employee of Neuronax. **M. Blanc:** A. Employment/Salary (full or part-time):; Employee of Neuronax. **F. Lalloué:** None. **S. Gobron:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.16/P10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Kuwait University grant No. OMICS -No. SRUL02/13

Title: Ferulic acid provides neuroprotection against kainic acid-induced neurotoxicity *in vitro*

Authors: *M. S. RAO, S. SMITHA
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Abstract: *Ferula asafoetida* is herbaceous plant of the umbelliferae family. Asafoetida is an oleo-gum-resin obtained from the exudates of the roots of the F. asafetida. Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid) is the active component in asafetida. FA is widely reported to exhibit anti-oxidative and anti-inflammatory functions. FA has been shown to possess scavenging activity toward hydroxyl radical, peroxy nitrite and oxidized low density lipoprotein in vitro and has anticonvulsant and antiepileptic properties. Recent evidences have shown that FA has beneficial effects against age-related diseases such as cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders. Objective of the present experiment was to investigate the neuroprotective effects of FA against kainic acid-induced excitotoxicity on cultured hippocampal neurons. Primary cultures of the hippocampal cells from the 18 days old embryonic hippocampus were grown for 10 days. These cultures were divided into control (C), kainic acid (KA), Ferulic acid (FA), and Kainic acid+Ferulic acid groups (KA+FA, n=6 in all groups). Control cultures continued to grow without any further treatment, KA, FA and KA+FA cultures were treated with KA(10µM), FA(10µM) and KA+FA(10µM+10µM) respectively for one week. Cell proliferation was assessed during first 24hrs of treatment by labeling the dividing cells with BrdU. Cell viability was assessed with MTT essay. Cultures were immunostained for Beta-3 tubulin (Tuj1) and glial fibrillary acidic protein (GFAP). Number of neurons (Tuj1positive) and glial cells (GFAP positive) were quantified. BDNF and VEGF contents in the cultured cells were analyzed by ELISA method. Cell proliferation and cell viability were

significantly increased in KA+FA group compared to C and KA group ($p<0.01$). FA treatment prevented neurodegeneration and hence significantly increased the number of neurons in KA+FA group compared to KA and C group ($p<0.01$). FA alone did not have any effect on cell proliferation, viability and number of neurons. Number of astrocytes were also found to be significantly increased in KA+FA group compared to KA and C cultures ($p<0.01$). Increase in the number of neurons and astrocytes was confirmed by increase in Tuj1 and GFAP content by western blot analysis. The neurons and astrocytes in the cultures treated with KA+FA had larger cell bodies and longer processes compared to treated with KA alone. BDNF and VEGF content showed significant increase in KA+FA culture compared to KA and C groups. We conclude that Ferulic acid protects the neurons from kainic acid exitotoxicity by increasing glial cell population and BDNF and VEGF.

Disclosures: M.S. Rao: None. **S. Smitha:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.17/P11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Omega 3 products and control juice used in this research were contributed by Smartfish AS, Gaustadalléen 21, 0349 Oslo.

Title: ω3 PUFAs as protectants against paracetamol-induced neurodevelopmental toxicity

Authors: *N. A. LABBA[1,2], M. G. HADERA[1,2], R. E. PAULSEN[1,2]
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Abstract: Both perinatal exposure to paracetamol (acetaminophen, APAP), and deficiency in essential omega 3 polyunsaturated fatty acids (ω3 PUFAs) have been linked to an increased risk of developing neuropsychiatric disorders such as ADHD. In the present study E17 chicken cerebellar granule neurons (CCGNs) and PC12 cells were co-administered with APAP and a commercial ω3 PUFA nanoemulsion prior to being exposed to a stressor in the form of serum deprivation or H2O2. An oil control composed of BSA-emulsified bulk ω3 PUFA oil with equimolar docosahexaenoic acid (DHA) as the nanoemulsion, as well as a manufacturer-supplied ω3 PUFA-free juice control were compared to the commercial ω3 PUFA nanoemulsion. In CCGNs APAP without exposure to stressor at concentrations ranging from subtherapeutic (25 µM) to severely hepatotoxic (5 mM) resulted in proliferative effects relative to untreated control at concentrations up to 1.6 mM ($p < 0.05$, $d = 3.67$) over 24 hour treatment, and up to 100 µM ($p < 0.005$, $d = 1.88$) over 48 hour treatment, as determined by the MTT viability assay. Toxicity was not detected in CCGNs even at 5 mM APAP. In 24 hour APAP treatment followed by a 5

hour exposure to H2O2, cell viability declined in a H2O2-dependent manner, from equivalent to unstressed control at 25 µM H2O2 to close no survival at 400 µM. APAP contributed slightly to loss of viability, though at non-significant levels. Co-administration of 30 µM ω3 PUFA nanoemulsion protected from viability loss at all APAP and H2O2 concentrations corresponding to an average of 141%, with the ω3 PUFA oil control at 133% and the juice control at 124%, of the viability of matched controls. In PC12 cells APAP elicited no effect in 24 hour treatment, whereas 48 hour treatment elicited proliferative effects up to 100 µM ($p < 0.01$, $d = 1.84$), and dose-responsive toxicity from 2 mM ($p < 0.05$, $d = -3.73$) and upward. Administration of ω3 PUFA nanoemulsion to PC12 cells from concentrations equivalent to 1 µM DHA and upwards resulted in a dose-dependent proliferative effect up to 30 µM ($p < 0.01$, $d = 2.17$) relative to untreated control as determined by the MTT assay. The ω3 PUFA nanoemulsion was also found to elicit a dose-dependent protective effect up to 30 µM against cell death in serum-deprived PC12 cells in both the MTT ($p < 0.005$, $d = 2.25$) and trypan blue exclusion ($p < 0.05$, $d = 4.59$) assays. These findings suggest that under oxidatively stressed conditions, APAP might confer additional neurotoxic insult. The findings also confirm that the formulation of the ω3 PUFA compound contributes to the previously established protection from oxidative stress.

Disclosures: N.A. Labba: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Smartfish AS contributed the omega 3 products and control juice that were used in the study.. **M.G. Hadera:** None. **R.E. Paulsen:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.18/P12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MU Research Council grant (17-009)

Title: Quercetin enhances the protective effects of docosahexaenoic acid (DHA): Studies with activated BV-2 microglial cells

Authors: *G. Y. SUN[1], R. LI[2], B. YANG[3], J. C. LEE[4], K. FRITSCHE[2], D. BEVERSDORF[2], Z. GU[5], M. GREENLIEF[2]
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Abstract: The abundance of docosahexaenoic acid (22:6n-3, DHA) in the phospholipids of mammalian brain has generated substantial interest in the search for its roles in regulating brain functions. Besides its involvement in membrane physical properties, DHA is also an essential

nutrient for the brain. To-date, n-3 polyunsaturated fatty acids in the form of fish oil is probably one of the most highly consumed supplements by humans. In our recent studies with microglial cells, DHA at 10-100 μM inhibited lipopolysaccharide (LPS)-induced NO and reactive oxygen species (ROS) in a dose dependent manner. DHA also suppressed LPS-induced stimulation of p-cPLA$_2$, an enzyme for release of arachidonic acid (20:4n-6, ARA) which is a source of lipid mediators involved in inflammatory responses. LPS-induced release of ARA also led to lipid peroxidation as demonstrated by the increase in 4-hydroxynonanal (4-HNE) levels. On the contrary, besides suppressing the LPS-induced inflammatory responses, DHA could offer hormetic effects through enhancing the nuclear factor erythroid-derived 2 (Nrf2) pathway, and synthesis of heme oxygenase-1 (HO-1), a powerful antioxidant enzyme. However, the high levels of DHA required to alter these pathways led to the question whether combination of DHA with other compounds with electrophilic properties can exaggerate the protective effects of DHA. Among the botanical polyphenols, quercetin is enriched in berries, onion, apples and other fruits, and has been used as a nutraceutical. Our earlier studies demonstrated ability for quercetin to suppress the LPS-induced inflammation as well as upregulation of the Nrf2-mediated antioxidant activities at 1-10 μM. In this study, we tested the hypothesis that quercetin together with DHA could provide additive protective effects through modulating the Nrf2 and NF-κB pathways. Our results show that supplementation with 10 μM DHA together with 2.5 μM quercetin to BV-2 microglial cells could produce greater inhibitory effects on LPS-induced NO and ROS and enhanced effects on Nrf2 pathway and HO-1 expression as compared with treating cells with DHA at 10 μM or quercetin at 2.5 μM alone. Taken together, these results show that low concentrations of quercetin can potentiate the protective effects of DHA in this cell model, and warrant further testing in an animal model.

Disclosures: R. Li: None. **B. Yang:** None. **J.C. Lee:** None. **K. Fritsche:** None. **D. Beversdorf:** None. **Z. Gu:** None. **M. Greenlief:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.19/P13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Antidepressants acting via LPA$_1$ counteract TNF-α-induced neuronal apoptosis by potentiating ERK1/2 and JNK signalling

Authors: *M. C. OLIANAS, S. DEDONI, P. ONALI
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Abstract: We recently reported that in immortalized HT22 hippocampal cells and primary mouse hippocampal neurons tricyclic and tetracyclic antidepressants inhibit TNF-α-induced cell

death by activating the lysophosphatidic acid (LPA) LPA_1 receptor coupled to transactivation of the FGF receptor. In the present study we investigated the intracellular signalling mediating the protective effects of the antidepressants. We found that in HT22 cells TNF-α triggered apoptosis through a pathway that involved activation of caspase 8, loss of mitochondrial potential, cytochrome c release into the cytosol, increased formation of active caspase 9 and 3 and cleavage of poly ADP-ribose polymerase (PARP). Pretreatment with the tetracyclic antidepressant mianserin failed to affect TNF-α stimulation of caspase 8, but counteracted the cytokine-induced mitochondrial permeabilization, cytochrome c release and the downstream activation of caspase 9 and 3. Exposure to TNF-α caused a rapid activation of p38 MAPK, JNK and ERK1/2. Pharmacological inhibition of p38 MAPK attenuated the cytokine-induced apoptosis, whereas blockade of either ERK1/2 or JNK had an opposite effect. Cell treatment with either mianserin or mirtazapine had no effect on TNF-α-induced p38 MAPK activation but potentiated the stimulation of JNK and ERK1/2. Moreover, the antidepressants enhanced the TNF-α-induced phosphorylation/activation of the pro-survival protein Bcl2 , a substrate of both JNK and ERK1/2. These data indicate that antidepressants antagonize TNF-α-induced neuronal apoptosis by up-regulating the pro-survival arm of the cytokine intracellular signalling.

Disclosures: M.C. Olianas: None. **S. Dedoni:** None. **P. Onali:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.20/P14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS091699

Title: Minimal neurotoxicity from long-term c3 transferase expression in the nigrostriatal pathway

Authors: R. V. GUPTA[1], A. J. SANTIAGO-LOPEZ[1,3], K. BERGLUND[1,2], *C.-A. N. GUTEKUNST[1], R. E. GROSS[1]
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Abstract: The Rho family of GTPases are key molecular switches that regulate growth of the neuronal cytoskeleton. Three Rho GTPases (RhoA, Rac1, and Cdc42) play a key role in the regulation of the actin and microtubule assembly and elongation; Rac1 regulates lamellipodia formation, Cdc42 regulates filidopa, and RhoA regulates axon growth. Injuries to the central nervous system (CNS) promote activation of RhoA, leading to axon growth collapse and cell death. RhoA is irreversibly inhibited through ADP ribosylation by C3 transferase (C3), a

bacterial exoenzyme derived from *Clostridium botulinum,* stimulating axonal outgrowth and branching. C3 gene therapy has been utilized in clinical trials for the treatment of acute spinal cord injury and shows promise as a therapeutic option for neurodegenerative disorders such as Parkinson's disease (PD), but its safety in long-term expression has not been well-studied. To evaluate the safety of RhoA inhibition, we engineered floxed adeno-associated viral (AAV-DIO-Ef1α-GFP-P2A-C3) vectors for gene delivery of C3 for long-term expression in the CNS. Two groups of TH-$Cre^{+/-}$ mice (n=5 per group) were injected unilaterally with either AAV-DIO-Ef1α-GFP-P2A-C3 or AAV-DIO-Ef1α-GFP in the substantia nigra and a third group of TH-$Cre^{-/-}$ mice (n=3) was injected with AAV-DIO-Ef1α-GFP-P2A-C3 in the same location. Additionally, a group of TH-$Cre^{+/-}$ mice (n=8) was injected unilaterally with 6-hydroxydopamine (6-OHDA), a known neurotoxin to dopaminergic neurons, in the medial forebrain bundle to serve as a positive control. Mice were assessed for amphetamine-induced rotation behavior at 14 and 28 days post-injection. After an additional 5 days, mice were sacrificed for brain sectioning and subsequent immunohistochemical analysis. Mice injected with C3 exhibited a similar mean number of rotations ipsilateral to the site of injection in comparison to control mice injected with GFP alone and significantly fewer ipsilateral rotations in comparison to mice lesioned with 6-OHDA. To determine whether long-term expression of C3 might induce apoptotic cell death, brain sections from mice infected with the floxed vectors were stained for the presence of cleaved activated caspase 3, a well-characterized marker of apoptotic cell death. Dopaminergic neurons expressing GFP-P2A-C3 or GFP alone did not exhibit any cleaved activated caspase 3 immunoreactivity. The lack of behavioral effect and absence of caspase activation demonstrate that virally-infected dopaminergic neurons express C3 without significant neurotoxicity, supporting its safety in long-term expression.

Disclosures: R.V. Gupta: None. **A.J. Santiago-Lopez:** None. **K. Berglund:** None. **C.N. Gutekunst:** None. **R.E. Gross:** None.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.21/P15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Indian Council of Medical Research (ICMR) No.BIC/12(23)/2012
Intramural funding from Rajiv Gandhi Center for Biotechnology
Senior Research Fellowship from Indian Council of Medical Research (ICMR)
Senior Research Fellowship from Kerala State Council for Science Technology and Environment (KSCSTE)
Senior Research Fellowship from Council of Scientific and Industrial Research (CSIR)
Senior Research Fellowship from Department of Science and Technology (DST)

Title: Design, synthesis and biological evaluation of tacrine derivatives as neuroprotective agents by targeting nmda receptor

Authors: *R. CHANDRAN[1], M. KUMAR[2], E. KOTI REDDY[3], R. S. JACOB[2], L. K[2], D. KV[1], E. J. VARIYAR[1], S. ANWAR[3], S. CHITTALAKKOTTU[1], R. V. OMKUMAR[2]
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Abstract: Impairments in cholinergic and glutamatergic neurotransmission contribute to progression of Alzheimer's disease (AD). Most of the approved drugs for AD treatment are acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate receptor (NMDAR) antagonists that work by restoring cholinergic neurotransmission and by limiting glutamate mediated excitotoxicity respectively. Tacrine was used as a drug for AD treatment due to its ability to inhibit AChE. It is also an antagonist of NMDAR although with reduced potency. Hence, at the therapeutic doses of tacrine that are sufficient to inhibit AChE, NMDAR inhibition would be limited. In addition, at the therapeutic doses, tacrine causes side effects such as hepatotoxicity. By increasing the inhibitory potency of tacrine, the dosage could be reduced to bring the hepatotoxicity within safety limits. With these objectives, novel tacrine derivatives were designed and were evaluated for their binding potency by using structural bioinformatics tools. The most promising derivatives were synthesized and their potency to inhibit AChE and NMDAR were evaluated. It was found that 14 derivatives among these had NMDAR inhibitory activity, a few of them showing more than 100-fold higher potency compared to tacrine. Thus, they also have the potential to be used in conditions in which NMDAR is the preferred primary target. Some derivatives also showed improvement in AChE inhibitory activity. Interestingly, some derivatives showed beta secretase inhibitory activity unlike tacrine. Thus, the derivatives were active against multiple therapeutic targets for neuroprotection. Hepatotoxicity of the derivatives seen as cytotoxicity in HepG2 cell line was similar or lesser compared to tacrine. Compound(s) with minimal IC_{50} value for NMDAR inhibition and minimal cytotoxicity were further tested for their neuroprotective properties in primary neuronal culture systems. Some derivatives were able to protect rat primary cortical neurons from glutamate induced excitotoxicity at significantly low concentrations (about 0.3 μM) compared to tacrine (IC_{50} value of 500 μM). Behavioral tests were also conducted to confirm the neuroprotective properties of some compounds in monosodium glutamate induced *in vivo* excitotoxicity model in rats.

Disclosures: R. Chandran: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Remya Chandran is designated as an inventor in the provisional patent application No. 201841015699, that includes the data mentioned in the abstract, Kannur University. **M. Kumar:** None. **E. Koti Reddy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eeda Koti Reddy is designated as an inventor in the provisional patent application No. 201841015699, that includes the data mentioned in the abstract, Vignan's Foundation for Science, Technology, and Research. **R.S. Jacob:** None. **L. K:** None. **D. Kv:** None. **E.J. Variyar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

funds); E. Jayadevi Variyar is designated as an inventor in the provisional patent application No. 201841015699, that includes the data mentioned in the abstract, Kannur University. **S. Anwar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shaik Anwar is designated as an inventor in the provisional patent application No. 201841015699, that includes the data mentioned in the abstract, Vignan's Foundation for Science, Technology, and Research. **S. Chittalakkottu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sadasivan Chittalakkottu is designated as an inventor in the provisional patent application No. 201841015699, that includes the data mentioned in the abstract, Kannur University. **R.V. Omkumar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ramakrishnapillai Vyomakesannair Omkumar is designated as an inventor in the provisional patent application No. 201841015699, that includes the data mentioned in the abstract, Rajiv Gandhi Centre For Biotechnology.

Poster

210. Neurotoxicity, Inflammation, and Neuroprotective Mechanisms: Preclinical

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 210.22/Q1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: LLU School of Behavioral Health Behavioral Neuroscience Laboratory

Title: Exploring the interaction between dietary polyphenols and recovery from anesthesia in *Drosophila melanogaster*

Authors: *J. M. NAPAN, L. S. VILLALPANDO, B. TOLAN, D. S. PATEL, C. BARCENAS, W. HARDEMAN, A. D. TROFIMOVA, R. E. HARTMAN
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Abstract: Behavioral studies with *Drosophila melanogaster* often require transient anesthesia for transportation and identification. However, CO_2, which is commonly used for fly anesthesia, has been shown to alter physiological parameters for as long as 24 hours after exposure. FlyNap is another commonly used fly anesthetic cocktail composed of triethylamine (50%), ethanol (23%), isopropanol (1%), methanol (1%), and “fragrance” (25%). Flies require several hours to recover from anesthesia using FlyNap, and it has been shown to increase the heart rates of mosquitos. However, little is known regarding its effects on behavior (e.g., motor function) following recovery. Additionally, previous research from our laboratory has demonstrated protective effects of dietary supplementation with pomegranate polyphenols in flies, mice, and humans.
Therefore, we hypothesized that increased lengths of exposure to anesthesia procedures (FlyNap,

CO_2, and cryoanesthesia) would be associated with longer recovery times and increased behavioral deficits in *Drosophila melanogaster*, even after "full" recovery, and that adding polyphenols to their food would improve recovery from anesthesia and ameliorate any anesthesia-induced behavioral deficits. Flies were exposed to varying lengths of exposure to FlyNap, CO_2, and cryoanesthesia followed by recovery and repeated behavioral assays for 1 week after anesthesia. Half of the flies consumed standard fly diet media, and half of the flies' diet was supplemented with polyphenols. Preliminary findings demonstrate that increased exposure time was associated with worse behavioral performance for at least 2 days after exposure. These results suggest that any behavioral studies done after anesthesia should take into consideration the possible long-lasting deficits induced by the anesthesia.

Disclosures: J.M. Napan: None. **L.S. Villalpando:** None. **B. Tolan:** None. **D.S. Patel:** None. **C. Barcenas:** None. **W. Hardeman:** None. **A.D. Trofimova:** None. **R.E. Hartman:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.01/Q2

Topic: C.10. Brain Injury and Trauma

Support: NIGMS-RISE R25 GM061838
Brain & Behavior Research Foundation (NARSAD)
RCMI8G12MD00760
UPR Medical Sciences Campus Chancellor's Office
School of Medicine Deanship

Title: Effects of closed head injury on conditioned fear in rats

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Abstract: Over 4 million soldiers and civilians suffer from traumatic brain injury (TBI) each year, many of who are diagnosed with cognitive and neurological dysfunction, such as excess fear. There are common mechanisms that contribute to the neurobiology of TBI and cognitive dysfunction. Notably, both can result in impaired learning and emotional regulation. Although epidemiological studies show a correlation between sustaining TBI and developing excess fear, animal studies show conflicting results. This may be due in part to limitations in current TBI models such as differences in the brain regions serving as the epicenter (main area of impact). To evaluate the potential link between TBI and cognitive dysfunction, a biological link must be examined using reliable injury models and behavioral tests. Using Pavlovian conditioning we

propose that TBI will impair fear or extinction in rats depending on what brain region will be targeted as the epicenter of the impact. There are homologous brain regions in rodents and humans needed for the expression of fear memories. Dysfunction in the amygdala, hippocampus (Hipp), and the medial prefrontal cortex (mPFC) underlie deficits in both rodents and humans with fear disorders. Notably, the effects of TBI to activity in homologous brain regions in the rodent are unclear. To address this knowledge gap, we mimic concussion in adult male rats using closed head injury (CHI) targeting the Hipp or mPFC as the epicenter by aiming at lambda or bregma, respectively. After recovery, delay fear conditioning is achieved by pairing an auditory stimulus (e.g. tone) with a foot shock, followed by subsequent tests for memory. Our preliminary results demonstrate that non-injured rats acquire a tone-shock association and express fear as indexed by a lack of movement save those related to breathing, known as freezing. Our design includes three groups: Group 1: CHI anterior to lamba, consistent with Hipp as epicenter; Group 2: CHI anterior to bregma, consistent with mPFC as epicenter, Group 3: Sham controls. To mimic the scenario in which TBI occurs prior to an aversive event, we are assessing the delivery of CHI prior to fear conditioning. This work may lead to novel approaches for understanding and treatment of patients with TBI and fear disorders.

Disclosures: M. Rivera-Lopez: None. **D. Sierra-Mercado:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.02/Q3

Topic: C.10. Brain Injury and Trauma

Title: Gender influences outcomes in mice after repeat concussive traumatic brain injury

Authors: *A. J. STUMP, M. A. OSTLIE, R. A. CHEENIYIL, J. T. TRAN, M. SHAABAN, J. P. LUNT, S. MINOSHIMA, D. J. CROSS
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Abstract: Introduction: Traumatic brain injuries (TBI) affect approximately 1.7 million individuals yearly in the United States alone. Repeat concussive traumatic brain injuries (rcTBI), seen primarily in combat veterans and athletes in contact sports, can lead to eventual tauopathies such as chronic traumatic encephalopathy (CTE). Before the onset of tauopathies, debilitating symptoms from rcTBI can be observed, including memory impairment, increased anxiety, and gait abnormalities. Previous research on rcTBI has focused mainly on males, both in animal studies and in clinical research. The aim of this study was to determine if gender alone influences outcomes after rcTBI in mice. Methods: We subjected 22 mice (C57BL6, n=11 male and n=11 female) to a mild impact directly on the skin and normal to the skull once daily for 5 days (5mm impact tip, 1mm depth, 5 m/s velocity, 100 ms dwell time; Impact One, Leica Biosystems). Mice

received behavior testing after rcTBI for both short and long-term spatial memory and anxiety. Elevated plus maze (EPM), which measures anxiety, was performed 4 days after final impact. Radial water tread maze (RWT), which measures spatial cognition, was performed 10-14 and 21 days after final impact. MRI (7T, T1w and T2 mapping) imaging was performed at 4 weeks after impact. Results: Behavior testing revealed female mice spent significantly less time in the closed arms of the EPM as compared to male mice (331.78±26.575s vs. 389.81±18.64s, $p \leq 0.05$). Female mice displayed significantly better short-term spatial memory than males (35.82±10.09s vs. 76.53±20.36s, $p \leq 0.05$). ANOVA between group analysis revealed male mice had a significant difference in time to complete the RWT between days 1 and 12, but between no other days ($p=6.26 \times 10^{-5}$). Female mice had significant differences in ANOVA between group analysis on multiple days (days 2 and 3 $p=0.05$, days 1 and 5 $p=1.27 \times 10^{-5}$, and days 1 and 12 $p=6.35 \times 10^{-8}$). Though both groups displayed spatial memory learning, females completed the maze in less time overall and learned the maze more quickly. Conclusions: This preliminary study indicates significant differences in spatial memory and anxiety outcomes between male and female mice. Females displayed better overall learning, short-term spatial memory, and less anxiety and more exploratory behavior than males. The results from this study may significantly impact the treatment of rcTBI between males and females.

Disclosures: A.J. Stump: None. **M.A. Ostlie:** None. **R.A. Cheeniyil:** None. **J.T. Tran:** None. **M. Shaaban:** None. **J.P. Lunt:** None. **S. Minoshima:** None. **D.J. Cross:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.03/Q4

Topic: C.10. Brain Injury and Trauma

Support: MOST104-2923-B-038-001-MY3

Title: Post-injury therapeutic effects of 3,6’-dithiopomalidomide on traumatic brain injury

Authors: *C.-T. LIN[1], L.-Y. YANG[1], P.-Y. TSAI[1], W. LUO[2], B. J. HOFFER[1], N. H. GREIG[2], J.-Y. WANG[1]
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Abstract: Traumatic brain injury (TBI) causes mortality and disability worldwide. TBI induces inflammation, microglial activation, oxidative stress and autophagy in brain tissue, resulting in neurodegeneration, cognitive and behavioral deficits. Pomalidomide (Pom), an FDA (USA)-approved immunomodulatory agent used to treat multiple myeloma, has been shown to be a more potent and better tolerated inhibitor of TNF-α than thalidomide. Subjecting Sprague-Dawley rats to controlled cortical impact (CCI) TBI, we previously demonstrated that Pom (0.5

but not 0.1 mg/kg, i.v.) administered once at 5 hr after TBI reduced contusion volume and improved functional deficits by mitigating neuronal apoptosis. Here, we compare the therapeutic efficacy of Pom to a new analog 3,6'-dithiopomalidomide (DP). DP (0.5mg/kg, i.v.), Pom (0.5mg/kg, i.v.) or vehicle was administered to rats at 5 hr after CCI. Motor asymmetry, evaluated by an elevated body swing test, and a modified neurological severity score (mNSS) assessment that is a composite of motor, sensory, balance and reflex tests, were performed before CCI and at 24 hr after. The degree of brain injury was evaluated by contusion volume and neuronal degeneration using cresyl violet and FluoroJade C (FJC) staining. DP and Pom treatment at 5 hr after TBI both significantly mitigated TBI-induced behavioral deficits at 24 hr post-injury. The contusion volume and the mean densities of degenerating (FJC-positive) neurons were significantly reduced by DP and Pom treatment; with DP proving more effective than Pom. DP and Pom significantly suppressed TBI-induced expression of proinflammatory cytokines, including TNF-α, IL-6, IL-1β. Immunostaining with the microglial marker ionized calcium-binding adapter molecule 1 (Iba-1) showed an increased degree of microglial activation after TBI, as revealed by their morphologic phenotypes. Upregulation of enzymes involved in the inflammatory processes mediated by oxidative stress, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), was also found in activated microglia after TBI. This microglial activation was ameliorated by DP treatment better than with Pom. TBI-induced autophagy was evidenced by increased protein expression of LC3-II and decreased expression levels of p62. These effects were attenuated by DP more than with Pom treatment. Our results suggest that post-treatment with DP significantly improves neurological functional outcome and reduces TBI-induced microglial activation and neuroinflammation, oxidative stress and autophagy. Our data suggest that DP may be developed as a potential therapy to ameliorate TBI-induced functional deficits.

Disclosures: C. Lin: None. **L. Yang:** None. **P. Tsai:** None. **W. Luo:** None. **B.J. Hoffer:** None. **N.H. Greig:** None. **J. Wang:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.04/Q5

Topic: C.10. Brain Injury and Trauma

Support: University of Melbourne Early Career Researcher Grant 2015
NHMRC Early Career Fellowship
Rebecca L Cooper Medical Research Foundation grant

Title: High-mobility group box protein-1 (HMGB1) mediates secondary injury after traumatic brain injury in pediatric mice

Authors: *B. D. SEMPLE[1,2], K. M. WEBSTER[2], M. SUN[2], S. R. SHULTZ[1,2], P. J. CRACK[3], T. J. O'BRIEN[1,2]
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Abstract: Release of high-mobility group box protein-1 (HMGB1), a pro-inflammatory damage-associated protein, is inversely correlated with poor functional outcomes after traumatic brain injury (TBI) in infants and children. To date, while HMGB1 has been considered a target of novel neuroprotective therapeutics in the adult brain after TBI and ischemic stroke, a role of this mediator has not yet been defined after traumatic injury at an early age. This study therefore aimed to determine the role of HMGB1 in neuroinflammation and functional outcomes after pediatric TBI, using a well-characterized model of controlled cortical impact to male postnatal day 21 mice. Immunoassay quantification of HMGB1 in the serum detected a robust elevation at 2 h after pediatric TBI, while extracellular release was detected in brain tissue by immunofluorescence staining at 3 d post-injury. Inhibition of HMGB1 by glycyrrhizin (Gly; 50 mg/kg i.p.), a natural extract from licorice root, was found to reduce HMGB1 levels after pediatric TBI, prevent brain edema, and reduce astrocyte and microglia activation in the injured hippocampus, as compared to vehicle-treated, age-matched TBI mice. Of note, differential effects on some acute outcome measures were noted when Gly treatment was commenced 1 h prior to TBI compared to 1 h post-injury, a finding that was unique from what has previously been shown in adult models of TBI. In a separate cohort of mice, behavior testing at 4 months post-injury revealed cognitive deficits in vehicle-treated TBI mice only, whereas Gly-treated TBI mice were comparable to sham controls, suggesting that acute inhibition of HMGB1 yielded long-term neuroprotection. Together, our findings demonstrate a robust increase in HMGB1 after injury to the pediatric brain, which mediates edema, inflammation and chronic neurocognitive outcomes. HMGB1 therefore appears to have a unique role in the pediatric injured brain, and may represent a promising candidate biomarker and novel target for therapeutic intervention.

Disclosures: B.D. Semple: None. **K.M. Webster:** None. **M. Sun:** None. **S.R. Shultz:** None. **P.J. Crack:** None. **T.J. O'Brien:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.05/Q6

Topic: C.10. Brain Injury and Trauma

Support: Ari and Regine Aprijaskis Fund
Dr. Miriam and Sheldon G. Adelson Center for the Biology of Addictive Diseases

Title: GM1 ganglioside prevents axonal regeneration inhibition and cognitive deficits in a mouse model of traumatic brain injury

Authors: *C. G. PICK[1], V. RUBOVITCH[2]
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Abstract: Traumatic Brain Injury (TBI) is one of the most common causes of neurological damage in young populations. It was previously suggested that one of the mechanisms that underlie brain injury is Axonal Outgrowth Inhibition (AOI) that is caused by altered composition of the gangliosides on the axon surface. In the present study, we found that in a mouse model of weight drop closed head traumatic brain injury, a significant reduction of GM1 ganglioside levels in the cortex was found. In addition, axonal regeneration in the brains of the injured mice was affected as seen by the expression of the axonal marker pNF-H and the growth cones (visualized by F-actin and β-III-tubulin). NeuN immunostaining revealed mTBI-induced damage to neuronal survival. Finally, as expected, spatial and visual memories (measured by the Y-maze and the Novel Object Recognition tests, respectively) were also damaged 7 and 30 days post injury. A single low dose of GM1 shortly after the injury (2mg/kg; IP) prevented all of the deficits mentioned above. These results reveal additional knowledge regarding the neuroprotective characteristics of GM1 in prevention of biochemical, cellular and cognitive changes caused by trauma, and may suggest a potential intervention for mTBI.

Disclosures: C.G. Pick: None. **V. Rubovitch:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.06/Q7

Topic: C.10. Brain Injury and Trauma

Support: NCRG Seed Grant
NIGMS 5P20GM109098-04
WVU

Title: Unilateral parietal traumatic brain injury increases risk-taking on a rat gambling task

Authors: J. OZGA[1], C. WHIRTLEY[2], C. O'HEARN[2], H. S. BHATIA[2], *C. VONDER HAAR[2]
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Abstract: Traumatic brain injury (TBI) affects more than 2.5 million people each year in the United States alone. Although most recover with minimal complications, 1-2% of people develop chronic behavioral and cognitive deficits. In particular, the development of psychiatric-like symptoms, including deficits in decision-making are relatively common. Prior work has

shown that severe bilateral frontal TBI reduces optimal decision-making on a rat gambling task (RGT), which is used to assess risk-taking in rodents. To determine if these effects are location-specific or general to TBI, the current study evaluated the effects of unilateral parietal TBI on RGT acquisition. Rats were pair-matched for rotarod performance, and then assigned to sham or TBI groups. Craniotomies were performed for sham and TBI animals centered at AP +2.4mm, ML +2.4mm from bregma and unilateral parietal lesions were delivered to TBI animals using controlled cortical impact (CCI; -2.5 DV @ 3 m/s). Following a 7-day recovery period, rotarod performance was assessed for three additional sessions. All rats were then trained on the RGT, a measure of risk-based decision making and response inhibition. During the RGT, choice occurs between four reinforcer/punisher options, two of which are considered relatively "safe" while the alternatives are considered "risky." Reinforcement can be maximized during this procedure if choice is for the "safe" options exclusively. Behavior was tested daily for 30 minutes until reaching stability (~8 weeks). Following stability, rats were sacrificed using transcardial perfusion and brains were dissected for subsequent lesion analysis using cresyl violet staining. Injured animals demonstrated deficits in motor function on the rotarod, reduced response inhibition, as well as increased risk-taking during the RGT as compared to sham animals, indicated by increased choice for "risky" options and reduced choice for "safe" options. These deficits became more pronounced and endured for eight weeks into the recovery period. These results are similar to previous work showing deficits in risk-based decision-making following bilateral frontal TBI via CCI. However, this study also suggests that responding during the RGT may not be solely frontally dependent. This work underscores the importance of assessing executive function following a variety of methods of TBI.

Disclosures: J. Ozga: None. **C. Whirtley:** None. **C. O'Hearn:** None. **H.S. Bhatia:** None. **C. Vonder Haar:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.07/Q8

Topic: C.10. Brain Injury and Trauma

Support: U.S. Air Force FA8650-17-2-6H10

Title: Exacerbation of traumatic brain injury neuropathology and behavioral deficits by hyperhomocysteinemia in a rat model of controlled cortical impact

Authors: *F. TCHANTCHOU[1], M. GOODFELLOW[1], C. MILLER[2], G. FISKUM[1]
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Abstract: The heterogeneity of traumatic brain injury (TBI) pathophysiology is a factor that hinders the development of a sustainable therapeutic agent. Stress, ageing and life style can cause the accumulation of neurotoxins such as homocysteine called hyperhomocysteinemia (HHCY), which may exacerbate combat and vehicle accident related TBI. We investigated the deleterious effects of pre-existing HHCY on TBI neuropathology and associated behavioral deficits in rats. Male Sprague-Dawley rats (250-300g) received intraperitoneal injections of L-methionine (300 mg/kg), once daily to induce and sustain HHCY while controls received saline. They were then subjected to TBI by controlled cortical impact (CCI) method under anesthesia with 3.5% isoflurane and body temperature maintained at 37°C using a heating pad. CCI was performed over the left parietal cortex with a 5 mm diameter piston, a magnetic impact of 5 m/s and penetration depth of 1.5 mm. CCI and sham rats were assessed for fine motor activity, working memory and anxiety-like behavior. They were euthanized at different time points and brain tissue was collected for histological and biochemical analyses. Statistical analysis was performed by one-way ANOVA with Tukey-Kramer post-test analysis. There were 4-12 rats/group and the study was approved by UMB IACUC.
Methionine injections induced six fold increase in homocysteine levels both in sham and CCI rats (n=6-10; $p<0.001$) compared to controls. Hyperhomocysteinemic (HHC) sham rats (n=6) showed relatively reduced working memory performance on days 8 and 15 post-injury compared to control sham and CCI rats. This deficit was more pronounced among HHC-CCI rats ($p<0.05$). HHC-CCI rats also exhibited increased anxiety-like behavior on days 3 and 9 post- trauma ($p<0.05$; n=11) compared to shams and non-HHC TBI rats. HHCY had no effect on motor activity. Histological analysis of brain sections at days 3 and 7 post-surgery revealed that HHC-rats presented cleaved caspase 3 apoptotic cell death far beyond the lesion site in the somatosensory 2 cortex and the hippocampus dentate gyrus, as well as in the contralateral hemisphere cortex, not observed in non-HHC rats. Similarly, HHCY caused increased expression of markers of blood brain barrier disruption, the intercellular adhesion molecule 1 and von Willebrand factor, associated with increased Evans blue extravasation and diffuse presence of activated microglia/macrophage.
In summary, HHCY exacerbated working memory deficits and anxiety-like behavior in rats that sustained mild TBI. This condition was associated with HHCY-induced apoptotic cell death, blood brain barrier disruption, and diffuse inflammation.

Disclosures: F. Tchantchou: None. **M. Goodfellow:** None. **C. Miller:** None. **G. Fiskum:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.08/Q9

Topic: C.10. Brain Injury and Trauma

Support: Defense Health agency 64682-307877-2.00

Title: A comparison of blast traumatic brain injury in mouse upright versus prone orientations using an advanced blast simulator (ABS)

Authors: *E. MCNAMARA[1], L. B. TUCKER[2], J. LIU[2], A. H. FU[2], Y. KIM[2], J. T. MCCABE[1]
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Abstract: The objective of this exploratory study is to determine how animal orientation to a shock wave alters physiological and behavioral outcomes. Male and female 8 week old C57BL/6J mice were exposed to a single blast overpressure ~ 15psi using an Advanced Blast Simulator (ABS). Animals were secured in a mesh holder in either a vertical orientation, exposing the ventral underbelly, or in a prone, nose-first position. Blood-brain barrier (BBB) permeability was the focus for physiological study. To visualize BBB damage, four markers (Evans Blue, Dextran 367, Dextran 3K, Dextran 10K) were administered via tail intravenous injection immediately prior to blast exposure. Animals were then sacrificed 4 or 24 hours later and immunohistochemical analysis was performed for IgG and BBB proteins. Depressive-like behavioral studies included the sucrose preference test (SPT), tail suspension test (TST), and forced swim test (FST). Anxiety-like behavior was tested through the elevated plus maze (EPM) or elevated zero maze (EZM) for mice in an upright orientation. Sham animals were treated identically except they were not exposed to a blast wave and all behavioral tasks were scored blindly.
Evans Blue (EB) and Dextran 10K appeared to be the most sensitive markers. Mice in an upright orientation displayed EB staining on brain parenchyma, while animals in a prone position did not. Dextran 10K, however, was sensitive to IgG staining in nose-first oriented mice. The lack of observable EB staining in prone positioned mice suggests that the upright blast exposure orientation causes more severe injury. Injured female mice also demonstrated increased IgG staining in the cortex and dorsal fornix/fimbria compared to injured males. The sex differences may be correlated with variations in body weight. No sex differences were found with the behavioral tasks, but the injured group showed a decreased preference index in the SPT indicating anhedonia-like behavior. A significant difference between sham and injured mice in the TST was revealed, but in the opposite direction than we hypothesized; the injured group showed less time immobile than the sham. No significant differences were found with FST, EPM, or EZM, but injured mice displayed less time in open areas during anxiety-like behavioral testing. We are in the process of studying mice in the prone orientation to stain for different BBB proteins and are analyzing behavioral data.

Disclosures: E. McNamara: None. **L.B. Tucker:** None. **J. Liu:** None. **A.H. Fu:** None. **Y. Kim:** None. **J.T. McCabe:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.09/Q10

Topic: C.10. Brain Injury and Trauma

Support: NIH-NICHD R37HD059288
U.S. Army Telemedicine and Advanced Technology Research Center W81XWH-12-2-0081

Title: Alterations in the volatile metabolome following traumatic brain injury

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Abstract: Traumatic brain injury (TBI) affects millions of people each year, and continues to be one of the leading causes of disability and death in the United States. Treatment of TBI is difficult given the challenges of its diagnosis and the lack of an objective hallmark to monitor throughout the course of treatment in patients. A prominent diagnostic approach under investigation involves the identification of biomarkers uniquely expressed after TBI. While most studies focus on potential biomarkers in the cerebral spinal fluid or blood, few studies have explored other bodily fluids, such as saliva, tears, sweat, or urine. The latter bodily secretions communicate information regarding an animal's health status via volatile metabolites. These chemical signals form the volatile metabolome. Previous studies have shown that immune activators and promoters of inflammation alter the mouse volatile metabolome, specifically mouse urine odor. Given the nearly universal presence/activity of inflammatory processes in neurological disorders, we examined the volatile metabolites of urine within a mouse model of mild TBI (mTBI) to determine if TBI alters the volatile metabolome: thus creating a signature endophenotype. A behavioral assay in which trained biosensor mice perform discrimination tasks and a chemical assay involving gas chromatographic headspace analyses were utilized to assess the distinctiveness, onset, and persistence of changes in the volatile metabolome of sham mice, mice receiving mTBI treatment, and mice receiving lipopolysaccharide (LPS) treatment. We found that mTBI leads to a significant change in the volatile profile of urine that is separate and discernable from the volatile profiles associated with LPS-induced inflammation and sham conditions. Our data suggest that mTBI alters the volatile metabolome, producing a distinct odor and metabolite profile - a TBI signature. Such a signature has the potential of informing a brain

injury diagnosis and serving as an objective hallmark to monitor during treatment and recovery, and thus requires further investigation.

Disclosures: H. Metheny: None. **G.K. Beauchamp:** None. **M. Opiekun:** None. **B.A. Kimball:** None. **A.S. Cohen:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.10/Q11

Topic: C.10. Brain Injury and Trauma

Support: VA Merit Review #I01RX001144

Title: Model of TBI and fear conditioning and their impacts during a subacute period of injury

Authors: *G. B. KAPLAN[1], K. RUMBIKA[3], L. WANG[4], K. A. LEITE-MORRIS[2], L. ALFILER[3], Y. D. TENG[5]
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Abstract: Mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD) have emerged as the signature injuries suffered by US military personnel in Operations Iraqi Freedom and Enduring Freedom due to an increased probability of developing PTSD symptoms following a deployment-related mTBI. In an effort to examine the behavioral and neurobiological consequences of these two conditions at a subacute phase of injury (2-3 weeks post-TBI), our project aims to develop a comprehensive model of comorbid mTBI and PTSD. The mTBI intervention is administered by lateral fluid percussion at 1.7 atm force (LFP) preceding exposure to a model for the PTSD condition. The PTSD condition was comprised of a conditioned fear response induced by tone-cued foot shock followed by a fear extinction paradigm. Fear acquisition training generated significantly increased conditioned freezing responses over time in fear-conditioned groups compared to naïve controls. Subsequent conduction of the novel object recognition task revealed that both LFP and fear paradigms significantly diminished cognition, measured by a fear and LFP/craniectomy interaction. Following fear extinction training in experimental groups, conditioned freezing decreased significantly over time. In addition, these results revealed an accelerated rate of extinction in groups previously exposed to surgical intervention in LFP/craniectomy (fear/LFP 1.7 atm) and the craniectomy control (fear/ LFP 0.0 atm) treatment groups relative to surgically naïve

controls. Consequently our focus became to examine the immunohistochemical responses in the infralimbic region (IFC), as it's a critical node involved in extinction learning, which showed significantly elevated neuroinflammatory responses for neuroinflammatory markers CD68, TNF-α, Iba-1 and IL-1β in fear/LFP 1.7 group compared to controls. Simultaneously in the IFC, there was an elevated release of neurotrophic factors including brain-derived and glial cell-derived neurotrophic factors in the fear/LFP 1.7 group relative to naïve and fear-only controls. In the subacute phase of injury, our model of coinciding TBI and fear interventions shows both an enhancement of fear extinction learning, and a co-occurring elevation of neurotrophic responses in the IFC. These findings signal to a potential window post-injury in which fear extinction processes are more robust. Future examination of time-specific windows is critical for delineation of neurobiological and pathophysiological mechanisms underlying the comorbid condition leading to more effective treatment approaches.

Disclosures: G.B. Kaplan: None. **K. Rumbika:** None. **L. Wang:** None. **K.A. Leite-Morris:** None. **L. Alfiler:** None. **Y.D. Teng:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.11/Q12

Topic: C.10. Brain Injury and Trauma

Support: NIH T32GM007752
NIH NS082092
NIH MH051699
DOD W81XWH-17-1-0455

Title: Lysophosphatidic acid signals through ependymal LPA_1 and LPA_3 to initiate premature infantile hydrocephalus

Authors: *N. C. LUMMIS, G. KENNEDY, P. SANCHEZ PAVON, A. FRANTZ, J. CHUN
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Abstract: Post-hemorrhagic hydrocephalus (PHH) is a neurological condition presenting with increased intracranial pressure that leads to ventriculomegaly, often causing severe cognitive and motor disability. While neurosurgical treatments to drain CSF reduce the lethality of this condition, these interventions are palliative and often require several revisions throughout a patient's lifespan. Previous studies have linked lysophospatidic acid (LPA) signaling, a bioactive lipid found in the blood, to the initiation of fetal hydrocephalus. However, PHH is most common in premature infants, a time point that is severely underrepresented in animal models of hydrocephalus. Therefore, we have developed an early postnatal mouse model to emulate

premature humans. Postnatal day 8 mice were injected with LPA or vehicle using a stereotaxic frame to simulate intraventricular hemorrhage. Early LPA-mediated disruption and loss of the ependymal cells, which generate CSF flow, was observed. Shortly following ependymal loss, ventricular expansion was observed, leading to significant ventriculomegaly and increased intracranial pressure 7 days following the insult. These effects can be prevented in a significant subset of mice by knockout of the LPA_1 or LPA_3 receptors, suggesting that pharmacological inhibition of LPAR signaling could reduce hemorrhagic sequalae or prevent hydrocephalus from developing.

Disclosures: N.C. Lummis: None. **G. Kennedy:** None. **P. Sanchez Pavon:** None. **A. Frantz:** None. **J. Chun:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.12/Q13

Topic: C.10. Brain Injury and Trauma

Support: Ministry of Science and Technology Grant MOST 106-2917-I-038 -001

Title: (-)-Phenserine ameliorates contusion volume loss, neuroinflammation, and behavioral impairments induced by traumatic brain injury in mouse

Authors: *S.-C. HSUEH[1,2,3], Y. LUO[1,2,3], N. GREIG[1,4], B. HOFFER[1,2,3], J.-Y. WANG[1,2], J. MILLER[3], Y.-H. CHIANG[1,2,5,6]
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Abstract: Traumatic brain injury (TBI) is one of the major causes of death and disability and affects an estimated 10 million people worldwide. Currently, there is no approved drug for ameliorating the pathological processes of TBI. Previous studies have shown that (-)-phenserine (phen), an acetylcholinesterase inhibitor originally designed as a candidate drug for Alzheimer's disease (AD), was tested in clinical Phase II studies and showed no adverse effects. Besides its anti-amyloid activity in AD, our previous data also showed phen can prevent several neurodegenerative mechanisms as well as reduce the cognitive impairments induced by mild TBI using a weight-drop mouse model. In this study, we used a mouse model of moderate to severe TBI induced by controlled cortical impact to assess the effects of phenserine on somatosensory

functions. Animals were treated with phen (2.5 mg/kg, BID) by intraperitoneal injection for 5 days started from injury day at a clinically translatable dose and the effects were evaluated by behavioral and histological examinations at 1 and 2 weeks post-injury. Phen significantly attenuated TBI-induced contusion volume, enlargement of the lateral ventricle, and behavioral impairments in sensorimotor functions. The morphology of microglia was shifted to an active form from a resting form after TBI, and phen dramatically mitigated the population ratio of activated to resting microglia, suggesting that phen also mitigates neuroinflammation following TBI. Taken together, these results show that post-injury treatment with phen over 5 days significantly reduced the lesion volume and the enlargement of the lateral ventricle caused by TBI. In addition, phen effectively reduced sensory and motor deficits at 7-14 days post-injury. These data suggest a potential development of this compound for clinical use in TBI therapy.

Disclosures: S. Hsueh: None. **Y. Luo:** None. **N. Greig:** None. **B. Hoffer:** None. **J. Wang:** None. **J. Miller:** None. **Y. Chiang:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.13/Q14

Topic: C.10. Brain Injury and Trauma

Support: DBT-BioCARe

Title: Amelioration of oxidative damage, neuronal cell death and behavioral impairments by pramipexole in CCI rodent model of traumatic brain injury

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Abstract: Background: Traumatic brain injury (TBI) is a heterogeneous condition occurs when an external mechanical force damages the brain tissue. Controlled cortical impact (CCI) is an experimental neurotrauma model that has been widely used to produce graded reproducible injuries in rodents that mimic important pathophysiological aspects of closed-head TBI seen clinically. Currently, no therapeutic drug is available that could potentially inhibit the neuronal cell death following TBI.
Objective: The aim of this study was to investigate the potential neuroprotective effects of pramipexole (PPX) in TBI model and explore the underlying mechanisms.
Materials and methods: In this study, Male Wistar rats were divided into four groups: sham group, TBI group, TBI+PPX (0.25 mg/kg) group, and TBI+PPX (0.50 mg/kg) group, each group having 10 animals. A CCI method was employed to induce TBI in rats. We evaluated behavior

and biochemical alterations after trauma. Modified neurological severity score was performed to assess the neurological deficits after 14 days of injury. Animals were sacrificed to evaluate biochemical and molecular changes. Oxidative damage and apoptotic factors were done in the rat hippocampus. The expression of pro-apoptotic and anti-apoptotic proteins in hippocampus were evaluated using western blot analysis.
Results: PPX treatment was able to significantly provide rescue from the oxidative stress through the reduction of free radicals and apoptotic factors. PPX could also mitigate neurobehavioral alteration by inhibiting the neuronal cell death.
Conclusion: These results indicate that PPX can attenuate oxidative stress and behavioral out comes after traumatic injury through anti-oxidant activity and anti-apoptotic mechanism, which provide potential therapeutic benefits in TBI.
Keywords: Apoptosis, behavioral dysfunction, oxidative stress, neuroprotection.

Disclosures: M. Salman: None. **S. Parvez:** None. **H. Tabassum:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.14/R1

Topic: C.10. Brain Injury and Trauma

Title: Voxel-wise analysis of FDG-PET imaging to assess repeat concussive brain injury and response to therapy in mice

Authors: *J. P. LUNT[1], M. A. OSTLIE[2], A. J. STUMP[2], S. MINOSHIMA[2], D. J. CROSS[2]
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Abstract: Introduction:When using mouse PET image analysis in repeat traumatic brain injury (TBI) models global analysis of the image presents challenges due to the Harderian gland found within the orbits of the eyes. Because the Harderian gland experiences such a great uptake in glucose it can prevent an effective global analysis of the brain. We are working to solve this problem by stereotaxically aligning the images and then masking voxels outside the brain. This has enabled us to gather data from a global analysis of these images and draw conclusions about the therapeutics used as well as the injury.
Methods:Under anesthesia, mice (n=24) received 250 µCi [18F]-FDG via iv for positron emission tomographic imaging. T1-weighted MRI images were acquired as a3D GRE Multi FOV sequence for acquisition. (0.6 mm slice thickness) PET Images were reconstructed using Tera-Tomo™ 3D PET OSEM reconstruction with 700µm spatial resolution, and a 256 x 256 x 159 matrix. Coregistered MRI scans were used in addition to MRI stereotaxically normalized atlas to create masked MRI template. Masked MRI image parameters were applied to coregistered FDG-PET images to create masked FDG-PET images. Masked FDG-PET images

were averaged to create an FDG-PET template for analysis. FDG-PET images compared using voxel-wise statistical analysis between treatment group and controls. Subjects received no Rx (n=9), intranasal *paclitaxel* (PTX) after the first impact (n=7), and sham impact animals (n=8). Subjects received no craniotomy before receiving one impact daily for 5 days (Impact One; Leica Biosystems, Buffalo Grove, IL, USA), directly on skin at midline, using a Leica impactor device (Depth=1mm, Velocity=5m/s, Dwell time=200msec, 5mm impact tip). Immediately after final CCI, single intranasal injection of saline (n=30) or 0.0175µmol (roughly equivalent to 20% of an IV dose for chemotherapy PTX (n=10) Shams (n=10) received equivalent anesthesia with no impact.
Result:Whole brain standardized uptake values (SUV, pseudo-quantitative assessment of FDG-PET) were 120.5±30.1, 90.3±18.7 and 129.2±23.0, mn±sd for SHAM, Saline and PTX respectively. $P \leq 0.05$.
Conclusion:The MRI scans were correctly oriented, stretched and warped to fit a template which was then used to mask regions of the scan that did not include brain tissue. This was used to find statistically significant data indicating positive effects as a result of intranasal PTX injections in mice.

Disclosures: J.P. Lunt: None. **M.A. Ostlie:** None. **A.J. Stump:** None. **S. Minoshima:** None. **D.J. Cross:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.15/R2

Topic: C.10. Brain Injury and Trauma

Title: High-throughput behavioral phenotyping of repetitive mild traumatic brain injury

Authors: A. M. CHOO, A. HACKETT, R. ZENOWICH, A. MORENO, A. BARBOZA, M. OSBORNE, I. MORGANSTERN, Q. CHANG, *T. HANANIA
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Abstract: Public awareness of the deleterious long-term effects of concussive brain injuries continues to increase due to media attention in professional sports as well as ever increasing diagnoses in military veterans exposed to improvised explosive devices in the battlefield. The vast permutations among injury parameters such as impact severity, interval between repetitive impacts, and total number of cumulative impacts is a barrier to the preclinical modeling of repetitive mild traumatic brain injury (rmTBI) using conventional behavioral assays. We utilize high-throughput computer vision behavioral phenotyping (SmartCube®) to map a spectrum of concussive doses. Bioinformatics analysis of over 2000 behavioral features show that repetitive impacts spaced 1 minute versus 10 minutes apart exhibit distinctive phenotypes. Activity metrics

such as stepping and rearing are decreased in both rmTBI groups at 24 hours after injury. The reduction in activity relative to baseline levels is still evident at 2 weeks after rmTBI but the recovery signature is greater when the impacts were spaced 10 minutes apart compared to 1 minute apart. Anxiety metrics indicate that rmTBI increases metrics such as grooming and sniffing at 24 hours. At 2 weeks, the signature of the anxiety metrics is increased in both impact interval groups with the 1 minute impact interval showing a greater increase in anxiety. These data suggest that SmartCube® has the sensitivity and speed to handle the immense combinations of injury parameters for mapping concussive doses.

Disclosures: A.M. Choo: None. **A. Hackett:** None. **R. Zenowich:** None. **A. Moreno:** None. **A. Barboza:** None. **M. Osborne:** None. **I. Morganstern:** None. **Q. Chang:** None. **T. Hanania:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.16/R3

Topic: C.10. Brain Injury and Trauma

Support: VA SPiRE RX002389

Title: Assessment of lithium as a short-term therapeutic agent for repetitive mild TBI featuring recovery from anesthesia

Authors: *J. FIDLER[1], O. MOODY[2], S. AGEZO[2], P. S. GARCIA[3], S. S. SHIM[1]
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Abstract: Effective treatment of repetitive mild traumatic brain injury (rmTBI) presents a substantial medical concern for veterans in the 21st century. Veterans with rmTBI have a significantly elevated risk of developing chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD). Prevention of progression of acute TBI into sustained neurodegeneration is critical for any successful potential therapeutic agent for rmTBI. Among its numerous roles in the CNS, lithium is a well-established inhibitor of glycogen synthase kinase-3 (GSK-3). Previous studies in humans and animal models have shown inhibition of GSK-3 to be a promising target for therapies preventing the development of acute TBI into CTE or AD. Here we assess treatment with diet-administered lithium for 4 weeks during and immediately following impact in a closed-head injury mouse model of rmTBI. During each of 4 cranial impact procedures, we monitor mice for display of hallmarks of emergence and cognitive recovery from anesthesia: first forelimb movement, return of righting reflex, cross-matched ambulation, ataxia attenuation, and notice of a sticky dot placed on the forepaw during

anesthesia. We report a robust delay in latency to all of these hallmarks for mice given rmTBI versus sham control. Following the final impact, we perform a battery of neurocognitive behavioral assessments, including open field recording, Y-maze spontaneous alternation task, novel object recognition (NOR), and water radial arm maze (WRAM). Whereas mice given rmTBI display reduced exploration of the center of an open field arena versus sham control, we do not detect a difference in overall activity level between groups. Finally, immediately following treatment, we assess hippocampal synaptic plasticity in an ex vivo slice model of LTP. Taken together, these data suggest that lithium has marginal therapeutic value for treatment of acute TBI when administered for 4 weeks in the period during and following injury. A longer period of treatment with lithium may prove to be more beneficial in prevention of the conversion of rmTBI to sustained TBI with CTE or AD. This will inform our translational research into clinical treatment of veterans with rmTBI.

Disclosures: J. Fidler: None. **O. Moody:** None. **S. Agezo:** None. **P.S. Garcia:** None. **S.S. Shim:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.17/R4

Topic: C.10. Brain Injury and Trauma

Support: NIH NS097750-03
NJCBIR CBIR16IRG017

Title: Role of adult-born granule cells generated in response to trauma in dentate circuit pathology

Authors: *L. CORRUBIA[1,2], E. J. NEUBERGER[1], V. SANTHAKUMAR[2,1]
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Abstract: Traumatic brain injury (TBI) is an on-going global epidemic that results in a variety of debilitating symptoms such as memory dysfunction and epilepsy. TBI facilitates a robust early increase in hippocampal adult neurogenesis up to one-week post-injury. Adult-born granule cells (abGCs) generated during the neurogenic burst after certain forms of brain injury have been shown to display altered morphology and migration, suggesting abnormal network integration and function (Ibrahim et al., 2016; Villasana et al., 2015). Here we use the fluid percussion injury (FPI) model of concussive brain trauma, which results in diffuse sub-cortical damage and hippocampal pathology, to examine the effect of injury-induced neurogenesis on circuit excitability and inhibition. Young male Wistar rats underwent FPI or sham injury (Li et al.,

2015) followed by a single intracerebroventricular injection of a VEGFR-2 antagonist, known to selectively suppress neurogenesis, or vehicle two hours later. Rats were then sacrificed one week later for slice physiology or examined one month later for latency to chemically induced seizures. In perforant path-evoked field recordings, selective suppression of TBI-induced neurogenesis reversed dentate hyperexcitability observed one week after injury, indicating abnormal network function of abGCs born after TBI. Reducing TBI-induced neurogenesis attenuated the heightened seizure susceptibility observed 30 days post-injury suggesting a role for TBI-induced abGCs in epileptogenesis (Neuberger et al., 2017). To specifically target abGCs born after TBI, we established the FPI model in inducible Nestin-CreERT2 mice and treated them with tamoxifen 3 days after FPI to label abGCs born immediately following injury. Ongoing studies in Nestin-CreERT2 reporter mice are examining the morphology, migration, and synaptic physiology of FPI-induced abGCs at 8 weeks post-injury to examine their network integration. The results of this study may help identify how abGCs born after brain injury contribute to increased dentate gyrus excitability.

Disclosures: L. Corrubia: None. **E.J. Neuberger:** None. **V. Santhakumar:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.18/R5

Topic: C.10. Brain Injury and Trauma

Title: Effects of liposome-encapsulated clodronate in a rat model of cerebral contusion injury

Authors: *H. NEGISHI, Y. TAKAMINE, Y. FURUKAWA, M. KOBAYASHI, T. KUMAGAWA, K. SHIJO, N. MORO, A. YOSHINO
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Abstract: Gliotransmitter ATP is released immediately after traumatic brain injury that will activate microglia and initiate inflammatory response. Several lines of evidence show the effectiveness of anti-inflammation therapy following traumatic brain injury. In the present study, liposome-encapsulated clodronate (CL), an agent to deplete macrophage/microglia, was systemically administrated via femoral vein immediately after cerebral contusion injury (CCI)in rats. Rats were randomly assigned to the following four groups; Sham-control, Sham-CL, CCI-control and CCI-CL groups. Control liposome was used as a control. One or 3 days after injury, brain samples were taken and expression of microglia and inflammatory cytokines were measured by western blotting and polymerase chain reaction. On post-injury day 1, expression of CD11b of the Sham-control group (12.7±2.6) and Sham-CL group (15.1±2.5) did not differ. In the CCI-control group, this value increased significantly to 72.7±14.2 compare to the two Sham groups. Administration of CL decreased the expression of CD11b to 20.9±8.8 that was

significantly lower from the CCI-control group. The expression of Galectin-3, a marker of activated microglia showed similar trends. In the CCI-control group, Galectin-3 increased significantly to 349.3±185.3 from 8.0±1.9 in the Sham-control and 8.3±2.1 in the Sham-CL groups. Galectin-3 level of the CCI-CL group was suppressed to 138.5±25.2 which was significantly lower compare to the CCI-control group. On post-injury day 3, expression of both CD11b and Galectin-3 reduced in both CCI-control and CCI-CL groups. Some but not all inflammation related cytokines were suppressed by CL administration. Systemic administration of CL reduced post-injury inflammation in a rat CCI model.

Disclosures: H. Negishi: None. **Y. Takamine:** None. **Y. Furukawa:** None. **M. Kobayashi:** None. **T. Kumagawa:** None. **K. Shijo:** None. **N. Moro:** None. **A. Yoshino:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.19/R6

Topic: C.10. Brain Injury and Trauma

Title: Effects of Pyrazol-3 and MRS2179 against gliosis in a rat model of cerebral contusion injury

Authors: *Y. TAKAMINE, H. NEGISHI, Y. FURUKAWA, M. KOBAYASHI, T. KUMAGAWA, K. SHIJO, N. MORO, A. YOSHINO
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Abstract: Several insult to the brain, including ischemia and trauma causes activation of astrocytes in the acute period. These activated astrocytes are thought to remain until the chronic period and form gliosis, although the precise mechanism is not known. Gliosis is known to exacerbate pathologies and prevent neuronal recovery. It is reported that blockade of transient receptor potential canonical 3 (TRPC3) by pyrazole-3 (Pyr3) prevents gliosis in a mouse thrombin stimulation model. Because TRPC3 is a calcium channel that increases intracellular calcium level, we hypothesized that prevention of calcium elevation in the acute period after injury will decrease gliosis in the chronic phase of traumatic brain injury. In the present study we used MRS2179 a selective P2Y1 receptor blocker that prevents calcium wave and evaluated the magnitude of gliosis in a rat cerebral contusion injury (CCI) model. Male Sprague-Dawley rats were randomized into four groups; Naïve group, CCI-control group, CCI-Pyr3 group and CCI-MRS2179 group. Dimethyl sulfoxide was used as a control. Drugs were directly injected into the contused tissue by implanted osmotic pump. Rats were sacrificed at day 3, 7 and 28 following injury and analyzed. Expression of TRPC3 and P2Y1 receptor were suppressed in CCI-MRS2179 group in 3 days post-injury. Three days after injury, the GFAP level was 607.8±152.8 in the CCI-control group, that was significantly higher compared to the Naïve group

(312.6±101.9). GFAP level of the CCI-Pyr3 group (368.5±237.5) and CCI-MRS2179 group (408.7±311.5) were elevated but not significantly different from the Naïve group. On day 28, GFAP level of CCI-control group increased to 1099.2±102.9 that was significantly higher compare to the Naïve group, but the GFAP level of CCI-Pyr3 group (889.7±371.2) and CCI-MRS2179 group (846.5±162.3) were significantly suppressed compared to the CCI-control group. Histologically, Holzer staining of both CCI-Pyr3 and CCI-MRS2179 group showed that gliosis around the contused tissue were reduced compared to the CCI-control group on post-injury day 28. TRPC3 blockade by Pyr3 and P2Y1 receptor blockade by MRS2179 in the early period post-injury both reduced gliosis in the chronic phase.

Disclosures: Y. Takamine: None. **H. Negishi:** None. **Y. Furukawa:** None. **M. Kobayashi:** None. **T. Kumagawa:** None. **K. Shijo:** None. **N. Moro:** None. **A. Yoshino:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.20/R7

Topic: C.10. Brain Injury and Trauma

Support: MOST104-2923-B-038-001-MY3
R01NS094152. NIH. USA

Title: Pifithrin-α oxygen analog and pifithrin-μ prevents TBI-induced neuronal damage through regulation of oxidative stress, neuroinflammation, autophagy and mitophagy

Authors: *L.-Y. YANG[1], N. H. GREIG[3], B. J. HOFFER[4], C.-W. PENG[2], J.-Y. WANG[5]
[1]Taipei Med. Univ., Taipei City, Taiwan; [2]Taipei Med. Univ., Taipei, Taiwan; [3]Drug Design & Develop. Section, LNS, Intramural Res. Program, Natl. Inst. on Aging, NIH, Baltimore, MD; [4]Scientist Emeritus, NIDA/NIH, Lyndhurst, OH; [5]Grad. Inst. of Med. Sci. TMU, Taipei, Taiwan

Abstract: Traumatic brain injury (TBI) is one of the most common causes of death and disability across the world. Our previous studies demonstrated that a p53 inhibitor, pifithrin-α oxygen analog (PFT-α (O)), significantly reduced cortical and hippocampal cell death, which is substantial following controlled cortical impact (CCI) TBI, and improved motor and cognitive functional outcomes via anti-apoptotic mechanisms. Here, we investigated whether inhibition of p53 using PFT-α (O) or another p53 inhibitor, pifithrin-μ (PFT-μ) provides neuroprotective effects via p53-dependent or -independent mechanisms. To define the underlying mechanisms, Sprague Dawley rats were subjected to experimental TBI followed by the administration of p53 transcriptional inhibitor PFTα (O), or p53 non-transcriptional inhibitor PFT-μ (2 mg/kg, i.v.) at 5 h after TBI. Brain contusion volume, as well as sensory and motor functions were evaluated at 24 h after TBI. Fluoro-Jade C staining was used to label degenerating neurons within the cortical

contusion region. Levels of mRNA encoding for p53, autophagy, mitophagy, anti-oxidant, anti-inflammatory related genes and proteins were measured by RT-qPCR and double immunofluorescence staining, respectively. PFT-α (O) or PFT-μ treatment enhanced sensory and motor functional recovery and decreased contusion volume at 24 h post-injury. PFT-α (O) and PFT-μ treatment also reduced degenerating neurons in the cortical contusion region; thereby providing neuroprotection. PFT-α (O), but not PFT-μ, significantly lowered p53 mRNA expression. PFT-μ treatment significantly elevated mRNA expression of the antioxidant enzyme heme oxygenase (HO)-1 mRNA after TBI. Furthermore, PFT-α (O), but not PFT-μ, increasesd mRNA levels of PTEN-induced putative kinase 1 (PINK1), a key protein that regulates mitophagy. In addition, 24 h pro-inflammatory cytokine (IL-1β, IL-6 and TNF-α) mRNA levels were significantly reduced by PFT-α (O) or PFT-μ administration after TBI. Double immunofluorescence staining demonstrated that PFT-μ significantly increased HO-1 positive neurons in the cortical contusion region. Moreover, TBI-induced autophagic marker localization (LC3 and p62) were supressed by PFT-α (O) and PFT-μ treatment. Our data suggest that both PFT-α (O) and PFT-μ provide neuroprotective actions through regulation of oxidative stress, neuroinflammation, autophagy, and mitophagy mechanisms and can potentially be developed as a novel treatment strategy for TBI-induced neuronal damage.

Disclosures: L. Yang: None. **N.H. Greig:** None. **B.J. Hoffer:** None. **C. Peng:** None. **J. Wang:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.21/R8

Topic: C.10. Brain Injury and Trauma

Title: The role of FPR1 receptor and their relationship to neuroinflammation and neurodegeneration in traumatic brain injury

Authors: *S. CUZZOCREA[1,2], R. SIRACUSA[1], E. GUGLIANDOLO[1], R. FUSCO[1], R. D'AMICO[1], R. DI PAOLA[1]
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Abstract: TBI is associated with a significant risk factor for the development of dementia, with the interaction between structural damage from TBI and neuroinflammation potentially driving this relationship. Formyl peptide receptor 1 (FPR1) is a G protein-coupled receptor mainly expressed by the cells of myeloid origin, where it mediates the innate immune response to bacterial formylated peptides. The purpose of our research was to investigate the role of the FPR1 in cerebral dysfunction and tissue injury associated with TBI and the subsequent long-term risk of dementia. Controlled cortical impact injury was performed on Fpr1 KO mice on the

C57BL/6 genetic background compared to C57BL/6 genetic background animals. The experimental design was divided in two steps. In the first step, brains were collected at 24 h after TBI. In the second step we investigated the chronic post-TBI neuroinflammatory response and its relationship to both dementia pathology and functional impairment up to 28 days post-injury. At 24h and 28 days post-injury, a behavioral battery test encompassing motor function, anxiety and cognition was carried out. Western blot and immunohistochemical analyses were performed to study a range of inflammatory, neurodegenerative and oxidative stress markers. In addition the apoptotic leves of BAX and BCL-2 and tunel were detected.
At both 24h and 28 days post injury, the performance of behavioral test was significantly increased in FPR1 KO mice, with TBI WT mice exhibited impaired cognitive activity at 28 days. Molecular analyses indicated that in absence of Fpr1 there was reduced expression of inflammatory parameters and apoptotic markers. In summary, our results demonstrated that the absence of FPR1 is able to reduce the development of neuroinflammation and tissues injury events associated with brain trauma 24h after injury, moreover we focused the FPR1 as an important protein in effecting the resolution of brain inflammation associated to TBI, providing as a novel therapeutic target in development of dementia.

Disclosures: S. Cuzzocrea: None. **R. Siracusa:** None. **E. Gugliandolo:** None. **R. Fusco:** None. **R. D'Amico:** None. **R. Di Paola:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.22/R9

Topic: C.10. Brain Injury and Trauma

Support: This project was supported by Career Development Award Number IK2 BX-003196 from the Biomedical Laboratory Research & Development Service of the VA Office of Research and Development to AMF
Biomedical Laboratory Research & Development Service of the VA Office of Research and Development I01BX000132 to KCHP

Title: Neuroendocrine dysfunction and neurobehavioral outcome following experimental traumatic brain injury

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Abstract: An estimated 2.8 million traumatic brain injuries (TBI) occur within the United States each year. Although women are less likely to sustain brain injuries than men, poorer long-term prognosis and worse neurobehavioral outcomes have been reported for women after TBI. The hypothalamic-pituitary-gonadal (HPG) axis contributes to sex steroid hormone production and may explain the enhanced deleterious effects in women following TBI. The present study assessed whether TBI may cause differential disruptions in the HPG axis in young adult male and female Sprague Dawley rats, and whether these disruptions were associated with cognitive and sensorimotor deficits. One week after lateral fluid percussion injury, injured females compared to sham females were impaired in spatial working memory and displayed HPG axis disruption, as evidenced by altered estrous cycling and significantly reduced 17-beta-estradiol (E2) and luteinizing hormone levels. One month after injury, estrous cycle disruptions and hippocampus-dependent memory impairments recovered in females. In contrast to females, no changes in cognition or HPG axis function were observed in males. Suppression of the brainstem-mediated acoustic startle response was observed for at least three months after injury in females but only transiently in males. These results suggest that females are more sensitive to the effects of TBI than males and disruptions in the HPG axis may contribute to cognitive impairments after brain injury.

Disclosures: A.M. Fortress: None. **P. Avcu:** None. **A.K. Wagner:** None. **C. Dixon:** None. **K. Pang:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.23/R10

Topic: C.10. Brain Injury and Trauma

Support: NSF GRFP DGE-1313583 JTH
Notre Dame Center for Zebrafish Research
Notre Dame Center for Stem Cells and Regenerative Medicine

Title: Establishing a scalable blunt-force traumatic brain injury model in adult zebrafish

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Abstract: Traumatic Brain Injuries (TBI) affect 60 million people annually worldwide and contribute to other neurological disorders, such as cognitive decline and stroke. Our goal is to develop a blunt force TBI model that is inexpensive, rapid, and recapitulates the injury seen in humans, in a model organism that exhibits neuronal regeneration. Unlike traditional TBI rodent models, zebrafish potentially fit all these criteria. We modified the well characterized blunt force

TBI method, the Marmarou weight drop, for adult zebrafish. Our modified Marmarou weight drop resulted in a reproducible and scalable mild, moderate, and severe TBI that shares key pathophysiological features found in human TBI, with subdural hematomas and cerebral edema. We characterized fish exposed to three categorical severities of TBI using the Shuttle Box assay to quantify the extent of learning and memory. Undamaged fish master the behavioral assay significantly faster than their TBI siblings at 24, 48, and 72 hours post injury (hpi) at all severity levels (n=9). However, four days following the mild and moderate trauma, injured fish were capable of learning the task as quickly as undamaged controls, suggesting that their learning capacity was restored (p=0.41, p=0.69). In contrast, fish exposed to severe trauma required several additional days post injury to learn the shuttle box assay (severe 7 dpi p=0.56, n=9). Memory impairment was also examined across the three severities resulting in consistent short-term memory loss and retention of long-term memory (n=12-21). Cerebellar cell death was examined through a TUNEL assay, where there were significantly more TUNEL positive cells with increasing severity, which were primarily restricted to the ventral lining of the rhombencephalic ventricle in moderate and severely damaged fish ($p<0.001$, <0.0001, n=10). To examine the extent of cell death, the TUNEL assay was paired with HuC/D and GFAP immunostaining to label neuronal and glial cells, respectively. We found significantly more neuronal HuC/D positive cells were TUNEL positive ($p<0.0001$, n=9) than glial GFAP positive cells (n.s., n=9). In response to injury, there was a significant decrease in HuC/D labeling 18 and 72 hpi (p=0.02, =0.0013), followed by a return to control levels 6 months post injury (p=0.27 n=4). Thus, we developed a TBI model that reproducibly mimics the learning and memory deficits observed in humans and results in cerebellar neuronal cell death. We will continue to examine the regenerative capacity of zebrafish to respond to blunt force trauma by examining the source of the proliferating cells, their migration, and differentiation of neuronal progenitors following TBI.

Disclosures: J. Hentig: None. **Y. Jung:** None. **D.R. Hyde:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.24/R11

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant EY02686

Title: Injury-induced plasticity in parietal-frontal motor networks of non-human primates

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Abstract: The mechanisms of long-term recovery after brain injury are not fully understood. Most previous studies investigated the plasticity within sensorimotor networks in primates after extensive motor cortex (M1) injuries, but little is known about the response to focal injuries to functional domains defined by 500ms long trains of intracortical microstimulation (ICMS). Two squirrel monkeys (*Saimiri sciureus*) were trained to perform reach-to-grasp task. In an aseptic procedure and under anesthesia, grasp, reach and other movement domains were identified in contralateral to trained hand motor areas (M1; premotor, PMC; posterior parietal, PPC) by ICMS. Then, the grasp domain in M1 (1st case) or in M1 and PMC (2nd case) was removed by aspiration. For next few months, lesioned monkeys were tested on reach-to-grasp task to evaluate the behavioral effects of cortical damage. In both monkeys, we observed deficits in grasping (increase in total number of digit flexes, speed and total movement duration). Two to three months later, when grasping behavior recovered, neuroanatomical tracers were injected in the cortex adjacent to the lesion, and in other movement domains to examine changes in connectivity, defined by comparison with intact brain connections. Changes in ICMS maps immediately after the lesion and after behavioral recovery were also evaluated. Lesions in grasp domain(s) instantly suppressed the movements evoked by ICMS from matching grasp domains, but not mismatched domains (e.g. reach or hand-to-mouth) in PMC and PPC. After grasping behavior recovered, in the monkey with M1 lesion some grasp movements in response to ICMS re-appeared in peri-lesion cortex. In monkey with M1 and PMC lesions, grasp movements never returned to M1 peri-lesion cortex, but this cortex was invaded by hand-to-mouth movements, normally represented in adjacent to grasp domain. Interestingly, grasp movements reestablished in PMC peri-lesion cortex. Stimulation of PPC after recovery evoked grasping behavior in both monkeys. These results suggest that functional recovery occurs after focal cortical lesions, and that greater capacity for reorganization after such lesions is expected in representations higher in the cortical hierarchy. Tracer injections revealed strong connections of both, M1 and PMC peri-lesion regions with the ipsilateral PPC grasp domain. M1 peri-lesion cortex was also very strongly connected with the contralateral M1 grasp domain. These results suggest that recoveries from focal motor lesions may be mediated by the reorganization of cortex around the lesion, and remote areas (even contralateral) may contribute to compensatory recovery of the affected forelimb.

Disclosures: I. Stepniewska: None. **H. Qi:** None. **A.F. Manabat:** None. **J.H. Kaas:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.25/R12

Topic: C.10. Brain Injury and Trauma

Support: HD069620, HD069620-S1, NS060005, NS084967

Title: Amantadine plus environmental enrichment after experimental traumatic brain injury confers an additive effect on motor and cognitive improvement

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Abstract: Traumatic brain injury (TBI) is a significant health care issue with limited treatment options. Amantadine (AMT) is a pharmacotherapy with dopamine receptor agonist activity that has been shown to improve cognition after experimental TBI. Another therapeutic strategy that has consistently been shown to confer cognitive and motor recovery after TBI is environmental enrichment (EE), which consists of a complex living space, novel stimuli, and increased social interaction that is vastly different from standard (STD) housing, and is considered a preclinical model of neurorehabilitation. *Hence, the goal of this study was to test the hypothesis that combining AMT and EE would lead to greater motor and cognitive performance after TBI than AMT alone.* Anesthetized adult male rats received a controlled cortical impact of moderate severity (2.8 mm tissue deformation at 4 m/s) or sham injury and then were randomly assigned to enriched or STD housing where AMT (20 mg/kg) or vehicle (VEH; 1.0 mL/kg) was administered intraperitoneally 15 min before testing every day for 19 days. Motor function (beam-balance/beam-walk) and spatial learning/memory (Morris water maze; MWM) were assessed on post-operative days 1-5 and 14-19, respectively. Both AMT alone and AMT plus EE performed significantly better than the non-treated STD-housed group on motor and cognition ($p < 0.05$). Moreover, the AMT plus EE group performed better than the AMT alone group ($p < 0.05$), which indicates an additive effect and confirms the hypothesis. The findings provide support for combinational therapies after TBI to optimize outcome.

Disclosures: I.H. Bleimeister: None. **J.L. Wellcome:** None. **G.C. Bao:** None. **M.S. Helkowski:** None. **T.R. Lam:** None. **M. Wolff:** None. **C.O. Bondi:** None. **A.E. Kline:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.26/R13

Topic: C.10. Brain Injury and Trauma

Title: Trauma-induced mitochondrial hyper-proliferation, FGF-21 depletion, and thymic involution in mice susceptible to post traumatic stress disorder (PTSD)

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Abstract: Mitochondrial dysfunction has been increasingly implicated in several psychopathologies. Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder induced by exposure to a traumatic event. We recently showed that mitochondrial function was significantly reduced in the brains of mice affected by PTSD-like symptomatology. Here we investigate additional multi-system effects of trauma exposure and PTSD-susceptibility associated with mitochondrial function and stress response in these animals. We previously induced PTSD-like symptomatology in a cohort of 48 WT FVB mice, identifying 7 PTSD-vulnerable animals and 16 PTSD-resilient animals. PTSD-susceptible animals were found to have significantly reduced brain mitochondrial electron transport chain (ETC) capacity compared to PTSD-resilient animals. We subsequently isolated genomic DNA from the brains of the animals and performed qPCR for mtDNA copy number. We also collected blood plasma from these animals and performed ELISA for the metabolic stress hormone FGF-21. Thymi from these animals were fixed, sectioned, and stained for gross histology. For all tests, we compared the 7 PTSD-vulnerable and 16 PTSD-resilient animals to 12 naïve animals not exposed to trauma. Trauma-exposed animals and PTSD-vulnerable animals showed an increase in brain mtDNA copy number, a decrease in plasma FGF-21 concentration, and a decreased thymic medullar/cortical ratio, compared to naïve animals. Brain mtDNA copy number, plasma FGF-21 concentration, and thymic medullar/cortical ratio varied significantly between PTSD-vulnerable, PTSD-resilient, and naïve animals. These data indicate that trauma exposure may induce PTSD-vulnerability-associated mitochondrial dysfunction and a subsequent compensatory mitochondrial hyperproliferation. The metabolic stress hormone FGF-21 is induced by transcription factors that also promote mitochondrial metabolism and biosynthesis. Circulating FGF-21 produced in the liver works in an endocrine fashion and protects mitochondria from oxidative damage. Trauma-induced FGF-21 depletion may contribute to mitochondrial dysfunction in the brains of PTSD-vulnerable animals. Reduced thymic cortical/medullar ratio is indicative of thymic involution which has been associated with chronic stress and can have long-term effects on immune health. Overall, our results indicate that trauma exposure and PTSD-vulnerability can have multi-system effects that may impact PTSD diagnosis, prevention, and treatment, though further investigation will be required to elucidate how these systems interact and contribute to the complex etiology of PTSD in humans.

Disclosures: G. Preston: None. **T.L. Emmerzaal:** None. **F.J. Kirdar:** None. **E. Morava:** None. **T.L. Kozicz:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.27/R14

Topic: C.10. Brain Injury and Trauma

Support: MH086530
MH093459

Title: Lasting cholinergic-attentional impairments and brain cytokine expression following mild repeated concussion in mice with a vulnerable cholinergic system

Authors: *M. SARTER[1], A. KOSHY CHERIAN[1], N. C. TRONSON[1], V. V. PARIKH[2], R. D. BLAKELY[3]
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Abstract: Concussion is a subtype of traumatic brain injury characterized by functional alterations of the brain with little or no macroanatomical damage. Repetitive mild concussion (rmCc), as sustained by contact sports players and military personnel, is one of the most common types of brain injury, resulting in persistent cognitive, particularly attentional, impairments. Based on our previous finding that choline transporter (CHT) heterozygosity limits the capacity of cholinergic neurons to sustain elevated levels of cholinergic activity, here we asked whether rmCc bestows relatively more severe attentional-cholinergic impairments in CHT heterozygous ($CHT^{+/-}$) mice. Wildtype (WT) and $CHT^{+/-}$ mice were trained to performance criterion in the Sustained Attention Task (SAT), and subjected to sham (SH) or rmCc, using a modification of the impact method described by Kane et al. (2012). Mice practiced the SAT 5-6 days a week and received five Cc events, each separated from the next by 7 days. rmCc robustly and permanently decreased hit rates in $CHT^{+/-}$ but not WT mice. Brains from subsets of mice were harvested immediately following the final SAT session after the 5th rmCc. As expected, CHT-mediated choline transport in frontal cortical synaptosomes was significantly lower in $CHT^{+/-}$ when compared with WT mice. rmCc lowered choline transport in both genotypes, therefore nearly completely abolishing uptake in $CHT^{+/-}$ mice. However, rmCc did not reduce the density of cortical cholinergic terminals, suggesting a functional silencing of these terminals in rmCc-treated $CHT^{+/-}$ mice. Determination of brain cytokine levels indicated lasting rmCc-induced increases in the levels of 10 cytokines in $CHT^{+/-}$ mice, with CCL4 showing the greatest elevation. Additional histological analysis confirmed the presence of activated microglia in several brain regions of rmCc-treated mice of both genotypes, and in the basal forebrain of $CHT^{+/-}$ mice only. Taken together, these results suggest that lasting increases in brain cytokine levels may mediate the rmCc-induced near silencing of CHT function and the attentional impairments in $CHT^{+/-}$ mice. Humans expressing a CHT subcapacity variant may be relatively more vulnerable to the impact of brain injuries.

Disclosures: M. Sarter: None. **A. Koshy Cherian:** None. **N.C. Tronson:** None. **V.V. Parikh:** None. **R.D. Blakely:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.28/R15

Topic: C.10. Brain Injury and Trauma

Title: Developing a mouse model of hemorrhagic stroke using high-intensity focused ultrasound and microbubbles

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Abstract: Hemorrhagic stroke is a devastating neurological disease that often results in permanent disability or death. The incidence is not decreasing and, despite being the subject of active preclinical and clinical investigation, treatment options remain limited. Currently the most commonly used mouse model of hemorrhagic stroke involves autologous blood injection, in which blood is extracted from the tail artery of a mouse then injected into its brain. This model is useful to study the toxic effects of blood components on the brain but lacks vascular damage. The ability to effectively model disease in animals is a key factor in the translation of research to clinically relevant interventions. Here we have developed a mouse model of hemorrhagic stroke utilizing high-intensity focused ultrasound and microbubbles. Focused ultrasound has been heavily studied for various therapeutic applications including blood-brain-barrier opening to facilitate drug delivery. When applied using high pressures and intensities this technique is noted to cause vessel rupture, micro-hemorrhage, and histological damage. By adjusting the parameters of the focused ultrasound we have created reproducible intracerebral hemorrhage with cellular and molecular changes classically seen in hemorrhagic stroke. This model, by more closely approximating the pathophysiology of hemorrhagic stroke, has the potential to improve the translation of preclinical research to therapy.

Disclosures: C.M. Collier: None. **H. Zhang:** None. **E. Konofagou:** None. **C. Troy:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.29/R16

Topic: C.10. Brain Injury and Trauma

Support: NIH/NIGMS P20GM0103423

Title: Free Fallin': Investigation of the force of acceleration on rats using a new method for inducing mTBI

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Abstract: Mild traumatic brain injuries (mTBI), including concussions, have significantly increased in the last decade and evidence is mounting of their adverse, and potentially long-lasting, cognitive and emotional effects. These effects and the underlying pathological changes to neural function are not precisely understood and depend significantly on animal models. Accordingly, a wide array of injury models exist; many entail dropping weight onto an animal's head or making more precise injuries through closed cortical impacts or fluid percussion. Overall, though, they aim to produce aspects of a human head injury, including biomechanical responses and neurological sequelae, and yet each have limits to how accurately they may produce acceleration and rotational impacts in ways comparable to how the injuries occurs in humans, particularly sports-related injuries or falls. Recently we sought to better represent the mechanism of injury as it frequently occurs in humans by developing a new model of mTBI for use with rodents. This model is unique in that the rodent is secured to a rotating platform arm with the head positioned off the edge. The platform arm is raised and released, propelling the head toward a stationary impact zone. The purpose of the present experiment was to quantify the acceleration forces that rats sustain using this method and to document that those forces are comparable to human mTBI. To do this, 16 male (85-180 g) and 16 female (76-140 g) Sprague Dawley rats underwent the mTBI procedures. Digital video footage was collected for each injury and frame-by-frame analysis was used to calculate acceleration upon impact. This was done by recording the distance traveled across a fixed-width grid pattern in consecutive frames and applying the following formula: $a = (v_1 - v_0) / \Delta t$. Based on these calculations, we estimated that rats experienced a force of 6.8 +/- 1.9 g prior to impact. For comparison, acceleration forces of 98 +/- 28 g have been reported in humans. Accounting for overall mass, brain weights, and other factors that distinguish rats and humans, we estimate that these values align well though they may indicate greater forces acting on the rats during injury. Also under investigation are data from a force plate sensor located in the impact zone and findings, so far, point to a significant correlation between rats' body weight and force plate output values and revealed a second impact after the first that was also examined. Taken together, the results of the present study confirm that our newly developed procedures produce forces in rats that accurately model those recorded in humans and offer an innovative alternative for mTBI and concussion research.

Disclosures: M.P. Richard: None. **A. Rudinski:** None. **P. Wirth:** None. **P.D. Berkner:** None. **M.J. Glenn:** None.

Poster

211. Brain Injury and Trauma: Animal Models of Brain Injury

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 211.30/R17

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant 1S10OD021598

Title: Chorioamnionitis results in cerebellar microstructure abnormalities: A preclinical investigation

Authors: *J. E. CAMACHO[1], T. R. YELLOWHAIR[1], J. C. NEWVILLE[1,2], S. ROBINSON[3], J. R. MAXWELL[1], L. L. JANTZIE[1,2]
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Abstract: Preterm infants are at risk for neurodevelopmental deficits including cerebral palsy, attention deficits, and cognitive delay. The cerebellum, a region vital for normal motor control, motor learning, language, and cognitive processing, is vulnerable to injury in the third trimester. The superior and inferior cerebellar peduncles provide connections between multiple brain regions, including the motor cortex, vestibular system, and spinal cord, and are integral to cognitive and motor skills. Injury to these neural networks beginning *in utero* in the setting of chorioamnionitis and preterm birth could profoundly impact neurodevelopment. Using our established rat model of chorioamnionitis (CHORIO), we hypothesized prenatal injury would cause diffusion tensor imaging (DTI) abnormalities and microstructural changes to the cerebellar peduncles. On embryonic day 18 (E18), a laparotomy was performed on pregnant Sprague-Dawley dams to induce CHORIO with transient uterine artery occlusion and intra-amniotic injection of lipopolysaccharide (LPS, 4µg/sac). The laparotomy was then closed and dams recovered. Shams had a laparotomy for 60 min with no other intervention. Rat pups matured with their dams. On postnatal days 15 (P15) and 35 (P35), brains were perfused for *ex vivo* DTI on a 4.7T scanner (n=3-8/group). T-tests were performed with statistical significance defined as $p<0.05$. Fractional anisotropy (FA) was significantly increased in the superior and inferior cerebellar peduncles in P35 shams compared to P15 shams, consistent with advanced myelination with increasing age ($p <0.05$). Following CHORIO, FA at P35 was reduced 26% in the inferior cerebellar peduncles in the CHORIO animals compared to shams (0.428 ± 0.02 vs. 0.318 ± 0.02, $p<0.01$). Analyses of directional diffusion in the inferior cerebellar peduncles revealed a 35% increase in radial diffusion in CHORIO rats compared to shams (3.3 ± 0.1 vs. 4.5 ± 0.2 $x10^{-4}$, $p<0.001$), concomitant with a 14% increase in axial diffusion (6.1 ± 0.2 vs. 6.9 ± 0.2 $x10^{-4}$, $p<0.05$). Similarly, axial diffusion was increased by 25% (5.3 ± 0.3 vs. 6.6 ± 0.3, $p<0.05$) in the superior cerebellar peduncle in CHORIO rats compared to shams. Taken together, these data

indicate cerebellar white matter microstructural abnormalities and decreased structural coherence in CHORIO rats, which may be indicative of impaired anatomical connectivity, specifically within the preterm infants who later develop learning and coordination deficits. Sophisticated imaging may delineate radiologic biomarkers of cerebellar injury secondary to consequences of preterm birth and assist in the development of future therapies.

Disclosures: J.E. Camacho: None. **T.R. Yellowhair:** None. **J.C. Newville:** None. **S. Robinson:** None. **J.R. Maxwell:** None. **L.L. Jantzie:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.01/R18

Topic: C.10. Brain Injury and Trauma

Support: Center for Neuro regenerative Medicine Intramural Grant

Title: Changes in cerebellar connectivity following cognitive rehabilitation in traumatic brain injury

Authors: *E. CORDERO[1,2,3], S. I. GIMBEL[1,3,4], M. L. ETTENHOFER[2,4,3]
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Abstract: Abnormalities in the coordinated activation of brain regions are common in individuals who have experienced a traumatic brain injury (TBI). These abnormalities can cause cognitive impairments as well as post-concussive symptoms. Previous studies in TBI have demonstrated abnormalities in the functionality and connectivity of cortical brain regions often involved in executive functioning and memory tasks. In healthy individuals, activity in these same regions is correlated with activity in Crus I and Crus II of the cerebellum. The literature indicates that Crus I and Crus II take part in the refinement of processes in their associated cortical structures by way of discrete, closed looped circuits. Injury to the connectivity of these cortico-cerebellar networks may lead to additional cognitive impairments within the TBI population. In the current study, we assessed the effect of a cognitive rehabilitative intervention on executive-functioning-specific, cortico-cerebellar networks before and after cognitive rehabilitation for TBI. Seven volunteers with a history or traumatic brain injury participated in an interventional study that included a pre-intervention MRI resting-state scan, six-weeks of cognitive driving rehabilitation conducted in a virtual environment, and a post-intervention MRI resting-state scan. Based on previous findings in healthy controls, we expected correlated activation between Crus I/Crus II and cortical structures including the thalamus, precuneus,

posterior cingulate, anterior cingulate, medial frontal gyrus, and caudate. In our sample of participants with TBI, there was no correlation between Crus I/II and these cortical regions during the pre-intervention scan. After the intervention, however, these individuals showed increased correlated activity between Crus I/II and subregions of all six structures in comparison to the pre-treatment visit. This analysis illustrates potential abnormalities in functional connectivity between the cortex and the cerebellum associated with TBI. In addition, the current findings suggest that neurorehabilitative interventions may result in coordinated reactivation of Crus I/II and their associated cortical areas after TBI.

Disclosures: E. Cordero: None. **S.I. Gimbel:** None. **M.L. Ettenhofer:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.02/S1

Topic: C.10. Brain Injury and Trauma

Support: U.S. Army Medical Research and Materiel Command Award #W81XWH-13-1-0095

Title: Brain bases of cognitive recovery following rehabilitation for traumatic brain injury

Authors: *S. I. GIMBEL[1,2,3], M. L. ETTENHOFER[2,4,3,1,5], E. CORDERO[2,4,1], A. SAFFORD[2,4], B. BRANDLER[2,4,6], B. GUISE[4], M. ROY[4,5], L. CHAN[5,7]
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Abstract: Many patients with traumatic brain injury (TBI) have persistent cognitive deficits, including decreased attention and working memory. This study is part of a clinical trial examining the brain bases of cognitive deficits related to TBI and subsequent functional recovery. Initial behavioral findings showed improvements in working memory and processing speed among those who received intervention, and fMRI analyses were performed to evaluate the brain bases of these effects. Twenty-four patients who had sustained a TBI (14 mild, 10 moderate/severe) completed a comprehensive neuropsychological and MRI exam. Of these, 11 went through 6 weeks of virtual reality driving intervention and completed a second neuropsychological and MRI exam (7 immediate treatment, 4 waitlist control). During the fMRI, patients performed a 0-back task where they indicated via an MRI-safe button box whether a number appearing on the screen was a 6 or a 9. They then performed a 1-back task, where they kept the item (6 or 9) in mind, then indicated whether the next item was the same or different as the previous item. Examining activation in visit 1 specific to working memory (1-back minus 0-

back) showed increased activity in bilateral DLPFC and prefrontal cortex, anterior insula, medial superior frontal gyrus, left thalamus, bilateral supramarginal / angular gyrus, precuneus, and left posterior middle temporal gyrus. Following intervention, patients showed less global activation, with regions of activity only in the bilateral middle frontal cortex, posterior middle frontal gyrus, and supramarginal gyrus; there was reduced activity related to working memory load for the group that went through the intervention compared to the control group. Examining brain activity related to TBI severity, those with moderate/severe TBI showed reduced activation in the working memory network compared to the mild TBI group. While preliminary, these results suggest that successful cognitive rehabilitation of working memory in TBI may be associated with increased efficiency of brain networks, evidenced by normalization of brain activity during cognitive processing (i.e., reduced activation). Considering the mixed/negative results of many clinical trials for cognitive rehabilitation of TBI, these results highlight the importance of examining brain activity related to cognitive rehabilitation of attention and working memory.

Disclosures: S.I. Gimbel: None. **M.L. Ettenhofer:** None. **E. Cordero:** None. **A. Safford:** None. **B. Brandler:** None. **B. Guise:** None. **M. Roy:** None. **L. Chan:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.03/S2

Topic: C.10. Brain Injury and Trauma

Title: Neuropsychological assessment outcomes following cognitive rehabilitation training for children and adults with traumatic brain injury

Authors: *A. L. MOORE[1], C. LEDBETTER[2]
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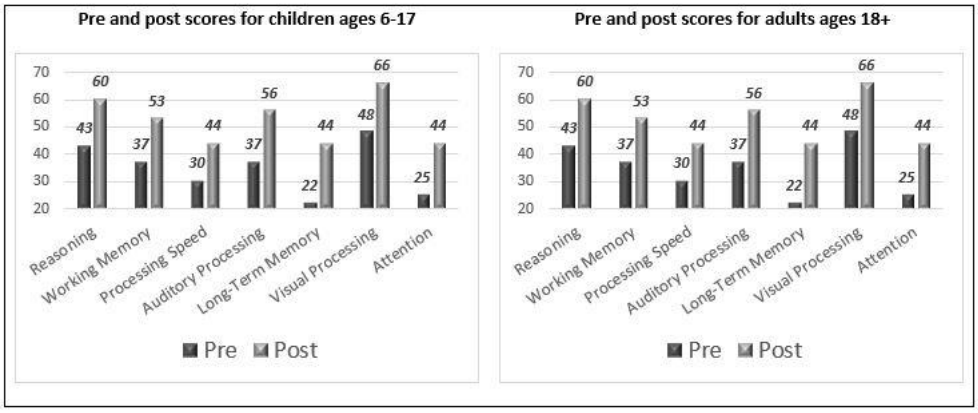
Abstract: BACKGROUND: Clinician-delivered cognitive rehabilitation training shows promise for remediating functional and cognitive deficits associated with traumatic brain injury. **OBJECTIVE**: The current study examined the neuropsychological outcomes and real-life changes for *n* = 329 cases of traumatic brain injury following an average of 95 hours of intensive, metronome-based cognitive rehabilitation training with ThinkRx, a clinician-delivered brain training program. **METHODS**: We collected baseline and outcome scores on standardized neuropsychological tests and a qualitative exit survey from *n* = 329 individuals with traumatic brain injury of various severity ranging in age from 6 to 87. Each participant attended an average of 95 hours of training. The training procedures were delivered one-on-one by a clinician and targeted multiple cognitive skills including working memory, long-term memory, processing speed, visual processing, auditory processing, logic and reasoning, and attention. **RESULTS:**

Training effects included statistically significant and clinically-significant gains on neuropsychological outcome measures as well as self-reported behavioral changes. Gains in cognitive skills were similar for children and adults. **CONCLUSION**: The improvements across outcome measures following ThinkRx cognitive rehabilitation training suggest that an intensive, metronome-based cognitive training intervention delivered by a clinician may be a viable option for remediating the cognitive deficits associated with traumatic brain injury for children and adults.



Disclosures: A.L. Moore: A. Employment/Salary (full or part-time):; LearningRx. **C. Ledbetter:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.04/S3

Topic: C.10. Brain Injury and Trauma

Title: Cognitive rehabilitation for brain injury: Insight from diffusion tensor mr imaging

Authors: *C. LEDBETTER[1], D. M. CARPENTER, III[2], T. MILLER, 80919[3], A. L. MOORE[3]
[1]LSU Hlth. Sci. Ctr. - Shreveport, Shreveport, LA; [2]Univ. of Colorado, Colorado Springs, CO; [3]Gibson Inst. of Cognitive Res., Colorado Springs, CO

Abstract: Background: ThinkRx, an intensive, 60+ hour, clinician delivered, one-on-one, multi-construct cognitive rehabilitation training program, has been shown to remediate cognitive skill deficits resulting from acquired and traumatic brain injury. In previous work with this population we have reported normalization of the default mode network as measured by resting state functional MRI following cognitive training. However, the underlying structural changes

associated with training related gains in a brain injury population have yet to be investigated. **Objective:** The purpose of this work was to assess changes in white matter structure and connectivity using Magnetic Resonance Diffusion Tensor Imaging (DTI). **Methods:** Using a multiple case study design that included eight subjects with varying origins, degrees and durations of brain injury the effects of the ThinkRx cognitive rehabilitation program were evaluated. Baseline and outcome measures were collected using the Woodcock Johnson IV - Tests of Cognitive Abilities, Conners Continuous Performance Test III, the Patient Competency TBI rating scale, and MR imaging. MRI scans were acquired on a Siemen's 3T scanner and the the study protocol included acquisition of a T1-weighted high resolution anatomical image, a T2-weighted FLAIR image, diffusion weighted images, and a 12-minute resting state EPI BOLD functional scan. White matter analysis was performed using FreeSurfer, TRACULA and BrainSuite.
Results: All subjects showed cognitive skill gain in working memory, long-term memory, processing speed, visual and auditory processing, fluid reasoning, attention, and a significant increase in IQ score (>20 IQ score points).
First and second level analysis of white matter fiber tracts and regions of interest (ROI) diffusion metrics including fractional anisotropy (FA) and mean diffusivity (MD) were measured. Overall, FA inversely correlated with injury severity and MD was positively correlated with injury severity. In multiple white matter tracts including the cingulate, FA was decreased post training.
Conclusions: Changes in white matter density noted in the current work support the hypothesis and previous functional analysis findings that training induced change occurs and is robust enough to be measured using MRI.

Disclosures: C. Ledbetter: None. **D.M. Carpenter:** None. **T. Miller:** A. Employment/Salary (full or part-time):; LearningRx part-time employment. **A.L. Moore:** A. Employment/Salary (full or part-time):; LearningRx.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.05/S4

Topic: C.10. Brain Injury and Trauma

Title: Morning bright light therapy improves sleep quality and pain interference in veterans with TBI

Authors: *A. A. MCBRIDE[1], J. E. ELLIOTT[1,2], N. M. BALBA[3], R. OPEL[1], P. TEUTSCH[1], M. LIM[1,2,4,3]
[1]VA Portland Hlth. Care Syst., Portland, OR; [2]Neurol., [3]Behavioral Neurosci., [4]Med., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Sleep-wake disturbances (SWD), including excessive daytime sleepiness, insomnia, hypersomnia, and circadian rhythm sleep disorders, are common after traumatic brain injury (TBI). In addition to SWD, chronic pain is also a common and debilitating symptom associated with consequences of TBI. In fact, ~50-70% of individuals with TBI experience SWDs and suffer from chronic pain. The relationship between SWD and chronic pain is bidirectional, such that impaired sleep exacerbates pain, while pain contributes to impaired sleep. Thus, improving sleep quality has the potential to ameliorate pain following TBI. Accordingly, the purpose of this study was to target an improvement in sleep quality through the use of morning bright light therapy, and thereby achieve an improvement in pain in Veterans with TBI. Veterans with (n=8, average age 47.1±21.3 years) and without (n=10, average age 62.5±17.1 years) TBI were consented and enrolled from the VA Portland Health Care System Sleep Disorders Clinic. Subjects were instructed to use a lightbox for at least 30 minutes upon awakening daily for 4 weeks. Participants wore an actiwatch (Philips Respironics Actiwatch-2) throughout the study to record rest-activity patterns and light exposure, including for 7 days before initiating light therapy to establish baseline metrics. Self-report measures were collected before and after lightbox use, including the Insomnia Severity Index (ISI), Patient Health Questionnaire (PHQ-9), Neurobehavioral Sleep Inventory (NSI), and, and NIH PROMIS Pain Intensity, and Pain Interference scales. Following 4 weeks of light therapy, age-controlled ISI scores decreased in Veterans with TBI (p= 0.035), which coincided with a reduction in pain interference (p=0.032), despite no change in pain intensity (p=0.266). Interestingly, 4 weeks of light therapy in Veterans without TBI did not result in improvements in ISI and pain scores. These data suggest that light therapy has a positive effect on sleep and pain management in Veterans with TBI. Further investigation is needed to elucidate how other comorbidities of TBI such as PTSD and depression affect these measures.

Disclosures: A.A. McBride: None. **J.E. Elliott:** None. **N.M. Balba:** None. **R. Opel:** None. **P. Teutsch:** None. **M. Lim:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.06/S5

Topic: C.10. Brain Injury and Trauma

Support: Norwegian Research Council through Medical Imaging Laboratory (MI-LAB) at NTNU

Title: The clinical and functional significance of global and local resting-state fMRI connectivity in chronic moderate to severe traumatic brain injury

Authors: *V. CONDE[1], E. L. DENNIS[4], J. N. EK[1], K. I. EVENSEN[2], T. FINNANGER[6], P. M. THOMPSON[5], A. VIK[3], T. SKANDSEN[3], A. K. HABERG[3], A. OLSEN[1]
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Abstract: Contradictory findings regarding whole-brain connectivity after traumatic brain injury (TBI) include reports of both hypo- and hyper-connectivity patterns when compared to healthy participants. Altered connectivity patterns seem to depend on injury severity, with more severe injuries leading to more pronounced alterations in long-range connectivity and poorer functional outcomes. However, it is unclear to what degree these alterations represent compensatory mechanisms and/or maladaptive changes, partly due to a lack of studies linking connectivity to specific clinical and cognitive indices in this patient population. Because the current evidence in relation to connectivity alterations is contradictory, we lack an understanding of the role of whole-brain connectivity in outcome after TBI. Here we aimed to disentangle the pattern of whole-brain connectivity changes in a sample of patients with moderate to severe TBI in the chronic stage (>1 year after injury, n = 70, 18 females, age range 16-66) compared to 70 matched healthy controls. We hypothesized that hypo- and hyper-connectivity patterns may coexist within the same patients, manifesting differently in long-range (global) versus local connectivity due to the known higher structural impact of TBI on long-range axons. In contrast to prior studies focusing on specific connectivity indices alone, we evaluated both long-range and local connectivity indices. We derived these measures from resting state functional magnetic resonance imaging (rs-fMRI) via data-driven exploratory analyses based on graph theory (Brain Connectivity Toolbox) and a voxel-based method (Regional Homogeneity) using the LONI pipeline (http://pipeline.loni.usc.edu/) and the C-PAC pipeline (https://fcp-indi.github.io/). The clinical significance of individual whole-brain connectivity patterns was evaluated by investigating associations with injury mechanism, injury severity, and global outcome (as measured with the Glasgow Outcome Scale Extended). Moreover, the link between connectivity measures and cognitive function was investigated, focusing on self-reported and performance-based cognitive control function which is strongly associated with everyday functioning after TBI. We present preliminary results comparing graph-based connectivity and regional homogeneity in patients with msTBI and healthy participants, and evaluate their clinical and functional significance.

Disclosures: V. Conde: None. **E.L. Dennis:** None. **J.N. Ek:** None. **K.I. Evensen:** None. **T. Finnanger:** None. **P.M. Thompson:** None. **A. Vik:** None. **T. Skandsen:** None. **A.K. Haberg:** None. **A. Olsen:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.07/S6

Topic: C.10. Brain Injury and Trauma

Support: NIH #UL1GM118964
NIH T32 AT002688
IK2 BX002712

Title: Trauma exposure potentiates the severity of chronic pain, sleep disturbances, and sensory sensitivity in individuals with TBI and PTSD

Authors: *N. M. BALBA[1], J. E. ELLIOTT[2], R. A. OPEL[5], K. B. WEYMANN[3], M. M. HEINRICHER[4], M. M. LIM[2]
[1]Behavioral Neurosci., [2]Neurol., [3]Sch. of Nursing, [4]Neurolog. Surgery, Oregon Hlth. & Sci. Univ., Portland, OR; [5]Veterans Affairs Portland Hlth. Care Syst., Portland, OR

Abstract: Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) share common sequelae, including sleep-wake disturbances (SWD) and chronic pain, each of which can exacerbate the other. Although each disorder is independently linked to this symptomology, it is unclear whether individuals with comorbid TBI and PTSD show greater impairment in sleep and pain than those with a single disorder. The purpose of this study was to examine differences in SWD and chronic pain in individuals with a history of TBI and/or PTSD. Veterans were recruited from the Portland VA Health Care System and completed a battery of self-report surveys related to SWD, PTSD, post-concussion symptoms, chronic pain, and sensory sensitivity. Participants were categorized into four groups based on their medical history: 1) "Neither", subjects with no TBI or PTSD (n=383); 2) "TBI", subjects with TBI, but no PTSD (n=67); 3) "PTSD", subjects with PTSD, but no TBI (n=126); and 4) "TBI+PTSD", subjects with both TBI and PTSD (n=63). Compared to subjects with TBI or neither condition, those in the PTSD and comorbid TBI+PTSD groups reported significantly worse insomnia scores (P <0.001) and increased daily impairment due to poor sleep (P <0.001). Additionally, subjects in the TBI+PTSD group displayed significantly worse pain complaints than the TBI or PTSD groups (P <0.001 and P <0.05, respectively), and had the highest rate of persistent headaches. They also showed significantly higher levels of photosensitivity (P<0.001) and phonosensitivity (P<0.001) than all other groups. We found a significant correlation between insomnia scores and self-reported pain scores in all subjects (R = 0.36), but this correlation was strongest in the TBI group (R = 0.37) and weakest in the Neither group (R = 0.29). Pain scores were also significantly correlated with PTSD and TBI severity scores (R = 0.30 and R = 0.42), as were insomnia scores (R = 0.53 and R =0.46).Taken together, these results suggest that individuals suffering from both

TBI and PTSD have a higher risk for SWD and chronic pain compared to individuals with either disorder alone. Understanding how TBI and PTSD interact to potentiate SWD and pain may help improve rehabilitation interventions in this population.

Disclosures: N.M. Balba: None. **J.E. Elliott:** None. **R.A. Opel:** None. **K.B. Weymann:** None. **M.M. Heinricher:** None. **M.M. Lim:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.08/S7

Topic: C.10. Brain Injury and Trauma

Title: The prevalence and stability of sleep-wake disturbances and fatigue following mild traumatic brain injury

Authors: *S. B. SAKSVIK[1], M. KARALIUTE[1], H. KALLESTAD[2], R. H. KARLSEN[2], T. FOLLESTAD[3], A. VIK[2,5], A. K. HABERG[2], R. F. ASARNOW[6], T. SKANDSEN[2,4], A. OLSEN[1,4]
[1]Dept. of Psychology, [2]Dept. of Neurosci. and Movement Sci., [3]Dept. of Publ. Hlth. and Nursing, [4]Dept. of Physical Med. and Rehabil., Norwegian Univ. of Sci. and Technol., Trondheim, Norway; [5]Dept. of Neurosurg., St. Olavs Hospital, Trondheim Univ. Hosp., Trondheim, Norway; [6]Psychiatry, UCLA Dept. of Psychiatry, Pacific Palisades, CA

Abstract: After mild traumatic brain injury (mTBI), individuals often report increased sleep need, poor sleep, daytime sleepiness and fatigue. These symptoms may be caused by brain injury specific mechanisms linked to dysfunctional sleep-wake networks in the brain, but also by general injury-related factors not related to the brain injury per se. Studies incorporating relevant control groups are therefore crucial for identifying etiological factors that can inform clinical practice and future studies aiming to determine relevant biomarkers. Here we present results from a longitudinal study of 379 mTBI patients and 82 matched trauma controls (TCs) with orthopedic injuries. Increased sleep need, poor sleep, fatigue and excessive daytime sleepiness was assessed premorbid (reported retrospectively), and at 2 weeks, 3 months and 12 months after injury. We identified patients as having clinical significant symptoms by applying conventional clinical cut-off values derived from the respective assessment tools. Mixed logistic regression models were used to evaluate group differences and the temporal development of problems was assessed with stability analyses. The point prevalence of increased sleep need was higher after mTBI as compared with TCs the first days after injury (63% vs. 39%), at 2 weeks after injury (45% vs 22%) and 3 months after injury (13% vs 1%). MTBI individuals reported more clinically significant symptoms than TCs with regard to poor sleep, fatigue and excessive daytime sleepiness at 2 weeks (17% vs 12%, 17% vs 3% and 19% vs 11%) and 3 months after

injury (16% vs 7%, 12% vs 3% and 13% vs 11%). The same was the case for poor sleep and fatigue at 12 months post-injury (15% vs 7% and 11% vs 3%), but the groups did not differ in levels of daytime sleepiness at this time point (11% vs 11%). Throughout the first year, mTBI patients had 3 times higher odds of having poor sleep and 8 times higher odds of having fatigue compared to TCs. The number of individuals with clinical significant symptoms in the acute phase was higher than before the injury in both groups, but these symptoms were more stable after mTBI than in TCs. Whereas the prevalence of sleep-wake disturbance and fatigue returned to premorbid levels 3 months after injury in the TC group, as many as 46% and 35% of the mTBI patients who reported problems at 3 months still reported such problems at 12 months. Our results show that brain injury specific mechanisms may be involved in the development and maintenance of sleep-wake disturbances and fatigue above and beyond those observed in TCs. Future work should focus on determining moderators and mediators that may further inform research and clinical practice.

Disclosures: S.B. Saksvik: None. **M. Karaliute:** None. **H. Kallestad:** None. **R.H. Karlsen:** None. **T. Follestad:** None. **A. Vik:** None. **A.K. Haberg:** None. **R.F. Asarnow:** None. **T. Skandsen:** None. **A. Olsen:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.09/S8

Topic: C.10. Brain Injury and Trauma

Support: HBP SGA1 7202070
NRC: 262950/F20
NRC_ 214079/F20

Title: Spontaneous EEG signal complexity as a continuous, graded index for state of consciousness in sleep and anesthesia

Authors: *A. S. NILSEN[1], B. E. JUEL[2], J. F. STORM[2]
[1]Brain signalling group, Univ. of Oslo, Oslo, Norway; [2]Brain signalling group, Inst. of Basic Med. Sciences, Univ. of Oslo, Oslo, Norway

Abstract: In recent years, several promising EEG based measures for assessing phenomenological consciousness (conscious vs. unconscious) have been developed and tested over a wide range of physiological/behavioral states. Some of these measures, calculated from spontaneous EEG, offer high temporal resolution, and the possibility of full automatization. Such measures are candidates for clinical applications such as classifying disorders of consciousness and depth of anaesthesia.Here we calculated signal complexity using Lempel Ziv (LZ)

compression (M. Schartner et al., 2015; M. Schartner et al., 2017) on spontaenous EEG from patients undergoing propofol anesthesia as well as during normal sleep. We report three main preliminary findings: (1) LZ complexity decreased abruptly at the onset of clinically observed loss of consciousness caused by propofol anesthesia, but a slow decrease at the onset of sleep; (2) only two randomly chosen EEG channels and minimal preprocessing was needed to accurately distinguish between conscious (awake, or REM sleep, assuming dreams) and unconscious states (propofol anesthesia, and assumed dreamless sleep in sleep stage N3-4); and, 3) LZ complexity was highly correlated with sleep stage (r=0.79).Based on our preliminary results, we suggest that: a) LZ complexity seems to be graded, possibly reflecting graded states of consciousness; b) LZ complexity is potentially useful as a clinical tool, being easy to use, with high temporal resolution, and potential for automatization; c) LZ complexity may be useful for developing a rapid and fully automated sleep stage classifier.

Disclosures: A.S. Nilsen: None. **B.E. Juel:** None. **J.F. Storm:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.10/S9

Topic: C.10. Brain Injury and Trauma

Support: Human Brain Project (HBP-SP3-SGA1 Conscious Brain 720270)
NRC (Neurophysiological assessment of consciousness 262950/F20)

Title: Changes in cortical complexity during anesthesia to one hemisphere (Wada test)

Authors: *S. HALDER[1], L. VENKAT RAGHAVAN[2], B. E. JUEL[1], A. S. NILSEN[1], J. F. STORM[1]
[1]Univ. of Oslo, Oslo, Norway; [2]Toronto Western Hosp., Toronto, ON, Canada

Abstract: Wada tests are performed prior to neurosurgery (epilepsy or tumour surgery) to determine which hemisphere is responsible for speech and memory. One hemisphere of the brain is anaesthetised at a time by injection of a short acting anesthetic agent (sodium amytal, etomidate, propofol) into the internal carotid artery via a catheter. This provides the unique opportunity to study a brain where one hemisphere is anaesthetized while the other is awake at the same time allowing for before-during-after comparisons that are not possible e.g. in split-brain patients.In previous work it has been shown that cortical complexity correlates strongly with consciousness level. We applied a measure of complexity measured by signal entropy of the spontaneous electroencephalogram (EEG), termed synchrony-coalition entropy (SCE), to 21-channel EEG recordings from three patients undergoing a Wada test using etomidate prior to epilepsy surgery. We found that low frequency oscillations dominated over both hemispheres

and restricted our further analysis to the high gamma band (70-120 Hz). We split the data into 1s epochs (256 samples) and two sets of 9 electrodes (one set over each hemisphere). SCE scores were smoothed with a 100 sample moving average.Of the three data sets, one was severely affected by artefacts and could not be reliably interpreted. The second recording showed lateralisation effects in SCE towards the last quarter of the recording (1h28 to 1h42), and the third showed similar effects in the middle (20m to 33m) and toward the end (50m to 58m) of the recording. Both data sets showed showed a reduction of complexity in the right hemisphere.In the two data sets which could be analysed, longer periods of SCE scores that were synchronous between hemispheres alternated with periods of divergence that were up to 14 minutes long. Further, analysis is being performed to validate if these time windows coincided with the clinically observed anaesthesia effects, along with additional steps to identify and minimise volume conduction effects.

Disclosures: S. Halder: None. **L. Venkat Raghavan:** None. **B.E. Juel:** None. **A.S. Nilsen:** None. **J.F. Storm:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.11/S10

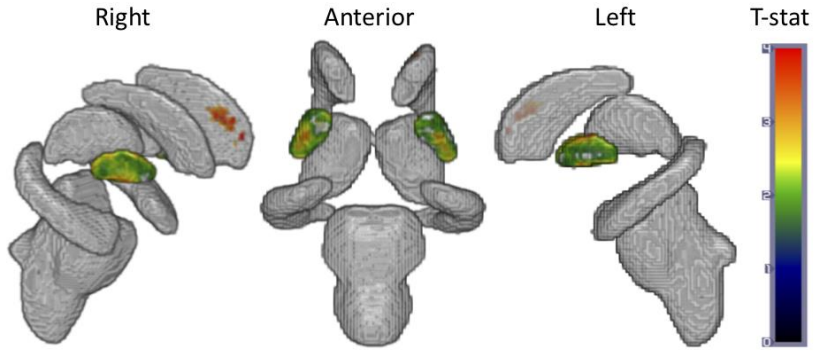
Topic: C.10. Brain Injury and Trauma

Title: Perturbational complexity index in severe brain injury

Authors: *E. S. LUTKENHOFF[1], S. CASAROTTO[2], M. MASSIMINI[2], M. M. MONTI[1]
[1]Psychology-Clinical, UCLA, Los Angeles, CA; [2]Dept. of Biomed. and Clin. Sci., Univ. of Milan, Milan, Italy

Abstract: The perturbational complexity index (PCI) provides an objective measure of consciousness independent of the patient's ability to interact with their environment and has been shown to reliably discriminate levels of consciousness in patients who had emerged from coma. PCI is calculated by measuring the spatiotemporal complexity of electrocortical responses after transcranial magnetic stimulation. In this study, we propose to calculate the association of subcortical pathologies in severe brain injury patients with PCI.
A convenience sample of 40 brain injury patients with moderate-to-severe anoxic and/or traumatic brain injury (29 male, 11 female; mean age = 51.2 years; age SD = 14.2 years) were enrolled in the study. Each patient underwent structural MRI scans and transcranial magnetic stimulation sessions to calculate PCI.
In this analysis, we modified FSL FIRST to allow for optiBET skull-stripping as well as the ability to remove pose and global scalings across different scanners. Eleven subcortical structures were segmented for each patient: R/L hippocampus, thalamus, caudate, globus

pallidus, putamen, and brainstem. This workflow creates a cohort average subcortex over all subjects, as well as, an image per subcortical region of interest that represents the localized shape for each subject's subcortex compared with the cohort. A general linear model along with non-parametric permutation tests were used to calculate vertex-wise statistics and standard FWE and TFCE corrections were applied.
Local shape change across the left pallidum, right pallidum, and left caudate are significantly associated with PCI (figure 1, right and left putamen removed for ease of display only). These results persist with or without the inclusion of age, post-injury duration, gender, and intracranial volume covariates. In conclusion, the pallidum is essential for the distributed interactions across the brain measured by the perturbational complexity index.



Disclosures: E.S. Lutkenhoff: None. **S. Casarotto:** None. **M. Massimini:** None. **M.M. Monti:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.12/S11

Topic: C.10. Brain Injury and Trauma

Support: Tiny Blue Dot Foundation

Title: Classifying disorders of consciousness across sites using diffusion tensor imaging and machine learning

Authors: *N. REGGENTE[1], Z. ZHENG[2], J. ANNEN[3], A. M. OWEN[4], S. LAUREYS[5], M. M. MONTI[2]
[1]Neurosci., Tiny Blue Dot Fndn., Santa Monica, CA; [2]UCLA, Los Angeles, CA; [3]Univ. of Liège, Liège, Belgium; [4]Western Univ., Brain and Mind Inst., London, ON, Canada; [5]Dept. of Neurol., Liège Univ. Hosp. ., Liège, Belgium

Abstract: Stratification of Disorders of Consciousness (DOC) typically includes the following states, listed in order of decreasing severity: vegetative state (VS, often referred to as unresponsive wakefulness syndrome [UWS]), minimally conscious state minus (MCS-, i.e., low-level behavior such as visual pursuit), and minimally conscious state plus (MCS+, i.e., high-level behavior such as language processing). Previous studies have suggested that the magnitude of disruption to thalamo-cortical circuitry could underlie the gradient of DOC severity. Indeed, thalamic projects to the cortex have proved informative enough for machine learning algorithms to reliably predict a DOC patient's state (Zheng et al., 2016). In an extension of this previous work, the current study employs a searchlight-mapping approach to identify cortical sites whose pattern of structural connectivity with the thalamus is self-similar enough within DOC groups to provide reliable information to a classifier as it is tasked with automatically labeling new patients. As such, we trained a support-vector-machine on a dataset of 24 patients and tested it on a separate dataset of 72 patients (and vice versa). Accuracy was determined by the percentage of times the classifier leveraged the data to make an assessment that matched the patient's clinician-determined diagnosis. Despite differences in scanning acquisition parameters across multiple sites, multiple brain regions contained projections from the thalamus that were reliable enough to make significant classifications in both testing scenarios. We present this work as a proof-of-concept for the automated labeling of DOC so as to bolster clinical confidence when defining a patient's state - a decision that often determines both the treatment routes afforded to those patients and their family's ethical deliberations.

Disclosures: N. Reggente: None. **Z. Zheng:** None. **J. Annen:** None. **A.M. Owen:** None. **S. Laureys:** None. **M.M. Monti:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.13/S12

Topic: C.10. Brain Injury and Trauma

Title: Characterization of direct pallidofugal connections with cortex and thalamus in humans

Authors: *Z. ZHENG[1], M. M. MONTI[2]
[1]UCLA, Santa Monica, CA; [2]UCLA, Los Angeles, CA

Abstract: Arousal and awareness are two defining dimensions of consciousness in clinical neuroscience. As arousal is thought to be primarily supported by brainstem nuclei, awareness may rely on the integrity of the cortex and its subcortical connections. While traditionally recognized as a system for motor control, the basal ganglia (BG) may also partake in a variety of cognitive and emotional processes as well as in the regulation of arousal and cortical activation. Through lesion studies in animals, the dorsal striatum and external globus pallidus (GPe) have

been identified to play important roles in promoting wakefulness and sleep, respectively. As the striatum as been studied extensively, little attention has been given to the study of GPe, which is the second largest component of the BG and contains the most expansive efferent connections, connecting with not only structures within but also outside of BG, including direct projections to frontal cortex and thalamus. These direct GPe connections have been previously identified in animals but not yet in humans. In this study, we aim to confirm and elucidate the pattern of "direct" GPe connectivity with the cortex and thalamus while employing the internal globus pallidus (GPi) as a control for comparison. High angular resolution diffusion imaging (HARDI) data from the Human Connectome Project (HCP) were used to carry out the connectivity analyses. We used probabilistic tractography with comprehensive a priori exclusion criteria to characterize the pattern of direct pallidal connectivity with the cortex and thalamus. Our results confirmed the existence of direct GPe connections with prefrontal cortex and thalamus in humans and uncovered different patterns of prefrontal and thalamic connectivity between GPe and GPi. Favoring connections with distributed prefrontal cortex and medial thalamus, GPe is situated in a position to influence key aspects of consciousness, including arousal and awareness. Conversely, GPi, preferring connections with more motor-related regions, remains a central player in the regulation of motor control. The current findings urge for an update to the mesocircuit model with the incorporation of GPe to shed light on the mechanisms underlying disorders of consciousness.

Disclosures: Z. Zheng: None. **M.M. Monti:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.14/S13

Topic: C.10. Brain Injury and Trauma

Support: Tiny Blue Dot

Title: Are changes in time-varying network dynamics truly the result of the level of consciousness or rather due to a general recovery of behavioral responsiveness? A systematic evaluation using fMRI

Authors: *J. S. CRONE, P. VESPA, M. M. MONTI
UCLA, Los Angeles, CA

Abstract: Properties of time-varying dynamics have been shown to reliably discriminate the level of consciousness in different experimental settings such as sleep, sedation, and disorders of consciousness. In these very settings, however, changes of the level of consciousness are also closely associated with changing levels of behavioral responsiveness. Thus, we pursued an

approach that allows us to address this conflation. We performed a longitudinal fMRI study during a 6 months recovery period of patients with disorders of consciousness. Patients were assessed within days after injury (acute session) and then again six months after injury (follow-up session). We divided the patients into two groups according to their level of consciousness. The first group recovered from unconsciousness during the 6 months period after injury (unconscious-conscious group), i.e., the patients revealed no signs of consciousness at the acute session while they demonstrated clear signs of consciousness at follow-up. The second group demonstrated signs of consciousness at both sessions (conscious-conscious group). Most importantly, even though recovery of consciousness was dissociated between groups, the *gain* in overall responsiveness between sessions (reflected by the total score of the behavioral assessment) was comparable across the two groups. With this dissociation, we can now test a specific pattern in the data (see Fig.1). Results indicate that consciousness is the driving factor (see Fig. 2).

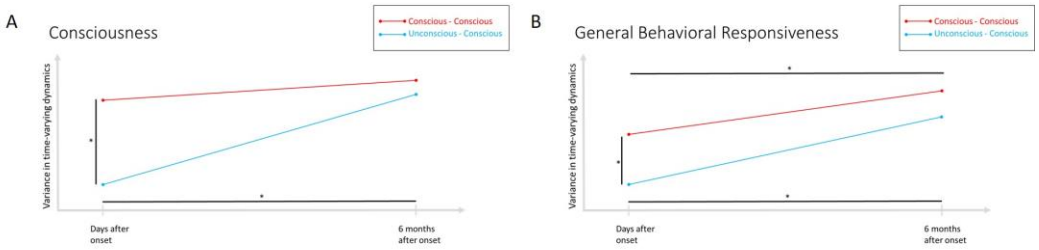


Figure 1. Schematic display of the expected patterns of variance of time-varying dynamics
If the level of consciousness is the driving factor for changes in time-varying dynamics, the variance in metrics across time should differ between the unconscious-conscious and the conscious-conscious group only at the acute session and between sessions only within the unconscious-conscious group (pattern A). If the differences across time do not exist for both groups, the general level of responsiveness can be ruled out as a driving factor. In contrast, if we find significant differences in time-varying dynamics between sessions also in the conscious-conscious group (pattern B) or between groups at follow-up, the level of consciousness can be ruled out as the driving factor.

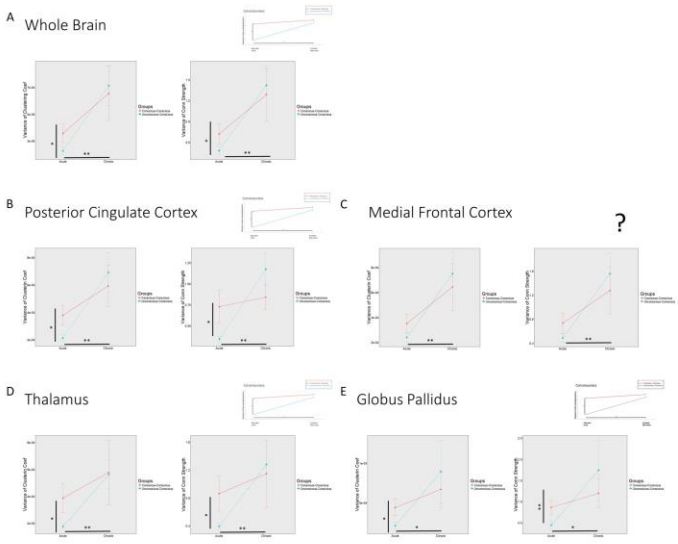


Figure 2. Differences in variance of time-varying dynamics for the whole brain (A) and each specific region of interest (B – E)
For each session, the time-varying dynamics of two of the most common topological brain metrics were calculated, i.e., clustering coefficient and connectivity strength. Variance in time-varying dynamics was assessed using a sliding-window approach. Results globally and in all regions of interest except in the medial frontal cortex confirm a pattern which suggests that the main driving source of change in dynamics is indeed the level of consciousness rather than the general level of responsiveness.

Disclosures: J.S. Crone: None. **P. Vespa:** None. **M.M. Monti:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.15/S14

Topic: C.10. Brain Injury and Trauma

Support: Tiny Blue Dot Foundation, Research Grant April 2016 - March 2019. Measuring consciousness: From theory to practice.

Title: A superior neuromodulating technique for the deep-brain? Non-invasive focused ultrasound pulsation modulates thalamic activity

Authors: *J. A. CAIN, R. BLADES, N. SPIVAK, M. M. MONTI
UCLA, Los Angeles, CA

Abstract: The deep nuclei of the brain, such as the thalamus, are known from clinical evidence and animal models to be crucial for maintaining cognitive function, consciousness, and arousal. However, because they fall outside the domain of existing non-invasive neuromodulatory techniques, their contribution to human cognition remains poorly characterized and our capacity to develop restorative interventions in cases where these regions are damaged remain limited.

Here, we have utilized the emerging technology of non-invasive low intensity focused ultrasound pulsation (LIFUP) to address this gap, directly and non-invasively modulating thalamic tissues in healthy individuals concurrent with functional magnetic resonance imaging (fMRI) in order to assess the influence of two modes of thalamic LIFUP on global brain activity. This work constitutes a first look at cortico-thalamic network dynamics through thalamic modulation in healthy subjects. Moreover, this work acts as a foundation for all future work utilizing LIFUP neuromodulation of the deep brain in research and in medicine. Namely, it is hoped that thalamic LIFUP stimulation may constitute an improved treatment for disorders of consciousness—a spectrum of neurological disorders including Coma, the Vegetative State, and the Minimally Conscious State; indeed, preliminary case studies utilizing this technique have demonstrated recovery. The medial and dorsal aspect of the thalamus was targeted, a region containing nuclei robustly implicated in cognitive functioning and arousal. In healthy volunteers (n=9), the thalamic target's structural and functional baseline connectivity were characterized in one session while, in two separate sessions, two distinct LIFUP modes were administered during the collection of blood oxygen level dependent data (BOLD). Additionally, a cerebral blood flow measurement was taken both before and after each LIFUP sonication. Pulsation was administered in 10-minute blocks alternating between 30s of LIFUP and 30s of no-LIFUP. The principle distinction between the two modes is a pulse repetition frequencies (PRF) of either 100 Hz or 10Hz; animal research demonstrates an excitatory and inhibitory effect on deep brain structures from these modes, respectively. A differential BOLD signal was found in the thalamus and in its principle cortical targets during baseline and during both modes of LIFUP sonication. These findings bolster previous characterizations of dorsal thalamic cortical connectivity and refine a theoretic framework from which to proceed in the use of LIFUP to both inhibit and excite deep-brain structures in a host of applications.

Disclosures: J.A. Cain: None. **R. Blades:** None. **N. Spivak:** None. **M.M. Monti:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.16/S15

Topic: C.10. Brain Injury and Trauma

Support: Alzheimer's Association Research Fellowship (AARF-17-529888)
Department of Veterans Affairs, Veterans Health Administration, Clinical Sciences Research and Development Merit Award (I01-CX001038)
Alzheimer's Association (NIRG-305779)
Veterans Affairs Biorepository (CSP 501)
National Institute of Aging (1RF1AG054156-01)

National Institute of Aging Boston University AD Center (P30AG13846; supplement 0572063345-5)
Department of Defense Peer Reviewed Alzheimer's Research Program (DoD-PRARP #13267017)

Title: TMEM106b risk variant is associated with pathological and clinical outcomes in CTE

Authors: *J. D. CHERRY[1,2,3], J. MEZ[4,5], Y. TRIPODIS[6], V. E. ALVAREZ[4,7], I. MAHAR[4,5], B. R. HUBER[13,5], M. L. ALOSCO[4,5], R. NICKS[14], B. ABDOLMOHAMMADI[4], P. T. KIERNAN[4], L. EVERS[4], S. SVIRSKY[4], H. M. GARDNER[15], G. MENG[15], C. J. NOWINSKI[16,5], B. M. MARTIN[6], N. W. KOWALL[15,5,4], R. C. CANTU[17,8,9], L. E. GOLDSTEIN[10,5], D. I. KATZ[4], R. A. STERN[11,5], L. A. FARRER[12], J. F. CRARY[18], A. C. MCKEE[4,5,15], T. D. STEIN[19,5,14]
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Abstract: Genetic risk in chronic traumatic encephalopathy (CTE) is poorly understood. A single nucleotide polymorphism (SNP) *rs1990622* in the *transmembrane protein 106b* (*TMEM106b*) gene locus has been identified as a genetic factor related to enhanced neuroinflammation during aging and is also associated with TDP-43 related neurodegenerative disease. Neuroinflammation and TDP-43 pathology are prominent features in CTE. Previous work has suggested that the SNP responsible for coding the TMEM106b protein, *rs3173615*, might have a relationship with CTE, however, the results were not significant. As *rs3173615* is in near perfect linkage disequilibrium with *rs1990622*, further investigation is warranted. The purpose of this study was to determine if *rs3173615* contribute towards increase risk for CTE, pathologic severity, or clinical features. 108 deceased athletes (85 with CTE; 23 controls) with a history of participation in American football were genotyped for *rs3173615*. The SNP was not significantly associated with CTE affection status or TDP-43 pathology. However, the SNP was associated with increased AT8 tau pathology and a non-significant trend towards increased neuroinflammation (CD68 density) in the dorsolateral frontal cortex (DLFC), the brain region where CTE pathology initially begins. Changes were most pronounced in early stages of CTE. Synaptic changes were measured via a PSD-95 ELISA from the DLFC. Similarly, among CTE cases, *rs3173615* was significantly associated with decreased PSD-95 protein level, adjusted for age at death, suggesting a relationship with decreased synaptic density. Finally, logistic regression demonstrated the presence of the major “risk allele” significantly increased the risk of an ante-mortem diagnosis of dementia by 2.49-fold per each allele present. Taken together, *TMEM106b* genotype may be risk factor for CTE pathological and clinical severity.

Disclosures: J.D. Cherry: None. **J. Mez:** None. **Y. Tripodis:** None. **V.E. Alvarez:** None. **I. Mahar:** None. **B.R. Huber:** None. **M.L. Alosco:** None. **R. Nicks:** None. **B. Abdolmohammadi:** None. **P.T. Kiernan:** None. **L. Evers:** None. **S. Svirsky:** None. **H.M. Gardner:** None. **G. Meng:** None. **C.J. Nowinski:** F. Consulting Fees (e.g., advisory boards); receives travel reimbursements for various unpaid advisory roles from the NFL Players' Association, Major League Lacrosse,WorldWrestling Entertainment (WWE), National Collegiate Athletic Association (. **B.M. Martin:** None. **N.W. Kowall:** None. **R.C. Cantu:** F. Consulting Fees (e.g., advisory boards); receives compensation from the NFL as senior advisor to its Head, Neck and Spine Committee, from the National Operating Committee on Standards for Athletic Equipment as chair of its Scientific Advisor. **L.E. Goldstein:** None. **D.I. Katz:** None. **R.A. Stern:** 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.; received research funding from the NFL, the NFL Players' Association, and Avid Radiopharmaceuticals Inc. F. Consulting Fees (e.g., advisory boards); is a paid consultant to Amarantus BioScience Holdings Inc, Avanir Pharmaceuticals Inc, and Biogen; and receives royalties for published neuropsychological tests from Psychological Assessment Resources. **L.A. Farrer:** None. **J.F. Crary:** None. **A.C. McKee:** 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.; Received funding from NFL and WWE. **T.D. Stein:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.17/S16

Topic: C.10. Brain Injury and Trauma

Support: K99 NS096116
U54 EB020403
R01 HD061504

Title: ENIGMA Pediatric msTBI: Preliminary results from meta analysis of diffusion MRI

Authors: *E. L. DENNIS[1], K. CAEYENBERGHS[2], T. BABIKIAN[3], A. OLSEN[5], G. HANTEN[6], H. S. LEVIN[7], C. C. GIZA[4], R. F. ASARNOW[8], P. KOCHUNOV[9], N. JAHANSHAD[10], P. M. THOMPSON[11], D. TATE[12], E. WILDE[13]
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[7]Cognitive Neurosci Lab., Baylor Col. Med., Houston, TX; [8]Psychiatry, UCLA Dept. of Psychiatry, Pacific Palisades, CA; [9]Univ. of Maryland, Baltimore, MD; [10]Neurol., IGC-INI @ USC, Marina Del Rey, CA; [11]Stevens Inst. for Neuroimaging & Informatics, Univ. of Southern California (USC), Marina del Rey, CA; [12]Univ. of Missouri, St. Louis, St. Louis, MO; [13]Univ. of Utah, Salt Lake City, UT

Abstract: Traumatic brain injury (TBI) is the most common cause of acquired disability in children and adolescents. TBI has a devastating impact on white matter (WM) tracts and can disrupt ongoing brain development. Previous studies in children with moderate-to-severe TBI (msTBI) have shown lower fractional anisotropy (FA) values, reflecting disrupted WM organization. Using the approach of the ENIGMA consortium (http://enigma.usc.edu), we examined the effects of injury on WM organization in pediatric patients across cohorts. Data were processed with a harmonized protocol based on tract-based spatial statistics (TBSS). FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were calculated and averaged within each of 5 midline and 19 bilaterally averaged white matter (WM) regions of interest (ROIs) from the Johns Hopkins University (JHU) atlas, as well as across the entire ENIGMA-DTI skeleton. Two longitudinal cohorts were meta-analyzed, one from UCLA and one from Baylor College of Medicine, summarized in **Table 1**. Many but not all of the participants contributed longitudinal data. Participants were clustered into two time points - post-acute (2-6 months post-injury, 58 TBI/86 control), and chronic (12-26 months post-injury, 60 TBI/58 control). Severity ranged between complicated mild and severe. Our primary model included age and sex as covariates. Results were corrected for multiple comparisons using a Bonferroni correction ($p<0.05/25 = 0.002$). We found significantly lower FA in the TBI group compared to controls at both timepoints, particularly in central WM. Within the TBI group at the post-acute phase, there was a significant effect of age at injury (covarying for sex and age at scan) in the superior longitudinal fasciculus and sagittal *stratum*, with higher FA in older patients ($p=0.0019$ and 0.0018 respectively). Within the TBI group there was also a borderline effect of sex, with higher FA in male than female patients in the inferior fronto-occipital fasciculus, internal and external capsules, corticospinal tract, and body of the corpus callosum. With the inclusion of additional cohorts, we can determine generalizability, and more fully address questions regarding sex differences, divergent outcomes, and cognitive function.

Demographic and clinical details on the UCLA and Baylor cohorts.

Postacute				
	UCLA		BCM	
	TBI	Control	TBI	Control
N	27	47	31	39
M/F	19/8	23/24	22/9	27/12
Age (average, SD)	14.2 (2.5)	15.5 (2.8)	14.2 (2.4)	12.0 (2.7)
GCS (average, SD)	9 (3.8)	NA	6.7 (4.1)	NA
TSI (weeks; average, SD)	13.7 (4.2)	NA	17.7 (3.0)	NA

Chronic				
	UCLA		BCM	
	TBI	Control	TBI	Control
N	26	29	34	29
M/F	20/6	18/11	23/11	20/9
Age (average, SD)	16.2 (2.3)	16.3 (2.8)	14.9 (3.0)	13.5 (2.8)
GCS (average, SD)	9.4 (3.7)	NA	7.2 (4.3)	NA
TSI (weeks; average, SD)	65.3 (7.9)	NA	86.8 (13.1)	NA
GCS=Glasgow Coma Scale, TSI=time since injury				

Disclosures: E.L. Dennis: None. **K. Caeyenberghs:** None. **T. Babikian:** None. **A. Olsen:** None. **G. Hanten:** None. **H.S. Levin:** None. **C.C. Giza:** None. **R.F. Asarnow:** None. **P. Kochunov:** None. **N. Jahanshad:** None. **P.M. Thompson:** None. **D. Tate:** None. **E. Wilde:** None.

Poster

212. Brain Injury and Trauma: Human Studies

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 212.18/S17

Topic: C.10. Brain Injury and Trauma

Support: ISF grant 0399306

Title: Disentangling the contributions of brain tissue fraction and composition to quantitative MRI of the aged human brain

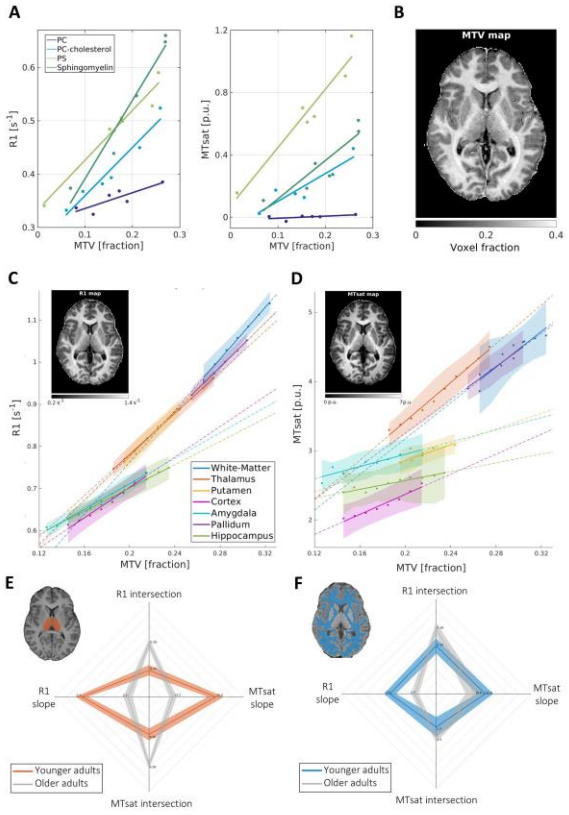
Authors: *S. FILO, O. SHTANGEL, A. MEZER
The Hebrew Univ., Jerusalem, Israel

Abstract: Introduction: Human brain aging is accompanied with drastic changes in tissue volume and composition. Quantitative MRI (qMRI) aims at characterizing such biological properties of brain tissue. However, qMRI parameters are influenced both by the tissue volume and the tissue composition and cannot be attributed to a specific biological process. We propose to evaluate the dependency of qMRI parameters on the macromolecular tissue volume (MTV). This dependency provides a novel MRI contrast with enhanced sensitivity to the molecular composition.
Methods: Human subjects: 38 healthy volunteers (23 under 31, 15 over 55) were scanned on a 3T MRI scanner for multi-parametric mapping: MTV and R1, MTsat, R2*, R2 and diffusion

imaging. Brain regions were segmented with FreeSurfer. Phantoms: We prepared liposomes with different phospholipid compositions and varying water concentrations. The same scanning protocol was used as for the human subjects.

Results: Both in phospholipids phantoms and in the human brain we found a linear dependency between qMRI parameters and MTV. In phantoms, this dependency changes as function of the phospholipid content (Fig. 1A). In the brain, the linear dependency provides a distinct molecular signature for different brain regions (Fig. 1C-D). Furthermore, we capture ageing-related changes that are sensitive to the tissue composition (Fig. 1E-F).

Discussion: We find a novel MRI signature that relates to the molecular composition of the human brain. The importance of this new approach is illustrated by providing a new dimension of comparison between younger and older subjects. Lipid and macromolecular properties of human brain tissue change across the lifespan. Here we show that a deeper understanding of such changes can be obtained in-vivo by evaluating the qMRI dependency on MTV. Our novel approach strengthens the link between qMRI parameters and the underlying tissue characteristics. In the future, this may provide unique signatures of biological processes in the normal and diseased human brain.



(A) Phantoms with varying water concentration and different lipid content were scanned (phosphatidylserine (PS), phosphatidylcholine (PC), PC-cholesterol, sphingomyelin). For each lipid phantom, R1 and MTsat are plotted against MTV (colored dots). The linear dependencies between R1 and MTsat to MTV are marked by lines.
(B) Representative MTV map.
(C,D) R1 (C) and MTsat (D) dependencies on MTV for different brain regions. MTV values were pooled into bins in different brain regions of a single subject (colored dots are the bins' median. shaded area represents the MAD). For each region, a linear fit was calculated (colored lines. Dashed lines are extrapolations).
(E,F) Molecular signatures of ageing-related changes in the Thalamus (E) and the White matter (F). Spider plots show the linear coefficients (slope and intersection) of R1 and MTsat relative to MTV for the two age groups (median is in colored line, shaded area represents the MAD).

Disclosures: S. Filo: None. **O. Shtangel:** None. **A. Mezer:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.01/S18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Spanish Ministry of Economy and Competitiveness and the European Regional Development Fund 2007-2013 (Grant number: BFU2014-56300-P)
Xunta de Galicia (Grant number: GPC2014/030)
Xunta de Galicia (Grant number: 2016-PG008)
Crowdfunding platform Precipita (FECYT; Spanish Ministry of Economy and Competitiveness; grant number 2017-CP081)

Title: Endogenous serotonin inhibits axon regeneration after spinal cord injury in lampreys by activating serotonin 1A receptors

Authors: *A. BARREIRO-IGLESIAS[1], D. SOBRIDO-CAMEÁN[2], M. RODICIO[3]
[1]Univ. of Santiago De Compostela, Santiago DE Compostela, Spain; [2]Dept. of Functional Biol., Univ. of Santiago De Compostela, Santiago de Compostela, Spain; [3]Dept. of Functional Biol., Univ. of Santiago De Compostela, Santiago DE Compostela, Spain

Abstract: Serotonin is mainly known for its role as a neurotransmitter and for playing a role in the development of the nervous system. However, only a few studies have looked at the possible role of serotonin in the regulation of axon or neuronal regeneration after injury, especially in vertebrates. We aimed to reveal the possible role for serotonin in the modulation of axonal regrowth following spinal cord injury (SCI) using lampreys as animal model. The brainstem of lampreys contains several individually identifiable descending neurons that differ greatly in their capacity for axonal regeneration after a complete SCI. This offers a convenient model to promote or inhibit axonal regrowth at the level of single neurons in the same *in vivo* preparation. First, we demonstrate that a serotonin treatment reduced axonal regeneration in descending neurons following a complete SCI. Rescue experiments using a cAMP analogue (dibutyryl-cAMP) suggested that the negative effect of serotonin is due to a reduction in cAMP levels. Then, we used *in situ* hybridization to reveal a possible involvement of the serotonin 1A receptor (5-HT1A) in this process. Our results, revealed a statistically significant correlation between the increase in the expression of this receptor 4 weeks post-injury and a lower regenerative ability of identifiable descending neurons. Finally, we show that blocking endogenous serotonin signalling through the 5-HT1A receptor, using a treatment with the 5-HT1A antagonist WAY-100,135 or by blocking 5-HT1A expression with translation blocking morpholinos, enhances axonal regeneration following SCI. Our results indicate that endogenous serotonin signalling through 5-

HT1A receptors inhibits axonal regeneration following SCI in lampreys. This study provides a new target of interest for SCI.

Disclosures: A. Barreiro-Iglesias: None. **D. Sobrido-Cameán:** None. **M. Rodicio:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.02/T1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant R01NS052741
NMSS Grant RG3367

Title: Targeting proteinase activated receptors are molecular drivers of the spinal cord injury microenvironment

Authors: *H. YOON[1], M. RADULOVIC[1], H. KIM[1], S. BOUCHAL[2], C.-I. CHOI[1], I. A. SCARISBRICK[3]
[1]Physical Med. & Rehabilitation, Rehabil. Med. Res. Ctr., [3]Physical Med. & Rehabilitation, Rehabil. Med. Res. Center, Neurobio. of Dis., [2]Mayo Clin., Rochester, MN

Abstract: Protease activated receptors (PARs) are G-protein coupled receptors capable of translating changes in the proteolytic microenvironment into adaptive and in some cases maladaptive cellular responses. Here we critically evaluated the roles of PAR1 and PAR2 as regulators of the response to traumatic spinal cord injury, (SCI) including cellular, molecular and neurobehavioral outcomes. Experimental contusion-compression SCI was elicited by application of a modified aneurysm clip (FEJOTA™, 8g closing force) to the L1/L3 spinal cord of 12-week old female wild type mice or those with genetic knockout of PAR1 or PAR2. Sensorimotor outcomes were determined the day after injury, then weekly until 30 days post injury (dpi). Sensorimotor outcomes evaluated included gait using the Basso Mouse Scale open field test, coordination using a ladder walk test, and strength in the Incline Plane test. Cellular and molecular correlates of changes in locomotor recovery were assessed by examination of spinal cord segments at the injury epicenter as well as spinal segments above and below at early (7 dpi) and more chronic time points after SCI (30 dpi). The response to injury in each case was quantified using genome wide RNA sequencing, in addition to validation using immunochemical, Western blot and real time PCR approaches. Results suggest that targeting either PAR1 or PAR2 promotes significant improvements in recovery of gait, motor coordination and strength after experimental SCI. Improvements in sensorimotor function were accompanied by reductions in inflammation and astrogliosis, including lower levels of glial fibrillary acidic protein, vimentin and STAT3. SCI-associated elevations in pro-inflammatory cytokines, such as

IL-1beta and IL-6, were also reduced in PAR knockout mice and significant sparring of myelin was observed. To address PAR-astrocyte dependent mechanisms, we demonstrated that PAR1 and PAR2 activating proteinases gate Ca^{2+} in purified astrocyte cultures. Astrocytes also exhibited PAR-dependent increases in IL-6 production and STAT3 signaling. In turn, IL-6 treated astrocytes showed elevations in PARs and PAR activating enzymes. Together these findings highlight PAR1 and PAR2 as essential regulators of inflammatory astrogliosis accompanying spinal cord trauma with effects occurring by feedforward- and feedback-signaling dynamics. Given the significant improvements in neurobehavioral outcomes observed in PAR knockout mice, these studies also suggest that PARs may serve as targets to modulate astrogliosis, reduce neural injury and promote an environment favorable to repair and recovery of function after spinal cord trauma.

Disclosures: H. Yoon: None. **M. Radulovic:** None. **H. Kim:** None. **S. Bouchal:** None. **C. Choi:** None. **I.A. Scarisbrick:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.03/T2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Shriners' Grant SHC-85101
Shriners' Grant SHC85400
Shriners' Grant SHC-85220
NIH Grant NS097846
NIH Grant NS092876

Title: Injury-induced Erk phosphorylation and retrograde transport in lamprey spinal cord

Authors: *L.-Q. JIN[1], K. HALL[1], S. L. LAM[1], J. HU[1], M. E. SELZER[1,2]
[1]Shriners Hosp. Pediatric Res. Ctr., [2]Dept. of Neurol., Temple Univ. Sch. of Med., Philadelphia, PA

Abstract: Activation of extracellular signal-regulated protein kinase (Erk), a member of the mitogen-activated protein kinase family, has been shown to mediate neurite outgrowth-promoting effects of many neurotrophic factors. Recently Erk has been recognized as one element of retrograde signaling complex that is transported to the cell body to illicit cell responses to stress stimuli. Most research on Erk have been conducted *in vitro* or in peripheral nerve. To confirm the role of Erk in retrograde signaling of axon injury, we observed the changes in phosphorylated (activated) Erk (p-Erk) by immunoblot and immunohistochemistry in spinal cord, and in phosphorylated c-Jun (p-c-Jun) in brain after spinal cord transection (TX). For

immunoblotting, three spinal cords and brainstems were pooled and homogenized for each time point (0, 0.5, 1.5, 3, 6, 24 hrs post-TX). Immunoblotting was performed with antibodies against p-Erk, total-Erk (t-Erk) in spinal cord, and p-c-Jun in brainstem. After TX, p-Erk and p-c-Jun levels were increased. A plateau (5-fold) increase was reached for p-Erk levels at 6 hrs, whereas the p-c-Jun plateau (2-fold) was reached at 0.5-1.5 hrs. Immunohistochemistry (IHC) confirmed the increase of p-Erk levels in TXed spinal cord. Twelve animals were assigned to one of 3 groups: 4 controls (without TX), 4 at 3 hrs post-TX (at the 7^{th} gill), and 4 at 6-hrs post-TX. Spinal cords were sectioned by cryostat microtome. Result showed: 1) p-Erk staining was week in control spinal cord. Staining for p-Erk increased at 3-hrs post-TX, and was even stronger at 6-hrs. The heaviest staining occurred within 1-1.2 mm of the TX site, becoming weaker rostrally. 2) At high magnification, heavily stained 3-5 μm particles were seen along the courses of axons at 3 and 6-hrs post TX, most heavily concentrated in the region of the TX. The differences in particle numbers between the TX groups and controls were statistically significant ($p<0.05$, ANOVA). 3) Strong immunopositivity also was found in glial cells and dorsal cells (intramedullary primary sensory neurons) near the TX site. The source of intra-axonal p-Erk post-TX is not known.

Disclosures: L. Jin: None. **K. Hall:** None. **S.L. Lam:** None. **J. Hu:** None. **M.E. Selzer:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.04/T3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Nathalie Rose Barr Studentship. International Spinal Research Trust

Title: A novel biomaterial-based Epac targeting approach to promote spinal cord repair

Authors: *A. GUIJARRO-BELMAR[1], M. VISKONTAS[1], X. BO[2], D. SHEWAN[1], W. HUANG[1]
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Abstract: Spinal cord injury (SCI) is a highly debilitating trauma affecting millions of patients worldwide with no cure. The challenges for spinal repair include a lack of intrinsic capacity for adult CNS neurons to regrow post injury and the inhibitory physical and chemical barriers formed at the lesion site. One of the most promising new avenues for spinal repair is to combine novel axon growth-promoting and tissue-engineering strategies, thus creating a permissive and encouraging environment for injured spinal nerve processes to regrow.
Elevated levels of cAMP have been shown to promote injured CNS neurons to sprout and extend

neurites, even in the presence of growth inhibitory molecules including chondroitin sulphate proteoglycans (CSPGs). cAMP is now known to signal via Epac, a guanine nucleotide exchange factor, which has two isoforms, Epac1 and Epac2, with the latter expressed mainly in postnatal neural tissue. By using primary neuronal cultures, immunocytochemistry and lentiviral tools, we herein demonstrate that specific activation of Epac2 significantly enhances neurite outgrowth of cultured postnatal rat cortical neurons and is able to overcome the inhibitory effects of CSPGs and mature activated astrocytes on cortical neuron growth *in vitro*.
With the aim to find an effective combinatorial strategy, we have further explored the suitability of a novel self-assembling hydrogel for spinal repair. The gel is a synthetic polymer with 3-D nanostructured networks that are similar to native extracellular matrix and can be functionalised with growth-promoting drugs. We show that this gel has appropriate stiffness, biocompatibility and biodegradation properties to promote cultured postnatal cortical neuron growth. By using an *ex vivo* model that mimics the *in vivo* environment after spinal injury, we demonstrate that the gel incorporated with a specific Epac2 agonist promotes significantly more axon regrowth than gel alone and without gel. By using a partial transection model of spinal injury, we further demonstrate that the spinal injured rats receiving implantation of the gel incorporated with the Epac2 agonist have much better locomotor function recovery than those rats having gel only implantation.
Our results demonstrate the potential of combining Epac2 activation with novel 3-D growth-supporting hydrogels to promote axon regrowth, thus contributing to new methods for spinal repair. Future studies will examine the efficacy of this combined strategy in a clinically relevant contusion model of spinal injury.

Disclosures: A. Guijarro-Belmar: None. **M. Viskontas:** None. **X. Bo:** None. **D. Shewan:** None. **W. Huang:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.05/T4

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Contributions of lumbar spinal cord maldevelopment to spasticity in cerebral palsy from preterm birth

Authors: *J. KIM[1], T. R. YELLOWHAIR[2], A. Y. OPPONG[1], C. L. SHROCK[1], F. S. CONTEH[1], L. L. JANTZIE[2], S. ROBINSON[1]
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Abstract: Preterm infants are at risk for cerebral palsy (CP). The most common cause of spontaneous preterm birth in the USA is chorioamnionitis (CAM) from bacterial infection. The connection between alterations in spinal cord development from CAM and subsequent motor deficits with CP has not been investigated in a clinically-relevant preclinical model, despite much evidence suggesting that descending neural networks heavily modulate motor movement. For example, central pattern generators (CPGs), found in the lumbar cord, are essential for movement of the lower extremities, regulating the left-right alternating pattern in humans and determining modular coordination. While active immediately after birth, CPGs still undergo significant maturation after term birth. Thus, preterm infants experience CNS injury co-incident with a critical developmental period in the spinal cord. This may partially explain why preterm survivors with CP have difficulty ambulating independently and expressing selective motor control. The potassium chloride co-transporter KCC2 influences the maturation of GABAergic and glycinergic receptors, while serotonin signaling can influence spinal KCC2 levels. We hypothesized that prenatal injury reduces lumbar KCC2 expression and alters expression patterns of serotonin and glycine receptors, and that these changes contribute to spasticity associated with CAM. In this study, we characterize the changes in the ventral lumbar spinal cord after prenatal CNS injury. We used an established rat model of CAM, induced on embryonic day 18 by transiently occluding the uterine arteries and injecting lipopolysaccharide (LPS), an endotoxin that mimics bacterial inflammation. Rat pups were born at term (E22, equated to 30 weeks human gestation). We have previously shown using detailed computerized gait analysis that these CAM rats as adults have gait deficits that are reminiscent of those of people with spastic diplegia. Immunohistochemistry, and as appropriate unbiased stereology, with Iba1 (microglia), GFAP (astrocytes), NeuN (neurons), glycine and serotonin receptor subtypes was done at postnatal day 15 (P15, infant), P21 (toddler), and P90 (adult). We found marked ventral horn neuronal loss ($n=4$, t test $p<0.01$). Here, we show for the first time that prenatal CNS injury from CAM leads to marked, sustained neuronal loss in the lumbar ventral horn, concomitant with a shift in the maturation of serotonin receptor subtypes, and apparent loss of glycine receptor subtypes. These results may inform novel repair strategies in toddlers who have CP and missed the opportunity for neonatal repair regimens.

Disclosures: J. Kim: None. **T.R. Yellowhair:** None. **A.Y. Oppong:** None. **C.L. Shrock:** None. **F.S. Conteh:** None. **L.L. Jantzie:** None. **S. Robinson:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.06/T5

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Identifying the most effective types of integration-free human iPS cell-derived neural stem/progenitor cells in the treatment of spinal cord injury

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Abstract: INTRODUCTION: We have previously demonstrated the therapeutic potential of transplanting human iPS cell-derived neural stem/progenitor cells (hiPSC-NS/PCs) in the treatment of spinal cord injury (SCI) models. Recently, we have produced integration-free hiPSCs using episomal vectors which is safer for clinical use. The purpose of this study is to assess the efficacy of integration-free hiPSC-NS/PCs, and to investigate their genetic profiles in order to evaluate factors related to therapeutic efficacy. METHODS: Two integration-free human iPS cell lines were prepared (836B3-, 414C2-hiPSCs), and were induced to hiPSC-NS/PCs (836B3-, 414C2-NS/PCs). ES cells were also used for analysis as a target for comparison of hiPSCs. hiPSC-NS/PCs were transplanted into the injured spinal cord of NOD-SCID mice, and phosphate buffered saline (PBS) was injected to the control group (414C2-NS/PCs; n=27, 836B3-NS/PCs; n=23, control; n=15). Transplanted cells were monitored using bio-imaging and evaluated histologically; and motor function was evaluated by basso mouse scale (BMS) score. HumanHT-12 was used to evaluate gene-expression analyses and single-cell-RNA-sequence was performed using Illumina-Hiseq2500. RESULTS: In the *in-vivo* study, better motor functional recovery was observed in the 414C2-NS/PCs group compared with the control group ($p < 0.001$). In contrast, 836B3-NS/PCs group showed no improvement in motor function, and formed undifferentiated tissues. The gene-expression profile of 414C2-hiPSCs resembled that of ES cells with clustering analysis, and 12 genes which included genome-stabilization gene such as DPPA3 and differentiation related genes such as IRX2 were highly expressed in 414C2-hiPSCs, similar to those found in ES cells. None of these findings, however, were observed in 836B3-hiPSCs. In single-cell-RNA-sequence, Delta-Notch signal positive cells which are important for neural differentiation were more abundant in 414C2-NS/PCs, whereas 836B3-NS/PCs only contained a small population (12% and 5%, respectively). DISCUSSION: In order to pursue our mission of conducting a clinical trial for SCI patients within the next several years, it is critical to build guidelines for selecting “effective” hiPSC-NS/PCs, such as 414C2-NS/PCs. Herein we showed that the key to good motor function recovery is to transplant integration-free hiPSC-NS/PCs that differentiate well within the spinal cord tissue. Our results suggest that examining hiPSCs quality with 12-gene markers and establishing hiPSC-NS/PCs that contain Delta-Notch (+) cells for more than 10% could be the criteria to select “effective” hiPSC-NS/PCs for SCI treatment.

Disclosures: T. Iida: None. **N. Nagoshi:** None. **J. Kohyama:** None. **O. Tsuji:** None. **M. Matsumoto:** None. **M. Nakamura:** None. **H. Okano:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.07/T6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NINDS 1R01NS092680-01A1

Title: Intracellular calcium release through IP_3R contributes to secondary axonal degeneration

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Abstract: Protecting axons following spinal cord injury (SCI) is an important therapeutic goal to improve neurological outcome; however, the complex cellular and molecular mechanisms that mediate secondary axonal degeneration remain poorly understood. Previously we showed that IP_3R mediated Ca^{2+} release contributes to axonal dieback and axonal loss following an *ex vivo* laser-induced SCI. Nevertheless, targeting IP_3R following a clinically relevant contusive SCI and determining its potential contribution to secondary axonal degeneration *in vivo* has yet to be explored. Here we used intravital microscopy to assess the role of IP_3R in secondary axonal degeneration in real-time after a contusion-SCI *in vivo.* To visualize Ca^{2+} changes specifically in dorsal column axons assessable to two-photon excitation, we bred *Avil* -Cre recombinase transgenic mice with "floxed" tdTomato (Ai9) and "floxed" Ai95 mice, which express the genetic Ca^{2+} indicator GCaMP6f. Adult triple transgenic mice were subjected to a mild (30 kdyn) T12 contusion SCI and received treatment with the IP_3R blocker 2-APB (100 μM, intrathecal delivery at 3hr, 24hr and 48hr following injury) or vehicle control. Blocking IP_3R at 3 hours after injury significantly increased axonal survival (48.9 % ± 3.02, 2-APB treated vs. 33.6 % ± 4.09 vehicle control; mean percentage normalized to baseline axonal counts; $p < 0.001$ by Mann-Whitney rank sum test), and significantly reduced axonal spheroid formation within the dorsal columns at 1 day after SCI (174.29 ± 46.81; 2-APB treated vs. 322.78 ± 48.88; vehicle control (axonal spheroids per mm^2); $p<0.001$ by t-test). Data are expressed as mean ± SD; n=4-6 mice/ group. Next, we measured Ca^{2+} changes in dorsal column axons at 1 day following SCI. Dystrophic axons within the penumbra of vehicle treated mice often displayed robust increases in Ca^{2+}, but this was significantly ameliorated after delayed treatment with 2-APB ($\Delta F/F=3.48 \pm 1.60$ 2-APB treated vs. 6.42 ± 2.77 vehicle control; mean ± SD; $p < 0.001$ by Mann-Whitney rank sum test; n=22-24 axons). Collectively, we show that IP_3R mediate increased Ca^{2+} release in axons and contribute to secondary axonal degeneration following contusive SCI *in vivo*.
Acknowledgment: Supported by NIH NINDS 1R01NS092680-01A1.

Disclosures: N. Pelisch: None. **A. Siladi:** None. **J. Nally:** None. **D.P. Stirling:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.08/T7

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Regulation of astrocytic aquaporin-4 and alpha-syntrophin following contusion spinal cord injury

Authors: *J. M. YONAN[1], D. K. BINDER[2]
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Abstract: Spinal cord injury (SCI) is characterized by an initial injury due to trauma, which is followed by a cascade of cellular events, resulting in a greater degree of secondary damage. One of these secondary events is the accumulation of edema at and around the injury site. This accumulation has been shown to correlate with injury severity and neurological outcome in both humans and animal models of spinal cord injury. The astrocytic water channel aquaporin-4 (AQP4) plays an important role in the regulation of water homeostasis under normal physiological conditions. Current evidence suggests that AQP4 water channels are the major route for accumulation of cytotoxic edema within cells and resolution of vasogenic edema from the extracellular space following spinal cord injury. To date, there is no evidence indicative of a mechanism by which AQP4 expression is regulated, only that its expression is dysregulated after injury. AQP4 is anchored to astrocytic end feet through interaction with alpha-syntrophin (αSyn) and the dystrophin-associated protein (DAP) complex to which it belongs. Preliminary data from our lab suggests a downregulation of both AQP4 and αSyn protein expression following spinal cord injury when tissue water content is at its peak. This information points to the possibility that loss of αSyn at perivascular astrocytic membranes results in loss of AQP4 and the inability to clear accumulation of water within the tissue parenchyma following trauma. Here we characterize the expression of AQP4 and αSyn protein following a severe contusion spinal cord injury in rats. Further insight into the regulation of AQP4 and its anchoring proteins could help lead to more effective therapies to attenuate edema formation, preserve tissue integrity and improve functional outcome.

Disclosures: J.M. Yonan: None. **D.K. Binder:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.09/T8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: KAKENHI JP 23110001
KAKENHI JP 16K21083
KAKENHI JP 18K15363

Title: Chondroitin sulfate disrupts autophagy and inhibits axon regeneration after neuronal injury

Authors: *T. OZAKI, K. SAKAMOTO, Y. GONG, K. KADOMATSU
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Abstract: In the adult mammal CNS, neuronal axons are incapable of spontaneously regenerating through the lesion site after injury. Upon injury, although regenerating axons display growth cones at their tips and expand to glial scar, growth cones are forced to swell and stop outgrowth at glial scar in the injury site. These abnormal growth cones are known as dystrophic endballs. The formation of dystrophic endballs is a hallmark of axons after injury. So far, it has been well established that an extracellular gradient of chondroitin sulfate proteoglycan (CSPG) at the glial scar is responsible for the dystrophic endball formation. Although dystrophic endballs display bizarre morphology and contain numerous vacuoles, molecular mechanisms and intracellular events underlying the dystrophic endball formation remain elusive. Here, we show that autophagy disruption is involved in the dystrophic endball formation by employing an *in vitro* model of a CSPG gradient. Using electron microscopy, we have identified a significant number of vacuoles in dystrophic endballs as autophagosomes, which contain cytosolic fractions. It has been also verified that a number of vacuoles are positive for LC3, a marker of autophagosomes. Moreover, Gene knockdown of SNARE proteins, which play the central role in the fusion of autophagosomes and lysosomes, led to the dystrophic endball-phenotype such as axonal outgrowth inhibition and accumulation of autophagosomes at axonal tips. Finally, we confirmed accumulation of autophagosomes in dystrophic endballs *in vivo*. Our study demonstrates that (i) vacuoles in dystrophic endball are autophagosome both *in vitro* and *in vivo*, (ii) in dystrophic endball, autophagosomes do not fuse with lysosomes, (iii) gene knockdown of SNARE proteins induce the dystrophic endball-phenotypes and (iv) novel pathway which is activated by CS and disrupt autophagy is involved in the dystrophic endball formation. Our data provide new therapeutic targets to axonal regeneration failure.

Disclosures: T. Ozaki: None. **K. Sakamoto:** None. **Y. Gong:** None. **K. Kadomatsu:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.10/T9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR
Wings for life
International Foundation for Research in Paraplegia

Title: Interleukin 1 alpha delivery in the central nervous system of mice induces a rapid decrease in numbers of mature oligodendrocytes

Authors: *F. BRETHEAU[1,2], M. LESSARD[2], S. LACROIX[1,2]
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Abstract: At the site of spinal cord injury (SCI), damage to cell bodies of neurons and glia results in the release of damage-associated molecular patterns (DAMPs), thus inducing sterile inflammation. This is followed by a second wave of tissue degeneration characterized by a delayed death of oligodendrocytes (OLs) and the demyelination of axons that survived the trauma. We recently demonstrated that damaged microglia at the site of SCI rapidly release the DAMP interleukin (IL)-1α, which in return triggers neuroinflammation and OL cell death. Accordingly, mice lacking the *Il1a* gene exhibit improved locomotor recovery compared to wild-type mice as early as day 1 post-SCI, as well as over time. Here, we further investigated the role of IL-1α in secondary cell death. We found that IL-1α injected intra-cisterna magna (i.c.m.) to C57BL/6 mice induced death of mature OLs at day 1 post-injection. The injection of IL-1α also triggered massive infiltration of neutrophils, as well as caused neuronal activation throughout the entire mouse spinal cord. Altogether, our data suggest that IL-1α released by damaged microglia after SCI regulates OL cell death and demyelination.

Disclosures: F. Bretheau: None. **M. Lessard:** None. **S. Lacroix:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.11/T10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS101298
Craig H Neilsen Foundation 460461
State of Florida
Department of Veterans Affairs

Title: Macrophage-mesenchymal stem cell interactions for spinal cord repair: *In vitro* observations and *in vivo* relevance

Authors: *I. MALDONADO-LASUNCION[1,3], M. OUDEGA[2], J. VERHAAGEN[4]
[1]The Miami Project to Cure Paralysis, [2]Dept. of Neurolog. Surgery, The Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL; [3]Vrije Univ. Amsterdam, Amsterdam, Netherlands; [4]Lab. of Regeneration of Sensorimotor Systems, Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: Mesenchymal stem cells (MSCs) transplanted in the injured spinal cord exert paracrine actions resulting in angiogenesis, neuronal survival, and axonal growth and myelination, which are often accompanied by functional improvements. An intraspinal MSC transplant encounters active immune cells that are mainly inflammatory macrophages. MSCs and macrophages are known to reciprocally interact thereby influencing the overall repair process. We studied the effect of MSC-macrophage interactions in vitro and explored the effects of inflammatory preconditioning of MSCs for repair of the injured spinal cord. We exposed MSCs to differently polarized macrophages or their conditioned medium and investigated the effects on MSC secretome and transcriptome. Exposure of MSCs to inflammatory macrophages increases their secretion of vascular endothelial growth factor (VEGF), which is important for the initiation of angiogenesis, and of anti-inflammatory cytokines, including IL4 and IL10, which are responsible for the polarization of anti-inflammatory and regulatory macrophages. Exposure to anti-inflammatory macrophages increases the secretion of platelet-derived growth factor (PDGF), which is important for a number of repair-related events including blood vessel stabilization. In addition, we exposed macrophages to synthetic or MSC-derived anti-inflammatory media and analyzed their phenotype. Co-culture of macrophages with activated MSCs induces a significantly higher increase in expression of anti-inflammatory markers compared with co-culture with naïve MSC. Our in vitro data provided the basis for exploring the effects of macrophage-mediated preconditioning of MSCs on their reparative potential for the injured spinal cord. Our results highlight the significance of macrophage-MSC interactions for MSC-mediated spinal cord repair.

Disclosures: I. Maldonado-Lasuncion: None. **M. Oudega:** None. **J. Verhaagen:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.12/T11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NJCSCR Grant CSCR17IRG007
The Reynolds Family Spine Laboratory Funds

Title: A novel modulator of the glial scar and astrocyte proliferation following spinal cord injury

Authors: *L. LI[1], L. NI[1], E. A. EUGENIN[2], R. F. HEARY[1], S. ELKABES[1]
[1]Neurolog. Surgery, [2]Microbiology, Biochemistry, and Mol. Genet., NJMS, Rutgers, The State Univ. of New Jersey, Newark, NJ

Abstract: The glial scar that forms at the injury epicenter following spinal cord (SC) trauma plays both beneficial and detrimental roles. Increased expression of chondroitin sulfate proteoglycans (CSPGs) at the glial scar has been implicated in inhibition of axonal re-growth. Reactive astrocytes are one of the principal cell types that form the glial scar and produce CSPGs. Astrocytes express toll-like receptors (TLRs), which are the first sensors of danger and initiators of neuroinflammation following SC injury (SCI). The role of TLRs in astrocyte function has been inadequately defined and is the focus of the present investigations, with particular emphasis on TLR9. We previously showed that a TLR9 antagonist, oligodeoxynucleotide 2088 (ODN 2088), administered intrathecally, improves functional and histopathological outcomes of SCI. ODN 2088 enhances white matter sparing and reduces neuroinflammation. We now report that intrathecal ODN 2088 treatment significantly decreases CSPG immunoreactivity and astrocyte proliferation at the glial scar in female C57Bl/6 mice sustaining a severe mid-thoracic (T8) SC contusion injury as compared to injured controls treated with vehicle. In pure SC astrocyte cultures, the addition of the TLR9 antagonist significantly decreases proliferation, supporting the notion of direct effects. Moreover, ODN 2088 inhibits astrocyte migration in an *in vitro* scratch wound assay whereas it enhances astrocyte-elicited chemotaxis of peritoneal macrophages which was evaluated by a trans-well migration assay *in vitro*. The effects of the antagonist on macrophage chemotactic migration were partly mediated by increased C-C motif chemokine ligand 1 (CCL1) release by astrocytes and were inhibited by addition of an anti-CCL1 blocking antibody to the cultures. ODN 2088-mediated modulation of astrocyte proliferation, migration and chemotaxis were dependent on TLR9 expression since they were not observed in $TLR9^{-/-}$ astrocytes. These findings suggest that the TLR9 antagonist could modify the glial scar and astroglial function. Ongoing studies are determining whether these changes result in altered axonal re-growth.

Disclosures: L. Li: None. **L. Ni:** None. **E.A. Eugenin:** None. **R.F. Heary:** None. **S. Elkabes:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.13/T12

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Examining the role of store-operated calcium entry on secondary axonal degeneration following SCI: An *in vivo* and *ex vivo* approach

Authors: *B. OREM[1], N. PELISCH[2], J. M. NALLY[2], D. P. STIRLING[3]
[1]Anatom. Sci. and Neurobio., Univ. of Louisville, Louisville, KY; [2]Neurolog. Surgery, [3]Neurolog. Surgery & Microbiology and Immunol., KY Spinal Cord Injury Res. Center/ Univ. of Louisville, Louisville, KY

Abstract: Axonal Ca^{2+} overload is established as a key mediator of axonal injury following spinal cord injury (SCI). Yet, therapeutically targeting external sources of Ca^{2+} have failed to preserve axons and improve neurological recovery in both pre-clinical and clinical studies. The Ca^{2+} hypothesis of neurodegeneration has been recently reignited with the discovery of the key mediators of store-operated Ca^{2+} entry (SOCE) in neurons and glia, and its vital role in maintaining Ca^{2+} homeostasis. Whenever calcium stores within the endoplasmic reticulum (ER) are eliminated, the stromal interaction molecule family of proteins, located on the ER, will oligomerize and translocate to the plasma membrane to bind to the Orai proteins. This binding will cause the Orai pore to open and allow Ca^{2+} to enter the cell. However, the role of SOCE in the context of SCI remains unexplored. Here, we assess the role of SOCE on secondary axonal degeneration in real-time using a laser-induced spinal cord injury (LiSCI) and an *in vivo* contusion model. We hypothesize that blocking SOCE with YM-58483, a store-operated calcium channel antagonist, will diminish secondary axonal degeneration. Briefly, the spinal cords are isolated from adult transgenic mice that express yellow fluorescent protein in Gracile fasciculus axons, perfused in artificial cerebrospinal fluid (aCSF), ablated using a laser tuned to 800 nm, and dynamic events are captured over time with two-photon excitation microscopy. We dissolved YM-58483 1 hr post LiSCI into the aCSF and continuously perfused for the remainder of the imaging session. We found that YM-58483 treatment significantly shortened axonal dieback length at 6 hr (YM-58483, 33.70 ± 18.96 μm; median ± 25th percentile; control, 44.96 ± 25.60 μm, $p<0.05$; ANOVA on ranks) post LiSCI proximal to the lesion. Additionally, YM-58483 significantly reduced axonal bystander degeneration (axons that are initially intact by the lesion but succumb to damage overtime) at 6 hr (YM-58483, 15. 749 ± 5.930 μm; mean ± SD; control, 21.587 ± 5.982 μm, $p<0.05$, RM ANOVA) post injury. For the contusion study, adult

Advillin-Cre:tdTomato mice that express tdTomato in sensory dorsal column axons, received a T12 30 Kdyn contusion and then were imaged at 24 hrs post SCI. YM-58483 (300 μM) was administered intrathecally 1 hr and 6 hr post-SCI. We found that YM-58483 significantly reduced spheroid formation at 24 hr post-SCI (YM-58483, 54.24 ± 15.85 spheroids/mm^2; mean ± SD; vehicle, 146.12 ± 55.92 spheroids/ mm^2; t-test). These data reveal a novel role of SOCE in axonal degeneration after SCI and suggest that blocking SOCE is axoprotective by preventing Orai channel-mediated Ca^{2+} influx.

Disclosures: B. Orem: None. **N. Pelisch:** None. **J.M. Nally:** None. **D.P. Stirling:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.14/T13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: AHW 5520383

Title: Role of IL-12, IL-23 and their receptors after spinal cord injury (SCI) and their impact on secondary damage

Authors: *A. KRONER-MILSCH
Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Spinal cord injury (SCI) is a severe condition with far-reaching effects on health and quality of life. The trauma to the spinal cord causes tissue destruction and functional deficits depending on the location and size of the injury. This primary damage is worsened by subsequent events, the secondary tissue damage, which include hemorrhage, inflammation, edema and production of reactive oxygen species. This secondary reaction contributes to the pathology and the severity of the functional deficits. The goal of this project is to assess and modulate aspects of the inflammatory response after SCI in order to minimize tissue damage and to promote an environment that is permissive for healing and repair. The pro-inflammatory cytokines IL-12 and IL-23 play an important role in pathological conditions of the nervous system by initiating and maintaining the pro-inflammatory response. Conditions in which IL-12 or IL-23 have a negative impact include autoimmune diseases including autoimmune neuropathy and Experimental autoimmune encephalomyelitis. Both IL-12 and IL-23 are expressed by a variety of immune cell types and can induce the production of other pro-inflammatory cytokines. In our model of moderate contusion injury in C57BL/6 mice, IL-12 and IL-23 mRNA was upregulated early after injury, as well as mRNA of the receptor subunits. Furthermore, IL-12p40 knockout mice showed improved recovery compared to wild type mice, using the BMS locomotor score, while IL-23p19 knockout mice are not different from wildtype controls.

Ongoing and future experiments will confirm expression patterns and behavioral results and assess the impact of IL-12 and IL-23 neutralization after SCI.

Disclosures: A. Kroner-Milsch: None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.15/T14

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Epigenetic regulation of axonal regeneration

Authors: *S. DI GIOVANNI[1], E. MACLACHLAN[1], I. PALMISANO[1], T. HUTSON[1], A. HERVERA[1], F. DE VIRGILIIS[1,2], M. DANZI[2], J. BIXBY[2], V. LEMMON[2]
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Abstract: Regeneration after peripheral nerve injury depends on the activation of key signalling events, the recruitment of transcription factors and histone acetylation. This does not occur after a central spinal injury, which is associated with regenerative failure. Whether specific histone marks and the recruitment of transcription factors confers a differential molecular signature between a central versus a peripheral axonal injury remained to be determined. Here, we performed RNAseq and ChIPseq for H3K27ac and H3K9ac in the sciatic dorsal root ganglia after central spinal cord or peripheral sciatic nerve injury, to identify key molecular events associated with regeneration vs regenerative failure. Data analysis showed that increased promoter enrichment of H3K27ac/H3K9ac occurs across various regenerative associated genes after sciatic injury only. Bioinformatics analysis identified a gene network enriched in transcription factors and histone acetylation. Indeed, we found that this complex is required for the regenerative growth of sensory neurons including after a spinal injury. Lastly, we identified the FDA approved HDAC inhibitor Panobinostat that activates this network to promote axonal regeneration after spinal cord injury.

Disclosures: S. Di Giovanni: None. **E. maclachlan:** None. **I. Palmisano:** None. **T. Hutson:** None. **A. Hervera:** None. **F. De Virgiliis:** None. **M. Danzi:** None. **J. Bixby:** None. **V. Lemmon:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.16/T15

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Morphological changes of layer-V pyramidal cells in motor-related areas in a primate model of spinal cord injury

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Abstract: Manual dexterity is critical to motor activities in daily life. It has been considered that manual dexterity strongly correlates with the development of cortico-motoneuronal connections in mammals. In spinal cord injury (SCI), the corticospinal tract (CST) is often injured with impaired manual dexterity. Thus, the enhanced plasticity of CST neurons is important to promote functional recovery after SCI. A previous work reported that the motor cortex was activated in parallel with restoration from impaired manual dexterity at an early recovery stage. This finding implies that the reorganization of the motor cortex may be crucial in the recovery process of manual dexterity. However, it remains unclear how the morphology of motor cortex neurons exhibits plastic changes at an acute stage after SCI. Here we investigated the complexity of dendrites and the density of dendritic spines in layer-V pyramidal cells in the motor-related areas, including the primary motor cortex (MI), the supplementary motor cortex (SMA), and the dorsal and ventral divisions of the premotor cortex (PMd, PMv), in normal and SCI model monkeys. The digit region of each motor-related area was identified by intracortical microstimulation (ICMS). The layer-V pyramidal cells in individual regions were visualized by Golgi staining, and Sholl analysis was employed to assess the complexity of their basal dendrites. For preparing an SCI model, unilateral lesions were made at the C6/C7 border of the spinal cord. In our model, the dorsolateral funiculus was fully injured to remove laterally-situated CST fibers. Behavioral assessment of motor functions was performed by using a reaching/grasping task. All monkeys were sacrificed ten days after SCI when impaired manual dexterity was still observed. We found that throughout the motor-related areas, the dendritic complexity was reduced and, also, the dendritic spine density was decreased in the SCI model, compared with the normal control. In the present study, we have defined that the dendritic morphology of layer-V pyramidal cells is largely changed at an acute stage after SCI.

Disclosures: Y. Takata: None. **H. Nakagawa:** None. **H. Yamanaka:** None. **M. Takada:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.17/T16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ISRT, Nathalie Rose Barr Studentship

Title: Regenerative metabolic signaling after nerve and spinal injury

Authors: *E. SERGER[1], G. KONG[2], I. PALMISANO[1], E. MCLACHLAN[1], S. DI GIOVANNI[1]
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Abstract: Mammalian axonal regeneration is limited in the injured peripheral nervous system (PNS) occur and it fails in the central nervous system (CNS) such as after a spinal cord injury (SCI), strongly contributing to unsuccessful functional recovery. While we have been gaining knowledge in regenerative neuronal signaling pathways, the role of metabolic signaling remains rather elusive. Here, we hypothesize that injury as well as metabolism related signaling pathways might converge to regulate the axonal regenerative ability of sensory dorsal root ganglia (DRG) neurons. We performed high throughput unbiased studies investigating changes in metabolism and cell signaling to identify key regulatory mechanisms for the success of sensory axonal regrowth after injury. Currently, we are investigating the mechanisms underpinning metabolic signaling dependent regenerative phenotype. We next intend to manipulate the identified key pathways by gene therapy and/or pharmacologically to enhance the regeneration program. This will ultimately offer a new pathway to clinical translation for nerve repair after injury.

Disclosures: E. Serger: None. **G. Kong:** None. **I. Palmisano:** None. **E. McLachlan:** None. **S. Di Giovanni:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.18/T17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The funds of Leading Talents of Guangdong Province #87014002

Title: Differentiation of NSCs under exogenous electrical stimulation on carbon nanotube multilayers

Authors: *R. ZHU, S. RAMAKRISHNA, L. HE
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Abstract: In modern neuroscience, exogenous electrical stimulation has been documented to potentially promote nerve regeneration; the mechanism, however, is not fully understood and thus remains to be elucidated. In this study, we fabricated carbon nanotube multilayered nanocomposites by layer-by-layer assembly of negatively charged carbon nanotubes (CNTs) with positively charged polymer. Neural stem cells were cultured on the multilayers with exogenous electrical stimulation. The differentiation of NSC, neurite outgrowth, electrophysiological functions, and gene expression were investigated. Our results showed that electrical stimulation could enhance neurite extension of NSC-derived neurons when cultured on the CNT multilayers. The presentation of electrical stimulation resulted in an almost 2-fold increase in neurite outgrowth relative to the control. We further observed the neurons cultured on CNT multilayers showed morphological diversity after electrical stimulation, and the intercellular relationship seemed to be increased. Multilayer carbon nanotubes combined with exogenous electrical stimulation could promote the growth and differentiation of neural stem cells in vitro and holds great potential in the development of in vivo nerve regeneration.

Disclosures: R. Zhu: None. **S. Ramakrishna:** None. **L. He:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.19/T18

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Synergism between enriched environment and conditioning lesion induces long distance regeneration via NOX2-dependent ROS production

Authors: *F. DE VIRGILIIS[1], T. HUTSON[1], I. PALMISANO[1], C. C. X. SANTOS[2], A. SHAH[2], S. AMACHREE[1], S. DI GIOVANNI[1]
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Abstract: In the last decades, it has been shown that Environmental Enrichment (EE) modulates a variety of biological processes affecting for example the immune and nervous system. For instance, several studies have shown that exposure to EE changes the level and activation of leukocytes in the bloodstream and can attenuate inflammatory pain after nerve injury.

Importantly, in a recent study from our lab, we showed that EE induces a lasting increase in axonal regenerative potential after injury via activity-dependent epigenetic reprogramming (Hutson et al. in revision for Science). Remarkably, the combination of exposure to EE with a sciatic nerve axotomy (SNA), which conditions the spinal cord to axonal regeneration, showed a significant synergistic effect on regenerative potential after spinal cord injury. This suggests that EE and SNA (EE+SNA) act synergistically via complementary molecular mechanisms. RNAseq gene expression analysis of L4-L6 sensory dorsal root ganglia (DRG) following EE+SNA revealed a striking upregulation of NOX2 complex subunit genes, compared to either EE or SNA alone. Therefore, we hypothesised that transcriptional dependent neuronal NOX2 activation plays an important role in axonal regeneration driven by EE+SNA. Here, we indeed show via conditional NOX2 neuronal deletion that NOX2 is required for EE+SNA-dependent regeneration of DRG sensory neurons. Additionally, we show that EE+SNA increases ROS level in DRG via NOX2. Subsequently, we identified STAT3 as putative transcription factor involved in NOX2 subunit genes complex transcription activation. Mechanistically, we show that the overexpression of a constitutively active form of STAT3 induces NOX2 complex subunit gene expression and outgrowth of DRG neurons *in vitro* and that STAT3 occupies NOX2 complex subunit promoters after EE+SNA *in vivo*. Additionally, we show that STAT3 deletion blocks EE+SNA-dependent increase in NOX2 expression and consequently NOX2-dependent ROS level in DRG neurons *in vivo*. Finally, we show that overexpression of a constituvely active NOX2 in DRG neurons induces regeneration and functional recovery after SCI. These data demonstrate that neuronal NOX2 expression is required for EE+SNA-dependent axonal regeneration after SCI via a STAT3 dependent transcriptional mechanism.

Disclosures: T. Hutson: None. **I. Palmisano:** None. **C.C.X. Santos:** None. **A. Shah:** None. **S. Amachree:** None. **S. Di Giovanni:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.20/U1

Topic: C.11. Spinal Cord Injury and Plasticity

Title: PRG3 attenuates CSPG and LPA induced neurite outgrowth inhibition through modulation of RhoA activation

Authors: *C. AGBAEGBU[1], P. YU[2], C. MENCIO[3], S. M. TILVE[4], H. KATAGIRI[5], H. M. GELLER[6]
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Abstract: Plasticity-related gene (PRGs) proteins, are integral membrane proteins characterized by six transmembrane domains and are a subclass of the lipid phosphate phosphatase (LPP) superfamily. A quantitative phosphoproteomic screen designed to determine global phosphorylation changes in neurons in response to chondroitin sulfate proteoglycans (CSPGs), revealed PRG3 as a protein whose phosphorylation state was most altered by exogenous CSPG treatment. Here, we report that PRG3 expression in primary neurons overcomes neurite outgrowth inhibition mediated by CSPGs. Furthermore, PRG3 attenuates lysophosphatidic acid (LPA) induced neurite retraction by modulating RhoA activation resulting in decreased phosphorylation of ERM proteins, myosin light chain II and myosin light chain phosphatase I. Furthermore, we show that PRG3 regulates RhoA activation by increasing RhoA affinity for RhoGDI. In summary, our data indicates that PRG3 protein regulates neuronal response to CSPGs and LPA, both inhibitory molecules to axonal outgrowth, by modulating the RhoA activation and therefore may promote neuronal plasticity. These studies will contribute to a more comprehensive understanding of the signaling mechanisms that regulate neuronal plasticity after CNS injury.

Disclosures: C. Agbaegbu: None. **P. Yu:** None. **C. Mencio:** None. **S.M. Tilve:** None. **H. Katagiri:** None. **H.M. Geller:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.21/U2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Veterans Affairs I01BX007080
The Miami Project
State of Florida
Maryland Stem Cell Research Fund (2018-MSCRFCO-4088)

Title: The effects of a pro-angiogenic, RGD-functionalized, nanofiber composite biomaterial on mesenchymal stem cell-mediated repair of the injured spinal cord

Authors: *A. E. HAGGERTY[1], X. LI[3], Y. NITOBE[1,4], I. MALDONADO-LASUNCION[1,5], K. YAMANE[1,6], M. MARLOW[1], H.-Q. MAO[3], M. OUDEGA[2,7,8,1]
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Abstract: Spinal cord injury (SCI) results in nervous tissue loss and so far untreatable functional impairments. Preclinical studies have demonstrated that a transplant of bone marrow-derived mesenchymal stem cells (MSCs) elicits paracrine effects resulting in anatomical repair and partial functional recovery. The effects of transplanted MSCs on spinal cord repair depend on their survival. MSCs are anchorage-dependent cells that are susceptible to *anoikis*, i.e., programmed cell death due to lack of adherence to a substrate. Thus, MSC transplant-mediated repair may be affected by lack of a binding substrate. It is known that MSCs adhere via integrin receptors to the tripeptide, arginine-glycine-aspartic acid (RGD). We investigated the effects of an RGD-functionalized nanofiber hydrogel composite biomaterial (NHC) on MSC transplant survival and the effects on anatomical repair and functional recovery in a clinically relevant adult rat model of spinal cord contusion. NHC consists of pro-angiogenic hyaluronic acid and axon growth-promoting nanofibers which form an injectable composite gel that closely resembles the physical properties (i.e. stiffness/porosity) of the spinal cord nervous tissue. NHC could target a multitude of factors that influencing MSC transplant survival and tissue remodeling after SCI. Pilot data suggests NHC improves MSC transplant survival and anatomical repair of the damaged spinal cord. This work is supported by the Miami Project, State of Florida, Maryland Stem Cell Research Fund (2018-MSCRFCO-4088), and Department of Veteran Affairs (I01BX007080).

Disclosures: A.E. Haggerty: None. **X. Li:** None. **Y. Nitobe:** None. **I. Maldonado-Lasuncion:** None. **K. Yamane:** None. **M. Marlow:** None. **H. Mao:** None. **M. Oudega:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.22/U3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH grant F30NS093811
NIH grant AR-42309

Title: Fibronectin EDA forms the chronic fibrotic scar after contusive spinal cord injury

Authors: *J. G. COOPER[1], S. JEONG[1], T. L. MCGUIRE[1], S. SHARMA[1], W. WANG[2], S. BHATTACHARYYA[2], J. VARGA, MD[2], J. A. KESSLER[3]
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Abstract: Gliosis and fibrosis after spinal cord injury (SCI) lead to formation of a scar that is an impediment to axonal regeneration. Fibrotic scarring is characterized by the accumulation of fibronectin, collagen, and fibroblasts at the lesion site and is a general feature of the SCI response in many species including humans. The mechanisms regulating fibrotic scarring after

SCI and its effects on axonal elongation and functional recovery are contentious and not well understood. In this study, we examined the effects of eliminating an isoform of fibronectin containing the Extra Domain A domain (FnEDA) on both fibrosis and on functional recovery after contusion SCI using male and female FnEDA-null mice. We demonstrated that FnEDA is expressed acutely following SCI and persists as an important structural component of the chronic fibrotic scar. Eliminating FnEDA did not reduce the acute fibrotic response but markedly diminished chronic fibrotic scarring after SCI. Glial scarring was unchanged after SCI in FnEDA-null mice. We found that FnEDA was important for the long-term stability of the assembled fibronectin matrix during both the subacute and chronic phases of SCI. FnEDA-null mice demonstrated reduced lesion volume and less fibrotic scarring at chronic time points. Motor functional recovery was significantly improved, and there were increased numbers of axons in the lesion site compared to wildtype mice, suggesting that the chronic fibrotic response is detrimental to recovery. Our data provide insight into the mechanisms of fibrosis after SCI and suggest that disruption of fibronectin matrix stability by targeting FnEDA represents a potential therapeutic strategy for promoting recovery after SCI.

Disclosures: J.G. Cooper: None. **S. Jeong:** None. **T.L. McGuire:** None. **S. Sharma:** None. **W. Wang:** None. **S. Bhattacharyya:** None. **J. Varga:** None. **J.A. Kessler:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.23/DP07/U4

Topic: C.11. Spinal Cord Injury and Plasticity

Support: University of Aberdeen
Tenovus Scotland
Scottish Rugby Union

Title: The potential of electric field for promoting neurite guidance in spinal cord injury regeneration strategies

Authors: *A. VARONE, Z. N. MUHAMAT, A. M. RAJNICEK, W. HUANG
Univ. of Aberdeen, Aberdeen, United Kingdom

Abstract: Introduction Spinal cord injury, for which there is no cure, can lead to permanent loss of neurological function. Reasons for failed axon regrowth include poor intrinsic growth capacity of adult CNS neurons, inhibitory chemicals and physical barriers formed post injury. Electric field (EF) stimulation is a promising strategy for spinal repair because it promotes directional neurite growth in cultured non-mammalian or embryonic neurons. Here, we investigated the effects of EF exposure on postnatal rat cortical neurons and organotypic spinal cord slices to

further explore its potential for spinal repair. **Methods**Cortices and spinal cords of Sprague Dawley rats at postnatal days 0-3 were used to culture cortical neurons and organotypic spinal cord slices. Neurons were cultured directly in the EF migration chamber for 48h before applying EFs ranging from 50 to 350mV/mm for 3-6h. To examine if an EF could overcome the effects of inhibitory molecules present post-spinal injury, 10µg/ml Chondroitin Sulphate Proteoglycan-6 (CSPG6) was added to the culture medium during EF exposure. Spinal cord slices were prepared at 350µm thickness and lesioned with surgical blades to produce a 700µm lesion gap. Four days after lesion, slices were transferred to the migration chamber and 50mV/mm EF was applied for 24h. **Results**Cortical neurons showed an increase in the proportion of neurites facing the anode and facing perpendicular to the EF vector compared to the random growth of controls without an EF. This bias increased as the EF strength increased, with 220mV/mm being optimal. However, EF stimulation did not increase neurite length compared to no-EF conditions at any field strength. Moreover, the EF stimulation overcame the inhibitory effects of CSPG6 on growth of anode facing cortical cell neurites. In spinal cord slice cultures, there was a substantial increase in the alignment of re-growing axons when an EF was applied at 50mV/mm for 24h compared to the non-EF condition. Alignment was abolished when an Epac antagonist or Rho agonist were present in the culture medium.**Summary**This is the first demonstration that EF stimulation promotes directional growth of cultured postnatal rat cortical neurons and that an EF aligns growth of re-growing axons in an ex vivo model of spinal injury. Future studies will investigate its *in vivo* efficacy alone and in combinational with other spinal repair strategies.

Disclosures: A. Varone: None. **Z.N. Muhamat:** None. **A.M. Rajnicek:** None. **W. Huang:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.24/U5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH grant NS16446 to JHK
Craig H. Neilsen Foundation to JLR, JHK

Title: Transcriptome profiles in somatosensory system of monkeys after unilateral dorsal column spinal cord injury

Authors: *J. L. REED[1], H.-X. QI[1], C.-C. LIAO[1], T. A. HACKETT[2], J. H. KAAS[1]
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Abstract: In our primate model of recovery after sensory loss, we use a selective, unilateral lesion of the dorsal column somatosensory pathway for the arm and hand in the cervical spinal cord of monkeys. This deprives the brainstem cuneate nucleus (Cu) of activation, in turn depriving the hand representations of the thalamic ventroposterior lateral nucleus (VPL) and cortical area 3b. We propose that studies of gene expression in neurons and glia throughout the nervous system over selected recovery periods could advance our understanding of cellular mechanisms of recovery from injury in the somatosensory system. Similar studies have focused on the spinal cord and motor-related cortex. In this exploratory study, we sampled tissue from 4 major somatosensory stations in 2 adult macaque monkeys (*Macaca mulatta*): 1 female that received a unilateral dorsal column lesion (DCL) at C4, 2 weeks before tissue collection; and 1 male without a lesion. The 4 somatosensory targets were: dorsal horn of C3, Cu, VPL, area 3b. Samples were prepared for RNA sequencing (RNAseq) from both sides of the DCL case ('intact' and 'lesion') and from the complementary tissue of the control case. Differential gene expression ($\log_2$ fold change, FC) was examined in each tissue type to determine gene candidates with changes in expression ($|FC| > 1$, $p < 0.05$ for at least 1 comparison). Overall, 770 genes were upregulated and 452 downregulated after DCL. The majority of genes with altered expression were found in the spinal cord (695 genes in DCL-lesion vs control), with fewer identified in Cu (261), VPL (114), and 3b (138). We report expected changes and new findings. Growth associated protein 43, a marker of regeneration, had 1.3 FC in Cu for DCL-lesion compared to control, consistent with sprouting axon terminals. Serine proteinase inhibitor family A member 3, associated with neurodegeneration, was increased with 6 FC in Cu, 2.3 FC in VPL, and 1.1 FC in 3b for DCL-lesion versus control. Tenascin-C, linked to axon regeneration, was found in low levels but upregulated with 1.9 FC in Cu. We also confirmed the expression of neuronal and non-neuronal cell markers in our samples. For example, myelin basic protein (oligodendrocytes) expression was reduced in both sides of DCL spinal cord compared to the control case. Aquaporin 4 (astrocytes) expression differed by tissue type, but was not altered by DCL. Expression of microtubule associated protein 2 (neurons) and neutrophil cytolic factor 1 (microglia) did not differ across samples. In conclusion, differences in tissue expression profiles provide a basis to identify candidates for further study, including somatosensory targets that have not been previously investigated.

Disclosures: J.L. Reed: None. **H. Qi:** None. **C. Liao:** None. **T.A. Hackett:** None. **J.H. Kaas:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.25/U6

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Regulation of astrocyte polarity after spinal cord injury

Authors: *B. FENG[1], E. R. HOLLIS[2], Y. ZOU[3]
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Abstract: In response to damage from spinal cord injury, astrocytes become reactivated and start to proliferate. The morphology of astrocytes also undergoes dramatic changes. One of the striking changes is that the processes of astrocytes become polarized and oriented towards the lesion site in a highly organized fashion to form the glial scar. Reactive astroglial scars are thought to be both beneficial and inhibitory. How astrocyte reactivation is initiated and what cellular signaling pathways are involved in astrocyte polarization is unknown. As a major branch of non-canonical Wnt pathways, planar cell polarity (PCP) signaling is one of the evolutionally conserved mechanisms for directing cellular and tissue polarity. Our laboratory pioneered the finding that PCP signaling mediates growth cone turning in response to Wnt gradients. Here we found that 1) PCP components are abundantly expressed in astrocytes in the brain and spinal cord; 2) Conditional knockout of PCP component Celsr3 specifically in astrocytes limits astrocyte activation and polarity after spinal cord injury. Therefore, we propose that the PCP signaling may control astrocyte polarization in glial scar formation.

Disclosures: B. Feng: None. **E.R. Hollis:** None. **Y. Zou:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.26/U7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NS07260601A1
Abbott Diagnostics
Neilsen Foundation
Brain Injury Research Center

Title: Astroglial signatures in neurotrauma - From injury-defined biomarkers to astrogliosis

Authors: *I. B. WANNER[1], S. SHEN[2], J. HALFORD[1], J. E. BURDA[3], M. V. SOFRONIEW[3], J. LOO[2]
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Abstract: Astrocytes are known for neurotrauma biomarkers and for reactive astrogliosis with scar formation; yet these have distinct pathophysiologies. To differentiate these injury stages, we

deciphered proteomic astrocyte-release signatures using a unique trauma culture model. Immature mouse and human astrocytes were purified, differentiated in serum-free medium and injured using abrupt pressure-pulse stretching of deformable membranes (Wanner, Meth Mol Biol 2012). Trauma-released proteins were quantified at different postinjury times using 2D gel spot measurements (Sondej, Sample Prep Biol Mass Spec 2011) or ratios of tandem isobaric mass tags. Dye-uptake and time-lapse studies quantified acute traumatic membrane wounding (mechanoporation) and delayed cell death. Release profiles contained cytosolic and vesicular proteins. Metabolic proteins, specifically related to monosaccharaide biosynthesis, were highly enriched at 30 min-5 hours postinjury compared to respective cellular reference proteomes (Levine, GLIA 2016; Fisher's exact multiple test, false discovery rate-corrected). Protein release signatures at 12-48 hours were significantly enriched for cytoskeleton and associated proteins. Acute-released proteins had a lower average molecular weight than delayed-released ones. Different cellular injury stages showed distinct proteomic signatures of acute membrane leak versus secondary lysis. Astrocyte trauma-release was substantially different from expression changes in reactive astrocytes two weeks after mouse crush spinal cord injury (Anderson, Nature 2016). Proteins involved in carbohydrate metabolism, glycolysis and energy generation dominated in acute trauma-release versus inflammatory proteins in sustained reactivity. Thus, acute astrocyte trauma is accompanied by protein depletion affecting astrocyte energy capacity and sub-acute structural maintenance, while reactive gliosis gene expression shows an inflammatory response and modulation of the extracellular environment among other things. Upon selecting for astrocyte enrichment (Cahoy, JNeurosci 2008; Zhang, Neuron 2016) and presence in cerebrospinal fluid (CSF) from traumatic brain injury (TBI) patients, we identified novel neurotrauma-specific biomarkers aldolase C (ALDOC) and brain lipid binding protein (BLBP) that associated significantly with cell wounding. GFAP fragments, in contrast, associated exclusively with astroglial death (Halford, JCBFM 2017). CSF and blood levels of the astrocyte injury-defined biomarkers capture the spectrum of mild-severe TBI and document their translational use for patient diagnosis and outcome prediction.

Disclosures: S. Shen: None. **J. Halford:** None. **J.E. Burda:** None. **M.V. Sofroniew:** None. **J. Loo:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.27/U8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant NS067092 (ARF)
NIH Grant NS069537 (ARF)
NIH Grant NS088475 (ARF)

Wings for Life Spinal Cord Research Foundation WFLUS013/13 (KM)
Wings for Life Spinal Cord Research Foundation WFLUS008/12, WFLUS 006/14 (ARF)
Craig H. Neilsen Foundation 224308 (ARF)
Craig H. Neilsen Foundation 313739 (JH)

Title: Early limb unloading elicits long-term motor deficits involving motorneuron hyperexcitability associated with persistent alterations in glutamatergic synaptic plasticity in spinal cord injury

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Abstract: Abnormal sensory afferent feedback from the lower extremities after spinal cord injury (SCI) has potential to induce neuronal dysfunction that contributes to long-term motor deficits. Here, we investigated the impact of aberrant afferent input after SCI using hindlimb unloading early after mild contusive thoracic injury in adult female SD rats (T9; 50 kdyn IH). Three days post-injury, subjects were randomized to two experimental groups: 1) hindlimb unloading (HU) by tail suspension for 2 weeks followed by normal-loading for 6 weeks, or 2) normal-loading control for 8 weeks. Outcome assessments included: i) BBB open-field scoring and kinematic gait analysis; ii) electrophysiological H-reflex testing; iii) biomolecular and automated high-resolution confocal microscopy analysis of plasticity-related changes in lumbar ventral horn motor neurons. The results demonstrated that HU worsened impairment of hindlimb coordination after unloading (BBB = 12 for HU vs 17 for normal-loading controls). H-reflex testing of hindlimb muscles at 8 weeks showed that HU induced chronic hyper-excitability of spinal reflex circuitry. Quantitative biochemistry of ventral spinal synaptoneurosomes revealed a chronic increase in AMPA receptor (AMPAR) subunit GluA1 serine 831 phosphorylation, while quantitative immunohistochemistry revealed a chronic increase in GluA1 at synaptic sites on spinal motoneurons, suggesting that HU induced maladaptive plasticity in the spinal cord. Data-driven multidimensional analysis identified strong association between AMPAR over-drive on motorneurons and time-dependent motor recovery, chronic motorneuron hyper-excitability after HU. Our findings suggest that early unloading-induced aberrant afferent input after SCI can worsen maladaptive plasticity undermining long-term recovery, and provide a mechanistic rationale for early post-SCI intervention with weight-bearing training for precision rehabilitation.

Disclosures: K. Morioka: None. **T. Tazoe:** None. **J. Huie:** None. **J. Haefeli:** None. **C.A. Almeida:** None. **J.A. Sacramento:** None. **J.C. Bresnahan:** None. **M.S. Beattie:** None. **S. Tanaka:** None. **T. Ogata:** None. **A.R. Ferguson:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.28/U9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: HMRF 05163296

Title: Shifting macrophage polarisation to the anti-inflammatory state in the injured CNS

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Abstract: The microenvironment of the injured spinal cord activates macrophages/microglia to acquire pro-inflammatory M1 polarization with but transient and few acquiring anti-inflammatory M2 polarization. Following chondroitinase ABC (ChABC) treatment of the injured cord in a rat model, we however found lowered proportion of pro-inflammatory macrophages/microglia. We therefore hypothesized that chondroitin sulfate (CS) proteoglycans upregulated in the injured environment influence the balance between M1 and M2 polarization states. To test this, naïve macrophages were derived from bone marrow samples collected from adult rats and then directed to the pro-inflammatory state in vitro with lipopolysaccharide supplementation in the medium. Treatment of the cultures with ChABC versus vehicle control revealed lowered expression of the M1 markers, inducible nitric oxide synthase and CD86, contrasting elevated expression of the M2 markers, arginase-1, CCL22 and IL10 (n = 4). With a rat model of acute spinal cord injury, ChABC treatment of the injured cord environment increased levels of the IL10 and TGF-β transcripts as compared to the vehicle control (n = 3). To test if M2 inducers such as IL10 are entrapped in pericellular CS of the M1 cells, proteins in the pericellular CS domain were biotinylated. After streptavidin-mediated pull-down, biotinylated IL10 was detected in Western blots (n = 2), suggesting pericellular CS of M1 cells as the sink for M2 inducers. The results add impetus to the development of strategies for timely shift to M2 polarization as a therapeutic goal. (This work is supported by HMRF 05163296)

Disclosures: D.K. Shum: None. **K. Tam:** None. **Y. Chan:** None.

Poster

213. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 213.29/U10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS R01NS081040
NINDS R56NS081040
Buoniconti Fund to Cure Paralysis
Miami Project to Cure Paralysis

Title: Role of macrophage lipid metabolism in inflammation after spinal cord injury

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Abstract: After spinal cord injury (SCI), a lipid-rich environment forms at the lesion site due to accumulation of myelin and cellular debris, inducing the formation of lipid-laden “foam cells” from infiltrating macrophages. This state of excessive lipid metabolism may contribute to the inflammatory milieu at the injury site. We sought to elucidate the mechanisms of foamy macrophage formation, their interactions with other cells at the injury site, and their contribution to the injury site pathology. Identifying and manipulating the physiological processes governing foamy macrophage dynamics in vivo and in vitro may address some of the factors that prevent tissue healing, providing a therapeutic target to promote neural regeneration and functional recovery after SCI.

Disclosures: J.S. Choi: None. **C.B. Ryan:** None. **L.M. Milich:** None. **J.K. Lee:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.01/U11

Topic: D.02. Somatosensation

Title: Modulation of initiation of swallows evoked by continuous laryngeal TRPV1 activation in anesthetized rats

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Abstract: Background: Patients suffering from chronic gastroesophageal reflux disease have difficulty in swallowing. Those symptoms may be caused by following long-term stimulation with gastric acid including hydrochloric acid (HCl) which activates transient receptor potential vanilloid 1 (TRPV1). The aim of this study was to investigate effect of continuous laryngeal TRPV1 activation on swallowing initiation.
Material and Methods: Experiments were carried out on Sprague-Dawley male rats anesthetized with urethane. To investigate the involvement of TRPV1 on swallowing initiation evoked by HCl (0.1 N, 3 μl) and capsaicin (10^{-5} M, 3 μl) chemical stimulation and airflow (40 ml/sec, 30 sec) mechanical stimulation to the larynx, topical administration of TRPV1 blocker, SB366791 (10^{-2} M, 3 μl) or DMSO (vehicle of SB366791) was applied to the laryngeal mucosa. In another experiment, the number of swallows was counted during the stimulation to laryngeal mucosa with HCl, capsaicin or 0.1% ethanol (vehicle of capsaicin) at a rate of 0.5 μl/sec over 60 min. The number of laryngeal airflow-evoked swallows was also measured following 60 min chemical stimulation. Finally, we investigated the effect of capsaicin stimulation on the threshold of the superior laryngeal nerve (SLN) -evoked swallow. Minimum amplitude of electrical SLN stimulation (6-140 μA, 10 sec, 30 Hz, 0.2 msec pulse duration) to evoke at least one swallow over 10 sec was defined as the swallowing threshold. Changes in the swallowing threshold value was evaluated during 60-min capsaicin stimulation every 10 min up to 60 min by comparing the values among the time points.
Results: TRPV1 blocker drastically reduced the number of swallows evoked by capsaicin and HCl stimulation, but did not affect that evoked by airflow stimulation. The number of swallows during continuous HCl or capsaicin stimulation decreased in a time-dependent manner. The number of airflow-evoked swallows was significantly lower following HCl or capsaicin stimulation compared with that following vehicle stimulation. The swallowing threshold of SLN stimulation was not significantly changed during 60-min capsaicin stimulation.
Discussion: These results suggest that the modulation of excitability in peripheral nervous system is involved in swallowing reduction by continuous laryngeal TRPV1 activation. We speculate that long-lasting TRPV1 activation may cause the swallowing impairment in GERD patients.

Disclosures: M. Yoshihara: None. **T. Suzuki:** None. **K. Nagoya:** None. **T. Tsujimura:** None. **M. Inoue:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.02/U12

Topic: D.02. Somatosensation

Support: NIH Grant DE023846
Neurosurgery Pain Research Institute at Johns Hopkins

Title: Phosphorylation of TRPV1 S801 contributes to inflammatory thermal hyperalgesia and spontaneous pain in mice

Authors: J. JOSEPH[1], L. QU[2], S. WANG[1], M. KIM[1], D. BENNETT[2], M. J. CATERINA[2], *M.-K. CHUNG[1]
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Abstract: Transient receptor potential vanilloid subtype 1 (TRPV1) is a nociceptive non-selective cationic channel that is activated by polymodal stimuli such as capsaicin, protons, and noxious heat. Despite clear contributions of TRPV1 to pathological pain in animal models, efforts to develop analgesic therapies based on global inhibition of this channel have been hampered by sensory and thermoregulatory side effects. One potential solution to this problem might be to develop strategies that selectively target TRPV1 functions associated with pathological pain, without interfering with its physiological roles. Under inflammatory conditions, many inflammatory mediators activate protein kinases such as PKA and PKC that phosphorylate TRPV1 at one or more residues and thereby enhance TRPV1 function, with consequent increases in nociceptor excitability. However, the causal relationships between specific TRPV1 phosphorylation events and pathological pain remain relatively unexplored. To directly investigate the roles of one specific TRPV1 phosphorylation event in vivo, we used CRISPR/Cas9 genome editing in mice to genetically alter a major TRPV1 PKC phosphorylation site, S801, to alanine. The sensory ganglion TRPV1 expression pattern in S801A knock-in (KI) mice was comparable to that in wildtype (WT) controls. However, sensitization of capsaicin-mediated currents following the activation of PKC was substantially impaired in sensory neurons derived from KI mice. Basal thermal and mechanical sensitivities of KI mice were identical to those of WT. However, complete Freund's adjuvant-induced thermal hyperalgesia was partially attenuated in KI mice. Ongoing pain from inflamed masseter muscle was also reduced in KI mice, and was further inhibited by the TRPV1 antagonist AMG9810. These results suggest that PKC-mediated phosphorylation of TRPV1 S801 partially accounts for inflammation-mediated thermal hyperalgesia and spontaneous pain in vivo. These results suggest that interference with TRPV1 S801 phosphorylation represents one potential way to attenuate pathological pain in the context of inflammation or injury that might spare basal sensitivity and reduce side effects associated with more general TRPV1 inhibition.

Disclosures: J. Joseph: None. **L. Qu:** None. **S. Wang:** None. **M. Kim:** None. **D. Bennett:** None. **M.J. Caterina:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Michael J. Caterina - inventor on a patent on the use of products related to TRPV1, which is licensed through UCSF and Merck and may be eligible royalties in association with that relationship. This. **M. Chung:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.03/V1

Topic: D.02. Somatosensation

Title: TRPA1 receptors are involved in the hypoxia-induced surfacing response of goldfish

Authors: *M. KASAI, S. HOSOSHIMA, A. KAWABATA, R. NAKASHIMA, T. IWAO, Y. HORINOUCHI, M. KIMURA, Y. YOKOGAWA
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Abstract: In mammals, transient receptor potential cation channel subfamily A member 1 (TRPA1) mediates the O2-sensing mechanisms for hyperoxia and hypoxia and is known to be activated by noxious cold and menthol. The present study investigates whether TRPA1 receptors are involved in hypoxic responses in goldfish. For acclimation, 5-8 goldfish were housed in a tank (20 × 25 × 40 cm, height × width × length) wherein the dissolved oxygen level (DO) was 4.3 mg/L. To record the surfacing responses to hypoxia, the fish were individually housed recorded for individual fish in dissolved oxygen in an experimental tank (20 × 24.5 × 5.5 cm) with a DO of 0.5, 1.5, 2.4, 3.4 and 4.3 mg/L. The DO levels were reduced by passing nitrogen and were monitored using a DO meter. The surfacing response was defined as the first instance of the fish's nose reaching the surface, and was quantified as numbers of air gasps for 1 min. Compared with control conditions (DO = 4.3 mg/L), exposure to heavy hypoxia (DO = 0.5, 1.5 mg/L) shortened the surfacing response latency (i.e., the time taken to move from the bottom of the tank to the water surface) and increased the number of air gasps on the surface, whereas mild hypoxia (DO = 2.4, 3.4 mg/L) did not produce any such responses. Pre-exposure to the TRPA1 receptor antagonist, HC-030031 inhibited hypoxic responses in a dose-dependent manner, when DO=0.5. A lower concentration (0.007 μM) of the TRPA1 receptors agonist allyl isothiocyanate (AITC) produced a hypoxic response and a decreased respiratory rate, both of which were inhibited by the TRPA1 receptor antagonist in a dose-dependent manner. Higher concentrations of AITC (0.07-0.1 μM) increased the respiratory rate, whereas concentration greater than 0.3 μM decreased the respiratory rate and produced no hypoxic response. These results demonstrate that the TRPA1 receptor is involved O2-sensing mechanisms of hypoxia in goldfish.

Disclosures: M. Kasai: None. **S. Hososhima:** None. **A. Kawabata:** None. **R. Nakashima:** None. **T. Iwao:** None. **Y. Horinouchi:** None. **M. Kimura:** None. **Y. Yokogawa:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.04/V2

Topic: D.02. Somatosensation

Support: NCSU startup fund
Postdoctoral fellowship by The Uehara Memorial Foundation

Title: The role of sphingosine-1-phosphate in the peripheral nervous system

Authors: *H. KITTAKA, J. DEBRECHT, S. K. MISHRA
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Abstract: Somatosensation such as pain, itch, touch, and temperature, are essential to detect environmental stimuli to escape, communicate and adapt. These stimuli can be detected by primary sensory neurons whose nerve endings are located in the skin. Although physical, chemical and biological stimulants were well investigated, the mechanisms of endogenous stimulants to the primary sensory neurons, especially lipids, are still largely unknown. In this study, we focus on one of the endogenous lipids, sphingosine-1-phosphate (S1P) and investigate the physiological roles of S1P in pain and itch.
First, we examined whether S1P directly induces neuronal responses in primary cultured mouse dorsal root ganglion (DRG) neurons, primary sensory neurons, by using a calcium imaging method. S1P application to DRG neurons increased intracellular calcium concentrations of DRG neurons. In order to distinguish whether the increased cytosolic calcium comes from extracellular space or from cytosolic organelles such as endoplasmic reticulum, we assessed the effect of calcium removal on the responses in DRG neurons and found that the increased cytosolic calcium concentration derives from the extracellular side of the DRG neurons. Transient receptor vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) are non-selective calcium-permeable cation channels, which are well known to be involved in pain and itch. We asked whether these two ion-channels are involved in S1P-induced responses in DRG neurons by using the antagonists and knockout DRG neurons lacking the function of each ion channel. The responding neurons to S1P are reduced by both the antagonists and in both the knockout mice DRG neurons, suggesting that TRPV1 and TRPA1 are involved in S1P-induced DRG responses. Next, we examined the effect of S1P on pain and itch sensations. We injected S1P into the nape of the neck to ask whether it induces itch and into the hind paw to measure acute pain and pain induced by heat, cold and mechanical stimuli. S1P induced these pain and itch behaviors in mice and experiments using TRPV1 and TRPA1 knockout mice indicated the involvement of TRPV1. In summary, our results provide insights into the S1P-induced sensory neuron responses through TRPV1 and TRPA1 and the S1P-induced pain and itch behaviors, depending on TRPV1.

Disclosures: H. Kittaka: None. **J. Debrecht:** None. **S.K. Mishra:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.05/V3

Topic: D.02. Somatosensation

Support: Ministry of Economy and Competitiveness SAF2009-11175
Ministry of Economy and Competitiveness PI12/0058
Ministry of Economy and Competitiveness SAF2010-14990-R
Ministry of Economy and Competitiveness SAF2016-77233-R
Generalitat Valenciana GRISOLIA/2008/025
MINECO BES-2011-047063
Human Frontier Science Program Long-Term Award LT000442/2012

Title: The role of the temperature sensor TRPM8 in the thermoregulatory and metabolic adjustments to mild cold ambient temperatures

Authors: *A. REIMÚNDEZ DUBRA[1], C. FERNÁNDEZ-PEÑA[2], G. GARCÍA[1], C. IGLESIAS[1], R. FERNÁNDEZ[1], P. ORDÁS[2], R. GALLEGO[3], J. L. PARDO-VAZQUEZ[1], V. ARCE[1], F. VIANA[2], R. SEÑARÍS[1]
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Abstract: The maintenance of homeothermy requires the coupling between thermosensation, thermoregulation and energy homeostasis. Ambient temperature influences energy homeostasis by regulating energy intake, thermogenesis and energy expenditure as part of the thermoregulatory responses. In this study we evaluated the putative role of TRPM8, the main cold thermoreceptor, in the interplay between these processes.
We used three types of mices: 1/ *Trpm8*$^{-/-}$ mice, generated by the laboratory of David Julius and obtained from The Jackson Laboratories (stock #008198). 2/ A BAC transgenic mouse line expressing the diphteria toxin receptor fused with GFP under TRPM8 regulatory sequences (*Trpm8DTR*$^{+}$), generated in the laboratory of Mark Hoon (NIH, Bethesda). 3/ For identification of TRPM8-sensory fibers we worked with a transgenic mouse line expressing eYFP under the TRPM8 promoter (*Trpm8-eYFP*$^{+}$*)* from the laboratory of Félix Viana (INA, CSIC, Alicante). Animals were exposed to different environmental temperatures in fed and fasting conditions. Core body temperature (Tc) and motor activity were determined using implantable radiotelemetric probes. The main thermoregulatory responses were evaluated: BAT functionality, tail vasoconstriction and BAT temperature by infrared thermography and food

intake, as well as non-thermoregulatory avoidance behaviors (cold-induced jumps). Finally, we studied the role of TRPM8 in the regulation of energy balance and homeostasis. We determined body weight growth, fat and lean mass, as well as hormonal and metabolic parameters in *Trpm8*$^{-/-}$ mice. We also examined TRPM8 expression and the presence of TRPM8 fiber innervation in metabolic organs and in the tail by RT-PCR and GFP immunofluorescence.
We demonstrated that TRPM8-deficient mice display a defective thermoregulation with an increase in tail heat loss, lower core body temperature and attenuated cold-induced jump escape behaviors. The impact on Tc was greater during fasting. Notably, we found TRPM8-sensory fibers surrounding the main tail vessels and innervating the portal vein. Finally, we showed that the absence of TRPM8 induced the development of late-onset obesity and metabolic alterations in mice raised under mild cold ambient temperature. All these findings highlight the relevant role of this ion channel in tail vasomotor regulation, thermoregulation and the coupling of energy homeostasis to thermoregulation.

Disclosures: A. Reimúndez Dubra: None. **C. Fernández-Peña:** None. **G. García:** None. **C. Iglesias:** None. **R. Fernández:** None. **P. Ordás:** None. **R. Gallego:** None. **J.L. Pardo-Vazquez:** None. **V. Arce:** None. **F. Viana:** None. **R. Señarís:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.06/V4

Topic: D.02. Somatosensation

Support: MINECO Grant SAF2016-77233-R
La Caixa-Severo Ochoa-2015

Title: Molecular determinants of cold-evoked responses in mouse visceral and somatosensory neurons

Authors: K. GERS-BARLAG, *F. VIANA
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Abstract: Members of the family of transient receptor potential (TRP) channels are known for being crucial molecular sensors for chemical, mechanical and thermal stimuli. Amongst them, TRP melastatin 8 (TRPM8) has been shown to be a sensor for mild cold and TRP ankyrin 1 (TRPA1) has been debated to be a sensor for noxious cold. Both channels are expressed in various tissues, including non-overlapping subpopulations of peripheral sensory neurons. Here they sense decreases in temperature, giving rise to neural activity that is processed for discriminative and thermoregulatory behaviors. However, responses to cold stimuli are also found in visceral neurons innervating internal organs, where their function as cold sensors may

not be as obvious as in somatosensory neurons. The aim of this study was to investigate and characterize the responses to cold temperature in visceral neurons and compare them to those found in somatosensory neurons. For this, we isolated neurons from visceral nodose ganglia (NG) and sensory trigeminal ganglia (TG) from 6-8 weeks old male wild type or genetically modified mice. Neurons were enzymatically and mechanically dissociated, cultured and used for calcium imaging experiments within 24 hours. Neurons were incubated with the calcium indicator dye Fura2AM and excited at 340 and 380 nm wavelengths to measure intracellular calcium levels. Cold ramps from 33 to 12 ºC were applied to cells in the presence or absence of TRP channel antagonists followed by various other TRP channel agonists. In visceral neurons from wild type mice ~ 24 % of neurons responded to a decrease in temperature and ~ 70 % out of these cold responders were also sensitive to the selective TRPA1 agonist allyl isothiocyanate (AITC). The mean temperature threshold of responders to cold was 18 ± 0.3 ºC (n=152). In neurons from TRPA1 KO mice, only ~ 5 % of cells responded to cold, whereas neurons from TRPM8 KO mice did not show a difference compared to wild type. This shows that TRPA1 channels are the main mediator of cold responses in visceral vagal neurons. In TG neurons, we also found ~ 20 % of neurons responding to cold; however, only ~ 45 % of these neurons responded also to AITC. Furthermore, there were two populations of cold responders: TRPM8 expressing neurons - identified with a GFP transgenic mouse - with a mean temperature threshold of 19 ± 0.8 ºC (n=34) and non-TRPM8 expressing neurons with a threshold of 15 ± 0.8 ºC (n=32). This indicates that in TG somatosensory neurons both TRPA1 and TRPM8 are required for transducing responses to cold stimuli.

Disclosures: K. Gers-Barlag: None. **F. Viana:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.07/V5

Topic: D.02. Somatosensation

Title: Over-activation of TRPV3 channels suppresses acute chemical itch

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Abstract: Transient receptor potential (TRP) channels are a group of ion channels located in numerous cell types throughout the body. TRPV3 is a member of the TRP Vanilloid subfamily. This non-selective cation channel is highly expressed in skin keratinocytes and is implicated in skin physiology and pathophysiology, thermal sensation and pain. Gain-of-function mutation of TRPV3 in humans causes Olmsted syndrome, a rare genetic disorder accompanied with severe itching, peripheral pain, and palmo-plantar hyperkeratosis. In this study, over-activation of

TRPV3 channels using gain-of-function TRPV3 mutant mice, was expected to produce increased intracellular calcium influx in TRPV3-expressing keratinocytes, resulting in increased pruritus. Unexpectedly, intradermal administration of a variety of chemical pruritrogens in transgenic mice produced significant decreases in scratching behaviors compared to wild type littermates. Additionally, transgenic mice displayed deficits in several measures of acute but not chronic mechanical pain. Our data indicate that over-activation of TRPV3 is not required to sensitize itch, but instead suppresses itch. Additional genetic modifiers or environmental factors may result in itch sensitization in Olmsted syndrome patients.

Disclosures: L.R. Horwitz: None. **M. Fatima:** None. **X. Cheng:** None. **H. Xu:** None. **B. Duan:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.08/V6

Topic: D.02. Somatosensation

Support: NIH grant DE17794
NIH grant DE22743
NIH grant NS87988

Title: Extracellular miRNA-711 induces acute itch via TRPA1 and contributes to chronic itch in a mouse model of cutaneous T cell lymphoma

Authors: *Q. HAN[1], R.-R. JI[1,2]
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Abstract: Increasing evidence suggests that extracellular miRNAs may serve as biomarkers for diseases such as cancer and chronic pain, but the physiological relevance of extracellular miRNAs is unclear. Our previous study showed that intraplantar application of miR-let-7b elicits spontaneous pain via activation of TLR7 and TRPA1 (Park et al., 2014). It is unclear if extracellular miRNAs can also evoke itch. Here we show that intradermal injection of miR-711 on the cheek induces scratching but not wiping. The miR-711-evoked pruritus requires TRPA1 but not TLR7. This pruritus is dose-dependent, and at higher concentrations, miR-711 evoked stronger pruritus and skin lesion but not pain, suggesting that miR-711 is a potent pruritogen. In contrast, intradermal AITC evoked both itch and pain at low concentrations but only pain at high concentration.
We also examined the role of miR-711 in chronic itch by developing a new mouse model of chronic itch that mimics human disease of cutaneous T cell lymphoma (CTCL) in which patients suffer from chronic itch. Intradermal inoculation of human Myla cells induces lymphoma

immune-deficient mice, which is associated with chronic itch lasting for more than 2 months. Mouse CTCL also resulted in increased serum levels of miR-711, secreted from cancer cells. In addition to miR-711, miR-21, miR-155, miR-326 are also upregulated in skin biopsies from the CTCL patients and serum of CTCL mice. However, intradermal injection of miR-21, miR-155, and miR-326 failed to induce pruritus, suggesting that specific sequences are required for miRNA to evoke itch. Strikingly, lymphoma-induced chronic itch is suppressed by intra-tumoral injection of a specific miR-711 inhibitor and TRPA1 antagonists. Furthermore, a blocking peptide that can specifically disrupt the miR-711/TRPA1 interaction also suppressed chronic itch after CTCL.
Our findings demonstrated an unconventional role of extracellular and naked miRNAs as novel itch mediators. Targeting extracellular miR-711, TRPA1, or miR-711/TRPA1 interaction may lead to new therapies for chronic itch associated with CTCL.
This study is supported by NIH R01 grants DE17794, DE22743, and NS87988.
References: Park, C.K., Xu, Z.Z., Berta, T. et al. (2014). Extracellular MicroRNAs Activate Nociceptor Neurons to Elicit Pain via TLR7 and TRPA1. Neuron 82, 47-54.

Disclosures: Q. Han: None. **R. Ji:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.09/V7

Topic: D.03. Somatosensation: Pain

Support: NIH Grant 1R01GM124055-01

Title: The role of transient receptor potential ankyrin 1 (TRPA1) in the development of muscle nociceptor sensitization caused by surgical injury

Authors: *D. SUGIYAMA[1], S. KANG[1], A. L. KEYES[2], T. J. BRENNAN[1,2]
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Abstract: We have previously shown that incised deep muscle tissue rather than skin has a central role in the genesis of non-evoked pain behavior after plantar incision in rats. We also have shown that transient receptor potential ankyrin 1 (TRPA1) ligands like hydrogen peroxide (H_2O_2) are produced in the wound, and that injection of H_2O_2 into muscle, but not into skin, causes significant nociceptive behavior via TRPA1. These findings suggest the contribution of TRPA1 to nociception caused by deep tissue incision. In this study, we evaluated the role of TRPA1 in the development of muscle nociceptor sensitization caused by surgical injury. Tissue levels of TRPA1 ligand 4-HNE measured by ELISA were greater in the incised gastrocnemius muscle compared to non-incised muscle on postoperative day 0 (76.9 ± 46.4

μg/mg of protein, p = 0.0070) and day 1 (66.5 ± 68.8 μg/mg of protein, p = 0.0314). During Fura-2 Ca^{2+}-imaging, H_2O_2 (100 μM - 5 mM) and 4-HNE (10 - 100 μM), respectively, elicited Ca^{2+} transients in 15 - 25% and 10 - 24% of cultured L3-5 dorsal root ganglion (DRG) neurons of Sprague-Dawley rats. Ca^{2+} transients evoked by H_2O_2 and 4-HNE were inhibited by TRPA1 antagonists HC-030031 (50 - 100 μM) or AP-18 (50 - 100 μM). No Ca^{2+} influx was elicited by 4-HNE or H_2O_2 in TRPA1 knockout mice. Next, we studied Ca^{2+} influx induced by H_2O_2 or 4-HNE in DRG neurons innervating skin vs. muscle, non-incised vs. incised muscle, and non-incised vs. incised skin. Muscle DRG neurons showed greater response to 1-mM H_2O_2 than skin neurons [15/110 (13.6%) vs. 6/108 (5.6%), p = 0.0432]. The response amplitude of muscle DRG neurons was also greater than skin neurons in the presence of 50-μM (196 ± 56 vs. 131 ± 10% above the baseline, p = 0.0003) and 100-μM 4-HNE (389 ± 143 vs. 246 ± 113%, p = 0.0012). Compared to DRG neurons innervating non-incised muscle, more neurons innervating incised muscle responded to 100-μM H_2O_2 (8.8 vs. 21.0%, p = 0.0075), 1-mM H_2O_2 (13.6 vs. 29.2%, p = 0.0051), 50-μM 4-HNE (13.1 vs. 24.4%, p = 0.0228), and 100-μM 4-HNE (21.0 vs. 32.7%, p = 0.0387). The response amplitude of DRG neurons innervating incised muscle was greater than those innervating non-incised muscle in the presence of 50-μM (363 ± 187 vs. 196 ± 56% above baseline, p = 0.0011) and 100-μM 4-HNE (514 ± 150 vs. 389 ± 143%, p = 0.0012). On the other hand, the prevalence of responders to these compounds was not different between DRG neurons innervating non-incised vs. incised skin.
Our data suggest that endogenous TRPA1 agonists increase in the wound tissue, and they elicit greater Ca^{2+} influx in DRG neurons especially those innervating deep muscle tissue after incision. Blockade of TRPA1 in deep tissue may provide an effective therapy for postoperative pain.

Disclosures: D. Sugiyama: None. **S. Kang:** None. **A.L. Keyes:** None. **T.J. Brennan:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.10/V8

Topic: D.03. Somatosensation: Pain

Support: MRC-DTG

Title: TMEM16A-TRPV1 signalling complexes in sensory neurons

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Abstract: The Ca^{2+} activated Cl^- channel (CaCC) TMEM16A (ANO1), is expressed in peripheral somatosensory neurons and has been implicated in nociception and inflammatory

pain; interestingly it also senses noxious heat in a similar manner to the classical heat sensor TRPV1. Our previous findings allude to close proximity between TMEM16A, G-protein coupled receptors and IP_3 receptors (IP_3R) at endoplasmic reticulum-plasma membrane (ER-PM) junctions but more importantly, coupling between TMEM16A and the internal Ca^{2+} stores via IP_3R. To further our understanding regarding the role of TMEM16A in nociception, we have investigated functional and physical coupling between TMEM16A and TRPV1 in rat dorsal root ganglion (DRG) neurons. To this end, we have utilized live confocal imaging; simultaneous monitoring of Cl^- channel activity and Ca^{2+} dynamics in DRG neurons transfected with a halide-sensitive EYFP mutant (H148Q/I152L) and loaded with fura-2 revealed that capsaicin (TRPV1 ligand) robustly activates CaCC. Interestingly, ER store depletion significantly reduced (but not abolished) the capsaicin-induced Ca^{2+} rises and CaCC activation, suggesting that Ca^{2+} release from the ER is a major aspect of TRPV1-mediated CaCC activation; this may be attributed to the PLC-activating ability of TRPV1. To further strengthen this notion, capsaicin application in CHO cells transfected with TRPV1 also induced ER Ca^{2+} mobilization, which was monitored using an ER-localised Ca^{2+} probe (CEPIA). Proximity ligation assays in DRG neurons established close proximity (<40nm) between TMEM16A and TRPV1; close proximity between TMEM16A and IP_3R1 was also observed. Stochastic optical reconstruction (STORM) microscopy was able to confirm close association of TMEM16A and TRPV1 channels in DRG neurons as well as close proximity of TMEM16A and IP_3R1, and between TRPV1 and IP_3R1 (within 100nm). Intriguingly, multichannel-complexes consisting of all 3 proteins were also present. In summary, our data reveal the composition of TMEM16A-containing signalling complexes in DRG neurons which include coupling between TRPV1 and TMEM16A through ER Ca^{2+} release. Given the relatively low Ca^{2+} affinity of TMEM16A, this may be a means by which TMEM16A activation is achieved, given the pre-established coupling between TMEM16A and IP_3R in DRG neurons.

Disclosures: S. Shah: None. **C. Carver:** None. **M. Shapiro:** None. **N. Gamper:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.11/V9

Topic: D.03. Somatosensation: Pain

Support: Internal funds from the Department of Anesthesiology, Stony Brook Medicine

Title: Inhibition of transient receptor potential vanilloid type 1 (TRPV1) receptor by serotonin in dorsal root ganglia neurons

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Abstract: Pain signals relayed to the dorsal horn of the spinal cord by primary nociceptors are subject to extensive modulation by local neurons and by neurotransmitters released from supraspinal centers. The transient receptor potential vanilloid type 1 (TRPV1) receptor is a polymodal molecular integrator in the pain pathway preferentially expressed in Aδ- and C-fiber nociceptors. Pharmacological and genetic studies support a major contribution of TRPV1 channels to the development of different chronic pain conditions, including thermal hyperalgesia associated with inflammatory pain, bone cancer pain, irritable bowel syndrome, and arthritis. There is substantial evidence that TRPV1 channels are expressed not only on the soma and peripheral terminals of nociceptors, but also on the central terminals which make synaptic contacts with second order neurons in the dorsal horn of the spinal cord. The presynaptic localization of TRPV1 channels on the central terminals of nociceptors is ideal to interact with neurotransmitters released in the dorsal horn of the spinal cord by descending fibers from supraspinal centers. Activation of presynaptic TRPV1 channels by endovanilloids or capsaicin has been shown to trigger the release of peptides and modulate neurotransmitter release from nociceptors. Serotonergic neurons from raphe nuclei project to the brainstem and to the spinal cord and provide the main source of serotonin. The aim of this project was to investigate whether serotonin could modulate the activity of TRPV1 channels expressed in nociceptors. The patch clamp technique was used in acutely dissociated dorsal root ganglia (DRG) neurons isolated from P18-28 rats. The TRPV1 current was isolated as the capsaicin-activated current during a ramp of voltage from -100 to +100 mV. The external solution was (mM): 151 NaCl, 2.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES. The internal solution was (mM): 125 CsCl, 10 NaCl, 2 $MgCl_2$, 10 HEPES, 10 EGTA, 4 MgATP, 0.3 NaGTP, 14 phosphocreatine, pH=7.2. In isolated DRG neurons, 1 µM serotonin inhibited the capsaicin-activated inward and outward current by 77 ± 15% and by 69 ± 8 % (n=10), and 300 nM serotonin inhibited the capsaicin-activated inward and outward current by 72 ± 6% and by 54 ± 5 % (n=7) respectively, with respect to control. The inhibitory effects of serotonin on the capsaicin-activated inward and outward currents were mimicked by 1 µM 5-nonyloxytryptamine oxalate (agonist at 5-HT1B receptor, inhibition by 81 ± 10 % and by 78 ± 8%, n=10, respectively). Taken together, the data suggest that serotonin can strongly modulate the activity of TRPV1 channels expressed in nociceptors and the effects are mediated mainly by activation of 5-HT1B receptors.

Disclosures: M. Puopolo: None. **J. Lauzadis:** None. **Y. Lu:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.12/DP08/V10

Topic: D.03. Somatosensation: Pain

Support: Washington University Pain Center and Department of Anesthesiology, Washington University School of Medicine in St. Louis, MO
NIH Grant NS069898
NIH Grant CA171927
Danish Diabetes Academy, supported by the Novo Nordisk Foundation
NIH Grant HL125805
NIH Grant NS065926
NIH Grant NS42595

Title: Macrophage angiotensin signaling triggers redox activation of sensory neuron TRPA1 and peripheral pain transduction

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Abstract: Pain is a widespread problem that is under-managed by currently available analgesics. Findings from a recent clinical trial on a type-2 angiotensin II (Ang II) receptor (AT2R) antagonist showed effective analgesia for neuropathic pain. AT2R antagonists have been shown to reduce neuropathy-, inflammation- and bone cancer-associated pain in rodents. We report that activation of AT2R in macrophages that infiltrate the site of injury, but not in sensory neurons, triggers an intercellular redox communication with sensory neurons via activation of the cell damage/pain-sensing ion channel TRPA1. Using behavioral readouts of pain hypersensitivity in mice, alongside use of *in vivo* pharmacological interventions, our study shows that both AT2R and TRPA1 required for peripheral mechanical pain sensitization induced by Ang II in both male and female mice. Our rigorous analysis found no AT2R expression in mouse and human dorsal root ganglia (DRG) sensory neurons. Instead, we report that expression/activation of AT2R on peripheral/skin macrophages (MΦs) constitutes a critical trigger of mouse and human DRG sensory neuron excitation. Ang II-induced peripheral mechanical pain hypersensitivity can be attenuated by chemogenetic depletion of peripheral MΦs. Furthermore, we show that AT2R activation in MΦs triggers production of reactive oxygen/nitrogen species, which trans-activate TRPA1 on mouse and human DRG sensory neurons, via cysteine-modification of the channel. Our study thus identifies a translatable immune cell-to-sensory neuron signaling crosstalk underlying peripheral nociceptor sensitization. This form of cell-to-cell signaling represents a

critical peripheral mechanism for chronic pain, and thus identifies multiple druggable analgesic targets.

Disclosures: D.P. Mohapatra: None. **B.A. Copits:** None. **A.D. Mickle:** None. **P. Karlsson:** None. **S. Kadunganattil:** None. **S. Haroutounian:** None. **S. Tadinada:** None. **A.D. de Kloet:** None. **M.V. Valtcheva:** None. **L.A. McIlvried:** None. **S. Jain:** None. **T.D. Sheahan:** None. **P.R. Ray:** None. **Y.M. Usachev:** None. **G. Dussor:** None. **E.G. Krause:** None. **T.J. Price:** None. **R.W. Gereau:** None. **A.J. Shepherd:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.13/V11

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant 16K19023
JSPS KAKENHI Grant 17K16992
The Nakatomi Foundation

Title: Chronic ocular dryness sensitizes TRPV1 on corneal cold-sensitive nerves

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Abstract: Sensory nerve terminals from the trigeminal ganglion are densely distributed in the cornea, contributing to the detection of nociceptive and non-nociceptive somatosensory information on the ocular surface. Chronic ocular dryness results in neuropathic firing of corneal nerves sensitive to cold stimuli, which may be related to the unpleasant sensation that occurs in dry eye disease. However, changes in the activity of the transient receptor potential vanilloid type 1 (TRPV1) channel, a polymodal nociceptive receptor, have not yet been elucidated in corneal cold-sensitive neurons. Therefore, in the present study, we investigated the effect of capsaicin, a TRPV1 agonist, on the firing activities of corneal nerves in chronic ocular dryness. Chronic ocular dryness was induced in guinea pigs by removing the bilateral exorbital lacrimal glands. Four to 6 weeks after surgery, extracellular single-unit recording of corneal nerve terminals was performed in a recording chamber superfused at 34ºC with a Peltier system. Additionally, in order to record intracellular calcium responses of the corneal trigeminal neurons, primary cultures of corneal neurons, labeled with FM1-43, were also prepared. Capsaicin (1 μM) increased spontaneous impulse activity in 43% and 46% of corneal cold-sensitive nerves in the sham surgery group and the lacrimal gland excision group, respectively. Significantly lower spontaneous firing was observed in the capsaicin-sensitive nerve terminals, relative to the

capsaicin-insensitive ones, in both experimental groups. The response latency to capsaicin was significantly reduced in the lacrimal gland excision group. Intracellular calcium concentration of the corneal cold-sensitive neurons, induced by a low concentration of capsaicin (0.03 μM), was significantly higher in the lacrimal gland excision group, while no significant difference in the experimental groups (sham vs. excision) was observed with a high concentration of capsaicin (0.3 μM). These results suggest that chronic dryness on the ocular surface, induced by lacrimal gland excision, enhances TRPV1 sensitization in corneal cold-sensitive nerves, which may be related to the hypersensitivity to nociceptive stimuli observed in dry eye disease.

Disclosures: T. Masuoka: None. **Y. Yamashita:** None. **M. Tawa:** None. **M. Nishio:** None. **I. Muramatsu:** None. **T. Ishibashi:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.14/V12

Topic: D.03. Somatosensation: Pain

Support: SRNSFG Grant 217076)

Title: Histaminergic and non-histaminergic itch is accompanied by thermal and mechanical hyperalgesia via TRPV1 and TRPA1 channels

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Abstract: Pain is associated with a wide range of injury and disease, and is sometimes the disease itself. Chronic itch is another common and costly problem, and the treatment of chronic itch has been largely unmet. Recent findings support the notion that histamine-evoked itch requires the presence of the transient receptor potential vanilloid 1 (TRPV1) channel in peripheral pruriceptors while the most non-histaminergic itch mediators require the TRPA1 channel. Both of these ion channels have previously been implicated in pain. In the presented study, we investigated whether chemical inducers of itch, including histamine and non-histaminergic mediators, elicit signs of thermal and mechanical hyperalgesia.
The experiments were carried out in male mice, < 50 grams in body weight. All procedures adhered to IASP Guidelines for the use of animals in research. The thermal paw withdrawal (Hargreaves) and mechanical von Frey paw withdrawal tests were used in this study. We measured nociceptive thermal paw withdrawal latencies and mechanical thresholds bilaterally in mice at various time points (5, 15, 30, 45, 60 and 120 min) post-injection following intraplantar injection of histamine or chloroquine, and of PAR2/MrgprC11 agonist peptides BAM8-22 and SLIGRL-NH_2 producing hyperalgesia.

We revealed that both histamine and non-histaminergic itch agonists (chloroquine, BAM8-22, SLIGRL-NH_2) resulted in significant thermal and mechanical hyperalgesia. When pretreated with the TRPV1 antagonist (AMG-517) we found a significant reduction of thermal and mechanical hyperalgesia. In the second session, pretreatment with the TRPA1 antagonist (HC-030031) produced a significant attenuation of thermal and mechanical hyperalgesia evoked by a non-histaminergic pruritogens as chloroquine, BAM8-22, and SLIGRL-NH_2.
We showed, thus, for the first time that histaminergic and non-histaminergic pruritogens elicit thermal and mechanical hyperalgesia along with and hyperknesis (itch elicited by strong stimulation) through the activation of TRPV1 and TRPA1channels respectively.
Acknowledgement. The work was supported by the grant from Shota Rustaveli National Science Foundation of Georgia (SRNSF #217076).

Disclosures: M.G. Tsagareli: None. **I. Nozadze:** None. **N. Tsiklauri:** None. **G. Gurtskaia:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.15/V13

Topic: D.03. Somatosensation: Pain

Support: University of Cincinnati startup

Title: Resolvin D3 is a potent inhibitor for transient receptor potential vanilloid 1 channel controls psoriasiform skin inflammation and pruritus in mice

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Abstract: Psoriasis is an usual chronic inflammatory skin disease and observed in about 1% to 3% of widespread population, and 60% to 90% of patients have pruritus as common and significant symptom. Nevertheless, our understanding of the pathogenesis of psoriasis is still unclear, and consequently there are few and mostly inadequate treatment opitions. However, clinical treatment with topical capsaicin have often suggested beneficial effects in reducing psoriasis and experimental ablation of its receptor TRPV1 (Transient receptor potential vanilloid 1) sensory nerves reduced psoriasiform skin inflammation in mice. It is related with releasement of CGRP. Recent study have demonstrated that Resolvins, a family of endogenous lipid mediators derived from ω-3 unsaturated fatty acids, are potent inhibitors for TRP channels and promote the resolution of various inflammatory diseases, including psoriasiform skin

inflammation. However, the molecular mechanisms underlying these resolution of psoriasiform skin inflammation and pruritus are unclear. RvD3 is a novel family member of resolvins and has properties like other resolvins. Here we report therapeutic effect of RvD3 in psoriasis. We found that systemic RvD3 blocks pruritus and alloknesis in acute and chronic phase of psoriasis. Score of symptom and thickness of epidermis in psoriasis are quietly less with multiple injections of systemic RvD3. Expression of interleukins (IL17c, IL17f, IL23 and IL23a) and marker of immune cells (ICAM-1) are inhibited by RvD3 in skin of psoriasis. Neuropeptide (CGRP) is less in DRG of psoriasis with RvD3. Moreover, RvD3 blocks capsaicin induced current in the dorsal root ganglion (DRG) and spontaneous pain. Thus, our findings provide new role of RvD3 for psoriasis treatment.

Disclosures: S. Lee: A. Employment/Salary (full or part-time):; University of Cincinnati. **R. Tonello:** A. Employment/Salary (full or part-time):; University of Cincinnati. **Y. Kim:** None. **C. Park:** None. **T. Berta:** A. Employment/Salary (full or part-time):; University of Cincinnati.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.16/V14

Topic: D.03. Somatosensation: Pain

Support: CESES Grant - Centro de Estudios Superiores en Estomatología y Ciencias de la Salud 2018

Title: TRPV1 receptors are located in Wistar rat tongue

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Abstract: Introduction: The tongue is a muscular organ innervated by sensory and motor neurons. The sensory neurons belong to fibers C and Aδ, which express Transient Receptor Potential to Vanilloid Type 1 (TRPV1). TRPV1 is proposed as modulator of perception of taste and the chewing process [1]. Despite the previous information, exist only a few studies that support this information due to the difficulty to find an appropriated study model.
Objective: Know the TRPV1 receptor localization on the Wistar rat tongue in order to propose it as a study model.
Methods and Materials: in this paper we use female Wistar rats (at puberty age 38± 2 days, n=5). The rats has been sacrificed to obtain the tongues by CO2 exposure and followed by a perfusion with intracardiac saline solution (NaCl, 0.9%) followed by paraformaldehyde (4%) in PBS, pH 7.4 (solution of PF-PBS). We dissected the tongues and they were fixed in 4%

paraformaldehyde-PBS. Therefore, the tongues were included in paraffin, followed a histological slides (5 µm) were performed. The slides were stained with hematoxylin and eosin (H&E) to determinate the tissues and cells. Finally, for the TRPV1 receptors localization we performed an immunohistochemistry technique (IHC). For H&E and IHC we took photographs and were saved in a PC. All the photographs were evaluated with the NIH ImageJ software.
Results: We found that the TRPV1 receptors are present on the Wistar rat tongue, and expresed in fungiform and filiform papillae, muscle, and salivary acini. We propose that TRPV1 might be involved in cellular proliferation of tongue during tisular damage, as well as the transmission of physical stimuli to the brain.
Conclusions: The Wistar rat is a very good experimental model for studying the functions of TRPV1 in Tongue.
References
1. Kawashima M, Imura K, Sato I. Topographical organization of TRPV1-immunoreactive epithelium and CGRP-immunoreactive nerve terminals in rodent tongue. Eur J Histochem. 2012 May 10;56(2):e21.

Disclosures: A. Molina: None. **B. Paiz:** None. **A. Jacinto:** None. **J. De La Rosa:** None. **V. Alatriste:** None.

Poster

214. The Role of TRP Channels in Pain and Itch

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 214.17/V15

Topic: B.04. Ion Channels

Support: National Natural Science Foundation of China (81471130)

Title: Peripheral matrix metalloproteinase-9 mediates bone cancer pain

Authors: *W. LIN, X. ZHANG, Y. ZHANG
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Abstract: Objective Matrix metalloproteinase-9(MMP-9) is one of the best studied members of MMPs family, it's involved in chronic pain, including inflammation pain, neuropathic pain, and cancer pain. However, the role of MMP-9 in bone cancer pain and the mechanism are still unknown. In this study, we investigated the distribution and the dynamic changes of peripheral MMP-9, TRPV1 channel and TNFα, as well as the role in rat bone cancer pain induced by intra-tibia inoculation of Walker 256 mammary gland carcinoma cells. **Methods** Rat bone cancer pain model was induced by intra-tibia inoculation of Walker 256 mammary gland carcinoma cells. Changes in mechanical or thermal pain were measured using von-Frey test and Hargreaves test. Distribution and dynamic changes of peripheral MMP-9,TRPV1 and TNFα during bone cancer

pain were revealed by immunofluorescence and western blot. The activation of MMP9 was tested by gelatin zymography. The effect of MMP9 on TRPV1 channel currents was identified by whole cell patch clamp. **Results** (1) The expression and activation of MMP-9 in ipsilateral bone increase after inoculation of Walker 256 cells, as well as the expression of TRPV1 and TNFα. (2) Peripheral MMP-9 is involved in the development of bone cancer pain. (3) MMP-9 sensitizes TRPV1 channel and induces allodynia and hyperalgesia. (4) MMP-9-induced sensitization of TRPV1 is mediated by TNFα. **Conclusion** There are large amount of MMP-9 produced and released in tumor bone and DRG neurons, which may proteolysise and activate the transmembrane pro-TNFα. The active-TNFα interacts with TNFR1 receptor and influences the expression and function of TRPV1 channe1, leading to the development and maintenance of bone cancer pain.

Disclosures: W. Lin: None. **X. Zhang:** None. **Y. Zhang:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.01/V16

Topic: D.03. Somatosensation: Pain

Support: DE026749
NS064022
DE022129

Title: Estrogen receptor alpha agonist PPT reversed the effects of letrozole in the thalamus of rats with zoster pain

Authors: *L. L. BELLINGER[1], M. RAO[1], C. P. STINSON[1], P. KINCHINGTON[2], M. B. YEE[2], P. R. KRAMER[1]
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Abstract: Background: Herpes zoster (HZ) or shingles results in pain of the orofacial region. Women report more pain associated with zoster and animal studies demonstrate that male rats have a reduced response to zoster pain. Previous studies in our lab suggested the thalamus controls zoster pain. Testosterone is converted into estrogen in certain areas including the thalamus by aromatase to modulate pain. We hypothesized that estradiol in the thalamus would bind estrogen receptor alpha (ERα) and alter zoster associated pain signaling. We tested our hypothesis by infusing rats with aromatase antagonist letrozole and estrogen receptor alpha agonist PPT (4,4',4''-(4-Propyl-[1*H*]-pyrazole-1,3,5-triyl)*tris*phenol). Methods: Male Sprague-Dawley rats (300 gram) were divided (n=8 group) into virus and control groups that received

MeWo cells containing Varicella Zoster Virus (VZV); the virus responsible for zoster or MeWo cells lacking virus. Guide cannulas were placed in the thalamic area using stereotaxic coordinates for local administration of the drugs. Virus injections (100 µl) were in the left whisker pad and contained either 50,000 pfu of virus or control cells. Both these groups were further divided in four drug groups: vehicle, or the aromatase inhibitor letrozole or PPT or PPT & letrozole. The motivational and affective aspect of nociception was measured using Place Escape Avoidance Paradigm (PEAP) assay. Measurements were completed once a week for two weeks and the thalamic tissue was isolated for immune-fluorescent analysis of neuronal activity using phosphorylated ERK antibody. Results: Blockade of aromatase significantly increased the VZV nociceptive response and neuronal activity in the thalamic region suggesting estradiol in the thalamus attenuates zoster associated pain. Infusion of ERα agonist PPT concomitant with letrozole reduced zoster pain versus the letrozole treatment group suggesting involvement of estradiol receptors. Conclusion: In conclusion, male rats show a reduced VZV pain response because aromatase derived estradiol interacts with ERα within the thalamus to reduce orofacial pain.

Disclosures: L.L. Bellinger: None. **M. Rao:** None. **C.P. Stinson:** None. **P. Kinchington:** None. **M.B. Yee:** None. **P.R. Kramer:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.02/W1

Topic: D.03. Somatosensation: Pain

Support: the Key Project of the National Natural Science Foundation of China Grant 31430034

Title: A central neural circuit for nociceptive hypersensitivity

Authors: *H. WANG, P. DONG
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Abstract: Pain is an unpleasant sensory and emotional experience and its processing has been studied extensively at the spinal level. But, pain processing in the central nervous system remains largely unknown. Here we found that zona incerta was involved in pain processing. Furthermore, in vivo optogenetic manipulation zona incerta and incerta-thalamus circuit bidirectionally regulated pain thresholds. Thus, our studies identify zona incerta is critical for pain processing. HW and PD contributed equally to this work.

Disclosures: H. Wang: None. **P. Dong:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.03/W2

Topic: D.03. Somatosensation: Pain

Support: NSFC 31230028
NSFC 81730095

Title: ASIC1a mediates pain hypersensitivity through regulation of synaptic plasticity in anterior cingulate cortex

Authors: *H.-S. LI[1], M.-G. LIU[2], X.-Y. SU[2], X. QI[2], X.-L. SONG[2], T.-L. XU[2]
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Abstract: Chronic pain is a serious debilitating disease for which effective treatment is still lacking. Ion channels are potentially good therapeutic targets for developing novel analgesics. Acid-sensing ion channel 1a (ASIC1a) has been implicated in nociceptive processing at both peripheral and spinal neurons. However, despite the prominent expression of ASIC1a in the brain, it remains elusive whether ASIC1a also contributes to pain perception at the supraspinal level. Here, we report that ASIC1a in anterior cingulate cortex (ACC) is required for inflammation-induced thermal and mechanical hypersensitivity. ACC-specific genetic deletion or pharmacological blockade of ASIC1a attenuates behavioral sensitization without affecting basal pain sensation. We show that ASIC1a selectively regulates cingulate long-term potentiation (LTP), a synaptic substrate of chronic pain. Using cell type-specific manipulations, we demonstrate that ASIC1a in excitatory neurons of ACC is a major player in cortical LTP and pain behavior. Mechanistically, we show that ASIC1a tunes pain-related cortical plasticity through PKCλ-mediated upregulation of membrane trafficking of AMPA receptor GluA1 subunit in ACC. These results suggest that ASIC1a critically contributes to higher level pain processing through synaptic potentiation in ACC, which may serve as a promising analgesic target for treatment of chronic pain.

Disclosures: H. Li: None. **M. Liu:** None. **X. Su:** None. **X. Qi:** None. **X. Song:** None. **T. Xu:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.04/W3

Topic: D.03. Somatosensation: Pain

Support: National Science Foundation Graduate Research Fellowship
NIH R00DA031777
Stanford University Anesthesia department
The New York Stem Cell Foundation

Title: Excitatory input from the anterior cingulate cortex to the dorsal periaqueductal gray promotes the affective component of pain

Authors: *J. DICKINSON[1], M. L. SMITH[3], G. F. CORDER[1], A. FRANCOIS[1], R. C. MALENKA[4], G. SCHERRER[2]
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Abstract: Pain is a conscious perceptual experience characterized in large part by its aversive qualities and consequent motivation for relief. Several decades of research have identified the Anterior Cingulate Cortex (ACC), a non-sensory cortical structure, as a critical region for the emotional dimension of pain. In both humans and rodents, acute and chronic pain excites the ACC, while lesions and reduced ACC excitability decrease the unpleasantness of pain. However, the ACC receives diverse inputs from a multitude of brain regions, and is engaged/ active during a variety of behavioral experiences beside pain. It thus remains unclear what circuit mechanisms in the ACC contribute to shaping pain experience, and how specific those circuits are to nociception. Many other studies indicate that the dorsal Periaqueductal Gray (dPAG) is a critical structure for the expression of defensive behaviors and the acquisition of learned responses to aversive stimuli. The ACC projects to the dPAG, but the contribution of this pathway to pain experience has not been resolved. Here, we tested the hypothesis that excitatory input from the ACC to the dPAG during pain facilitates the affective-motivational dimension of pain, but is not selective for nociception. We first examined ACC-dPAG connectivity using histology as well as optogenetics and electrophysiology in PAG slices. We found that ACC axons terminals terminate in dPAG and monosynaptically excite Vglut2+, but not Vgat+ dPAG neurons. Second, we genetically targeted the ACC neurons projecting to the dPAG with viral vectors to express the hM4Di inhibitory DREADD, and exposed the animals to an assortment of pain tests. We found that inhibition of the ACC-dPAG pathway reduced affective-motivational pain behaviors but not sensory-reflexive responses. Third, we optogenetically inhibited ACC-dPAG neurons

during social observation of pain and observed alterations in non-somatically induced pain experience. Finally, we used fiber photometry to record population neural activity in ACC and found that neurons projecting to PAG are engaged during a broad array of aversive, rather than exclusively painful, experiences. Collectively, these results establish the direct contribution of ACC-dPAG neural activity to the aversive experience of pain, and the necessity of this pathway to generate aversive behavioral responses. Furthermore, this pathway does not exclusively process nociceptive information but is engaged by a multitude of stimuli. These results point towards a mechanism by which contextual non-nociceptive and non-somatic sensory and emotional information can modify the experience of pain.

Disclosures: M.L. Smith: None. **G.F. Corder:** None. **A. Francois:** None. **R.C. Malenka:** None. **G. Scherrer:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.05/W4

Topic: D.03. Somatosensation: Pain

Title: Disrupted functional connectivity of mediodorsal thalamus in patients with irritable bowel syndrome

Authors: *K. YASUDA[1], T. IKUTA[2]
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Abstract: The responsiveness of the central nervous system (CNS) is not clearly understood in patients with irritable bowel syndrome (IBS). While the midline and intralaminar thalamic nuclei represents the affective or emotional dimension of pain and involves perception of the unpleasantness of pain, the role of thalamic nuclei in IBS is largely unknown. Here, we aimed to elucidate functional connectivity of the the parvocellular mediodorsal thalamus (MDpc, or central MD) disrupted in IBS patients. Using the resting state functional MRI data from enhanced Nathan Kline Institute Rockland Sample. We compared 35 individuals with IBS (IBS group) and 418 individuals without IBS (control group). The MDpc was defined using the Morel-Atlas and voxel-wise functional connectivity to MDpc was tested across the whole brain. The IBS group showed significantly greater connectivity between MDpc and right temporal pole, which has putative role in social and emotional processing. Although the pathophysiological implications from this finding are yet unclear, our study demonstrated that the MDpc-temporal pole connectivity is augmented in patients with IBS. The current results suggest that functional connectivity of MDpc is altered in IBS.

Disclosures: **K. Yasuda:** A. Employment/Salary (full or part-time):; euglena Co., Ltd.. **T. Ikuta:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.06/W5

Topic: D.03. Somatosensation: Pain

Support: SFI Grant 13/RC/2073

Title: The effects of optogenetic modulation of rat anterior cingulate cortical glutamatergic neurons on the affective component of pain

Authors: *S. JARRIN[1], A. PANDIT[2], M. ROCHE[3], D. P. FINN[1]
[1]Pharmacol. and Therapeut., [2]Ctr. for Res. in Med. Devices (CÚRAM), [3]Physiol., Natl. Univ. of Ireland - Galway, Galway, Ireland

Abstract: The anterior cingulate cortex (ACC) plays an important role in top-down control and the affective component of pain[1]. *In-vivo* optogenetics is a technique in which light-sensitive proteins, opsins, are used to modulate target populations of neurons with high temporal control in awake behaving animals. Commonly used opsins are channelrhodopsin-2 (ChR2) and archaerhodopsin (Arch) to activate or silence neurons, respectively. Optogenetic methodology has been a valuable tool in a wide range of neuroscience fields including pain research[2]. The aim of this study was to investigate the effects of optogenetic modulation of glutamatergic neurons in the ACC on formalin-evoked aversion and nociceptive behaviors in rats. Adult male Sprague-Dawley rats (n=10 per group) underwent stereotaxic injection of adeno-associated virus (AAV) and implantation of optic fibers into the ACC. The AAV encoded control fluorophores, ChR2, or Arch under the regulation of calmodulin kinase II alpha (CamKIIα) promoter for selective expression within glutamatergic neurons. Four weeks later, the effects of optogenetic stimulation on formalin-induced conditioned place aversion (F-CPA) were assessed. Data were analyzed using one-way ANOVA. We found that optogenetic inhibition of glutamatergic neurons in the ACC abolished F-CPA, while activation of the same neurons did not significantly affect F-CPA, compared with rats expressing the control fluorophore. These data suggest that glutamatergic neurons of the ACC play an important role in the aversive component of inflammatory pain in rats. **References**1. Calejesan, Kim, & Zhuo (2000) Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex. *European journal of pain (London, England)*, 83-96.2. Gu, Uhelski, Anand, Romero-Ortega, Kim, Fuchs, & Mohanty (2015) Pain inhibition by optogenetic activation of specific anterior cingulate cortical neurons. *PloS one*, 10, e0117746.

Disclosures: S. Jarrin: None. **A. Pandit:** None. **M. Roche:** 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.; Alkermes. **D.P. Finn:** 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.; Alkermes.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.07/W6

Topic: D.03. Somatosensation: Pain

Support: Wireless module is supported by SiChuan NeoSource BioTektronics Limited

Title: Simultaneous multi-region local field potential recording in response to noxious stimulus

Authors: *Z. WANG, Y. B. PENG
Psychology, The Univ. of Texas At Arlington, Arlington, TX

Abstract: Local field potential (LFP) is used to measure the combined activity of neurons within a brain region, ranging from several hundred micrometers to a few millimeters. It can be invaluable for understanding cortical functions. Like electroencephalography (EEG), LFP contains the frequency bands of delta (0-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (31-100 Hz). The purpose of this study was to record LFP from multiple regions of the brain simultaneously. The hypothesis is that the peripheral noxious input will evoke different responses in different brain areas, which are involved in emotional pain (e.g., anterior cingulate cortex (ACC), amygdala, ventral tegmental area (VTA)) and involved in sensory pain (e.g., primary somatosensory cortex (S1) and ventral posterolateral thalamic nucleus (VPL)). In this study, we recorded LFP from contralateral ACC, bilateral amygdala, and contralateral VTA simultaneously. Under isoflurane anesthesia, four electrodes were implanted into these brain areas in male Sprague-Dawley rats (n=12), LFPs were recorded for around 11 minutes as baseline, then 0.1mL formalin (3%) was injected to the left hindpaw of rats and LFP was recorded for 60 minutes. The raw data of LFP was processed by power spectrum analysis in MATLAB. The power of each frequency band was normalized by the average power of the baseline. Then one-way repeated measures analysis of variance (ANOVA) with LSD post-hoc test was conducted to compare the difference after formalin injection. The results indicated that: Overall, the relative change of LFP powers for theta, alpha, beta, and gamma bands were increased significantly after formalin injection ($p < .05$) for the contralateral ACC, bilateral amygdala, and contralateral VTA simultaneously, and lasted up to 60 minutes. For the delta

band, the relative change of LFP power kept decreasing before and after formalin injection ($p < .05$). There were no significant difference for the relative change of LFP powers among these four brain regions ($p > .05$). In conclusion, formalin-induced inflammatory nociception increases the LFP activities at the ACC, Amygdala, and VTA indicating the underlying signaling process at these brain regions.

Disclosures: Z. Wang: None. **Y.B. Peng:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.08/W7

Topic: D.03. Somatosensation: Pain

Support: NRF-2018R1C1B6002210
NRF-2015M3C7A1028392
NRF-2016R1A6A3A01006389
NIH grant MH099073

Title: Thalamocortical circuit mechanism of nociception gating involving cortical parvalbumin expressing interneurons in mice

Authors: *Y. HUH[1], D. JUNG[2], T. SEO[3], H. RHIM[4], Y. KWON[3], M. BIKSON[5], J. J. KIM[6], J. CHO[1]
[1]Catholic Kwandong Univ., Incheon, Korea, Republic of; [2]Korea Institude of Sci. and Technology(Kist), Seoul, Korea, Republic of; [3]Seoul Natl. Univ., Seoul, Korea, Republic of; [4]Korea Inst. Sci. Tech. (KIST), Seoul, Korea, Republic of; [5]Dept of Biomed. Engin., City Col. of New York, New York, NY; [6]Psychology and Neurobio. & Behavior, Univ. of Washington, Seattle, WA

Abstract: Nociception serves vital protective functions against bodily injury. The thalamocortical (TC) pathway, which transmits sensory information to the cortex, is essential for perception of nociception. The unique property of TC neurons to switch between tonic (single spike) and burst (high frequency spikes) firing modes have been suggested to be a critical component in modulating nociceptive signals. However, the precise mechanism by which the dual firing mode of TC neurons bifunctionally modulate nociceptive signals at the cortical level remains unknown. Here we present immunohistochemical evidence that burst, but not tonic, stimulation of TC neurons increased the activity of parvalbumin (PV) interneurons in the cortex. Functionally, we found that optogenetic stimulation and specific transcranial magnetic stimulation (TMS) of PV interneurons were capable of differential modulation of nociceptive

thresholds. Results support the role of PV interneurons as a key pain modulating component at the cortical level within the TC circuit.

Disclosures: Y. Huh: None. **D. Jung:** None. **T. Seo:** None. **H. Rhim:** None. **Y. Kwon:** None. **M. Bikson:** None. **J.J. Kim:** None. **J. Cho:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.09/W8

Topic: D.03. Somatosensation: Pain

Support: NIH NS 085413
CDMRP PR 100060

Title: Investigating mechanisms of network excitability in the casein kinase 1 delta (CK1δ) migraine mutant mouse

Authors: *P. S. SURYAVANSHI, P. SAWANT POKAM, K. BRENNAN
Univ. of Utah, Salt Lake City, UT

Abstract: Migraine affects 12% of the world's population, yet mechanistic understanding of migraine pathophysiology remains elusive. Transgenic mice harboring a mutation in the casein kinase 1 delta (CK1δ T44A) gene represent the first animal model of non-hemiplegic migraine. Like migraine patients, these mice have decreased sensory thresholds to mechanical and thermal pain after treatment with migraine trigger nitroglycerin. Like other migraine models, the have an increased susceptibility to cortical spreading depression (CSD), which models migraine aura. In this study, we used *in vitro* and *in vivo* whole cell electrophysiology to investigate the cellular and synaptic mechanisms that underlie the migraine relevant phenotypes of CK1δ T44A mice. At resting state, intrinsic cellular properties and synaptic currents in CK1δ T44A neurons were similar to WT littermates. However, CK1δ T44A neurons had hyperpolarized membrane potential compared to WT littermates, due to increased tonic. This might be predicted to yield a hypo-excitable phenotype in CK1δ T44A mice. However, upon network stimulation, excitatory (but not inhibitory) synapses in CK1δ T44A animals failed to adapt to high frequency stimulus trains, resulting in higher steady state excitatory currents. This was accompanied by increased action potential firing frequencies to current injection in CK1δ T44A compared to WT neurons. Finally, CK1δ T44A animals showed increased duration of cortical 'upstates,' and increased membrane potential variance during upstates. In conclusion, we observe an increase in neuronal and local network gain in CK1δ T44A, likely due to failure of excitatory synapses to adapt to intense stimulation. This increased excitability likely underlies the increased susceptibility to

CSD, and possibly the amplified pain response in this mutation. We suspect that the increase in tonic inhibition may be a compensatory response to a net excitable network.

Disclosures: P.S. Suryavanshi: None. **P. Sawant Pokam:** None. **K. Brennan:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.10/W9

Topic: D.03. Somatosensation: Pain

Title: Functional and structural changes in the amygdala of the blind mouse showing hyperalgesia

Authors: *T. SARA[1], S. ALAIN[2], D. R. GALLINO[3], M. CHAKRAVARTY[3], G. BRONCHTI[4], M. PICHE[5]
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Abstract: Sensory deprivation induces brain plasticity. These changes are thought to provide behavioural adaptation. For instance, the visual cortex of the blind is activated by auditory discrimination and thus, would enhance auditory abilities in blind compared with sighted individuals. Similar findings were observed for somatosensory functions. However, little is known about nociceptive processing and pain perception in blind individuals.
A recent study showed that congenital blind humans are hypersensitive to acute pain. Yet, the driving mechanism remains unknown. One potential mechanism underlying this hyperalgesia may involve the amygdala. Indeed, the central nucleus of the amygdala receives nociceptive inputs through projections from the spinal cord and plays an important role in nociceptive processing, chronic pain and hyperalgesia.
In the present study, the potential contribution of the amygdala to hyperalgesia in the blind was examined by comparing pain sensitivity as well as amygdala volume and activation by pain in the ZRDBA mouse, a unique model of blindness. The ZRDBA mouse strain was obtained through genetically controlled crossing between ZRDCT eyeless mice and DBA mice with normal vision. In the resulting ZRDBA strain, half of individuals are born sighted with normal eyes (heterozygous) and half are born anophthalmic (homozygous). Pain sensitivity was assessed with the formalin test in 40 mice, including 20 anophthalmic and 20 sighted ZRDBA mice. Amygdala volume was measured using postmortem structural MRI and morphometric analyses of Nissl-stained serial sections, while its activation by formalin pain was assessed using c-Fos immunohistochemistry. All experimental procedures were approved by the animal care

committee of “Université du Québec à Trois-Rivières”.
Results from the formalin test revealed that blind mice are hypersensitive to acute pain and show stronger c-Fos immunoreactivity in the amygdala (p=0.001) and in its central nucleus (p=0.01) compared with sighted mice. In addition, the total volume of the amygdala was larger in blind compared with sighted mice (p=0.01), although no group difference was observed for central nucleus volume specifically. Taken together, these results suggest that stronger activation and increased volume of the amygdala may underlie pain hypersensitivity in the blind.

Disclosures: T. Sara: None. **S. Alain:** None. **D.R. Gallino:** None. **M. Chakravarty:** None. **G. Bronchti:** None. **M. Piche:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.11/W10

Topic: D.03. Somatosensation: Pain

Support: Rita Allen Foundation & American Pain Society

Title: Inflammatory and neuropathic pain enhances neural excitability and synaptic transmission in a population of GRM2+ neurons in anterior cingulate cortex

Authors: *S. CHEN[1], A. N. REKER[2], S. DAVIDSON[2]
[2]Anesthesiol., [1]Univ. of Cincinnati, Cincinnati, OH

Abstract: The anterior cingulate cortex (ACC) is a limbic region associated with emotional processing of pain, however, the cellular neurophysiology and circuitry involved is incomplete. *GRM2* encodes the group II metabotropic glutamate receptor subtype 2 (mGluR2), a G-protein coupled receptor canonically coupled to Gi/o, which has analgesic properties and which we found is robustly expressed in ACC. Here, we focused on the physiological properties of the subset of *GRM2*+ neurons in the ACC under conditions of inflammatory and neuropathic pain. Both male and female adult $GRM2^{Cre}$; $Rosa26^{lsl\text{-}tdTomato}$ mice were used to identify *GRM2*+ neurons, which were pyramidal type with apical dendrites oriented to the brain surface and soma localized to layer 2/3. *GRM2*+ neurons did not co-express the markers of inhibitory interneurons, somatostatin or parvalbumin. Complete Freund’s adjuvant (CFA) and chronic constriction injury (CCI) of sciatic nerve were utilized to study the intrinsic membrane properties of *GRM2*+ neurons under inflammatory and neuropathic pain conditions. Using patch-clamp electrophysiology in brain slices of ACC, we found that *GRM2*+ neurons from inflammatory or neuropathic pain models exhibited significantly higher action potential discharge and sensitized membrane physiology compared to controls. This hyperexcitability was reversed by pharmacological activation of mGluR2, by the agonist APDC (1 μM). Retrograde tracer

fluorogold injection in ACC showed neuronal labeling in medial dorsal thalamus (MD), suggesting a synaptic connection between MD and ACC. To delineate the pathway from MD to ACC, rAAV5/hSyn-ChR2-mCherry was injected unilaterally in MD. To study synaptic activity at *GRM2+* neurons, miniature excitatory/ inhibitory postsynaptic currents (mEPSC/mIPSC) were recorded under voltage clamp at -70mV and +10mV respectively, with the presence of tetrodotoxin (TTX, 1 μM). We next used optogenetic activation to determine the amplitude and decay of evoked-EPSCs from MD. Optogenetic-evoked (20ms, 470nm) excitatory postsynaptic currents and paired-pulse (10ms pulse, 200ms inter-pulse interval) ratio were used to determine how pain models change synaptic transmission at the MD-ACC synapse. These results will enhance our understanding of the mechanisms of thalamo-limbic synaptic plasticity under pain condition.

Disclosures: S. Chen: None. **A.N. Reker:** None. **S. Davidson:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.12/W11

Topic: D.03. Somatosensation: Pain

Support: FP7 Paincage project n. 603191
Telethon grant n. GGP11179

Title: Congenital pain insensitivity mutation in nerve growth factor gene uncouples nociception from central features of pain in heterozygous humans and mice

Authors: G. TESTA[1], I. PERINI[2], M. MAINARDI[1], C. MORELLI[3], F. OLIMPICO[1], L. PANCRAZI[1,4], C. PETRELLA[5], C. SEVERINI[5], R. FLORIO[6], F. MALERBA[6,1], P. HEPPENSTALL[3], M. COSTA[4], I. MORRISON[7], *S. CAPSONI[1,8], A. CATTANEO[1,6]
[1]Scuola Normale Superiore, Pisa, Italy; [2]Dept. of Clin. and Exptl. Medicine, IKE, Linköping, Sweden; [3]European Mol. Biol. Lab. (EMBL), Monterotondo, Italy; [4]Inst. of Neuroscience, CNR, Pisa, Italy; [5]Inst. of Cell. Biol. and Neurobiology, CNR, Rome, Rome, Italy; [6]Rita Levi-Montalcini EBRI, Rome, Italy; [7]Linköping Univ., Linkoeping, Sweden; [8]Inst. of Human Physiology, Dept. of Med. and Surgical Specialties Sci., Univ. of Ferrara, Ferrara, Italy

Abstract: Hereditary Sensory and Autonomic Neuropathy (HSAN) type V is a rare autosomal recessive disorder characterized by the inability to detect painful stimuli, caused by the R100W point mutation (661C>T) in the *ngf* gene (Einarsdottir et al., 2004). Homozygous HSAN V patients show congenital insensitivity to pain leading to multiple fractures as a consequence of damage unawareness but do not display cognitive impairment. Heterozygous carriers, identified through pedigree and genetic screening, do not present with pain- or inflammation-related

deficits nor alterations in the peripheral sensory innervation. This clinically silent population provided us with the opportunity of investigating whether the R100W mutation might affect more subtle aspects of pain perception and processing. We conducted a parallel study in a cohort of HSAN V heterozygous human carriers and in heterozygous knock-in mice harboring the R100W mutation in the context of the human *ngfb* coding sequence ($NGF^{R100W/m}$ mice). $NGF^{R100W/m}$ knock-in mice reproduce the main clinical features of heterozygous HSAN V human carriers, showing no major deficits in sensory neuron development and no learning and memory deficits. Strikingly, when challenged in the fear conditioning test, $NGF^{R100W/m}$ mice show an impaired pain-dependent behavioral freezing reaction, despite normal responses to the noxious conditioning stimulus. This lack of pain related memory is paralleled by a lower cFos activation in the anterior cingulate cortex (ACC) and in motor brain areas. The response of $NGF^{R100W/m}$ mice to innate fear paradigms is instead normal. The expression of oxytocin, a known mediator of fear and pain, is decreased in both plasma and hypothalamus of $NGF^{R100W/m}$ mice. Likewise, human heterozygous R100W carriers, despite being able to perceive noxious stimuli and reporting subjective pain thresholds, show increased reaction latencies in response to painful stimulation and a decreased subjective urgency to react. *fMRI* brain imaging revealed, comparably to the c-fos mouse data, altered BOLD signals in rostral ACC, medial premotor cortex and striatal regions associated with pain behavior. These findings from both human carriers and knock-in mice provide new insights into the central consequences of growing without feeling pain, in addition to providing insight into how the brain constructs an essential perception for survival.

Disclosures: G. Testa: None. **I. Perini:** None. **M. Mainardi:** None. **C. Morelli:** None. **F. Olimpico:** None. **L. Pancrazi:** None. **C. Petrella:** None. **C. Severini:** None. **R. Florio:** None. **F. Malerba:** None. **P. Heppenstall:** None. **M. Costa:** None. **I. Morrison:** None. **S. Capsoni:** None. **A. Cattaneo:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.13/W12

Topic: D.03. Somatosensation: Pain

Support: Start up funds from Texas A&M University to M. Umorin
BRAIN Initiative NS104897 to X. Xu

Title: Nociceptive neurons in the ventral posterolateral thalamic nucleus are predominantly modulated by synaptic input from the reticular thalamic nucleus revealed by viral genetic tracing

Authors: *M. UMORIN[1], X. LIN[2], X. XU[3]
[1]Biomed. Sci., Texas A&M Univ. Col. of Dent., Dallas, TX; [2]Anat. and Neurobio., Univ. of California Irvine, Irvine, CA; [3]Anat. and Neurobio., Univ. California, Irvine, Irvine, CA

Abstract: There is a critical need to determine the location, connections and neurochemical identities of neurons participating in the transmission and modulation of pain in the CNS so that these circuits can be precisely targeted for pain intervention. Without such knowledge the development of effective, low side-effect pain treatments will be difficult. In this study I will report our progress using recent technological advancements to determine detailed neural activation patterns and synaptic circuit organization of neurons related to pain sensation and modulation in the thalamus. We have identified and visualized thalamic nociceptive neurons activated by chronic pain, using a strategy of genetic capture of active neurons on the basis of activity dependent c-fos gene expression. Specifically, pain-activated neurons are captured using Fos-CreER mice with tamoxifen-dependent recombinase CreERT2 under the promoter of the immediate early gene c-fos. These mice are crossed with Cre reporter Ai9 mice to express tdTomato fluorescent proteins. A noxious stimulus is evoked by injection of complete Freund's adjuvant (CFA) into the hind paw; only neurons that are functionally active within a limited time window of 4-OHT administration are genetically labeled. Then we build on this technical development to combine the Fos-CreER based strategy with new viral tracing of circuit connections to nociceptive neurons in the ventral posterolateral (VPL) nucleus. Genetically modified rabies is used to trace direct synaptic connections to pain activated neurons in VPL. In mice with intraplantar saline injection activated VPL neurons show presynaptic input from local neurons and zona incerta and, to a lesser extent, from reticular thalamic nucleus. In contrast, when activated by intraplantar CFA, VPL neurons show increased input from reticular thalamic nucleus. No long-range presynaptic inputs were detected. We conclude that VPL neurons transmitting noxious signals to cortex are predominantly modulated by inhibitory input from reticular thalamic nucleus.

Disclosures: M. Umorin: None. **X. Lin:** None. **X. Xu:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.14/W13

Topic: D.03. Somatosensation: Pain

Support: NSC 105-2325-B-001-010
NSC 105-2320-B-001-025-MY2
NSC 106-2321-B-001-043

Title: Modulation of central nociceptive transmission by P2X7 in thalamocingulate circuit

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Abstract: Interest in the role of ATP in synaptic transmission started growing since specific ATP-gated ion channels were reported to localize on primary sensory neurons and activation of these channels mediates ATP-evoked neuronal excitability. Among ATP receptor families, P2X7 receptors differ in many respects from the other subtypes of this family (P2X1-6). The short-time stimulation of P2X7 leads to the expected activation of cationic currents, upon repeated or prolonged ATP application the opening of a large membrane pore can be detected. In view of the great significance of peripheral P2X7 receptors in pain and inflammation, we set out to investigate the possible role of this receptor in the central modulation of pain signaling in the thalamocingulate pathway. Slices of the mouse brain containing both the medial thalamus and anterior cingulate cortex were used for the study. Whole cell recording with patch clamp method and Extracellular field currents were recorded with 64 channel multichannel electrical array (MEA system) with P2X7 agonist or antagonist. In vivo 16-multichannel recordings were done upon high-intensity nociceptive electrical stimulation from the Sciatic Nerve (SNS Sti) with or without application of P2X7 antagonists into Medial-thalamus. 64-channel MEA recordings reveal that the evoked response in ACC upward deflection after 10 ms of MT electrical stimulation, the BzATP treatment group was larger than those evoked in control groups. Wholecell patch-clamp recordings from ACC neurons revealed that extracellular P2X7 agonist BzATP application increased the membrane potential and spike numbers of EPSCs as well as the amplitude, whereas the P2X7 antagonist application of A-740003 could reserve or suppress the facilitated neuron activity by BzATP. *In vivo* MD site application of selective P2X7 antagonists reveal inhibition of ACC neuron activity in response to nociceptive SNS stimulation and selective P2X7 agonist application facilitate the ACC neuron activity. In brief, our data obtain valuable information to the controversy regarding the presence of P2X7 in the central nervous system which indicates the clear functional existence of P2X7 alone the thalamocingulate pathway, particularly on the ACC neurons in responses to P2X7 agonist or antagonist applications with or without thalamic inputs and in modulation of the peripheral inputs by SNS stimulation . Modulations of nociceptive transmission in the central thalamocingulate path via P2X7 targeting may contribute a new insight for further anti-nociceptive applications or promote knowledge of the physiological
roles of the P2X7 receptors.

Disclosures: Y. Kuan: None. **S. Cheng:** None. **B. Shyu:** None.

Poster

215. Pain: Thalamic and Cortical Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 215.15/W14

Topic: D.03. Somatosensation: Pain

Support: NIH Grant GM115384
NIH Grant GM1026911
NIH Grant NS100065

Title: Building a prototype rodent brain-machine interface for acute pain modulation

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Abstract: Pain diagnosis and treatment remain insufficiently developed. First, pain diagnosis continues to rely on behavioral reports rather than cellular mechanisms, leading to risks of under- or over-treatments. Second, while multimodal analgesic strategies have shown promise in clinic, newer and safer neuromodulation strategies are urgently needed to complement pharmacological and behavioral treatments. Our previous studies have shown that certain brain regions, such as the prefrontal cortex (PFC), can be optogenetically or electrically stimulated to provide analgesia, continuous stimulation will result in unwanted side effects. To address these challenges, we have developed a prototype brain machine interface (BMI) for acute pain onset detection and for demand-based therapeutic stimulation in free moving rats. Two 32-ch silicon probes, assembled with 3D printed drives, were implanted in the rat primary somatosensory cortex (S1) and anterior cingulate cortex (ACC) separately. In addition, an optic fiber is implanted in the PFC after AAV-CamKII-hChR2 injection. Mechanical pin prick or Hargreaves thermal stimulus were delivered to rats' hind limbs contralateral to recording sites. An unsupervised latent state-space model was used to detect the onset of acute pain signals based on ensemble spike activity, and we have implemented this system for online pain decoding. Our preliminary data have shown that we can achieve real-time decoding true positive rate >80%, and that pain detection can reliably trigger PFC stimulation to attenuate pain behaviors.

Disclosures: Q. Zhang: None. **Z. Xiao:** None. **S. Hu:** None. **Z. Chen:** None. **J. Wang:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.01/W15

Topic: D.03. Somatosensation: Pain

Support: CIHR grant FDN-148413
NSERC grant CRD-399680

PS is the recipient of a Canada Research Chair in Neurophysiopharmacology of Chronic Pain
Institut de pharmacologie de Sherbrooke and Sherbrooke Neuroscience centre (research fellowship to ÉBO)

Title: Bias towards β-arrestin-2 mediates the analgesic effects of apelin receptor-selective ligands

Authors: *É. BESSERER-OFFROY[1,2], M. LAFRANCE[1,2], M.-A. DANSEREAU[1,2], M. OUIRZANE[1,2], N. BODE[3], A. MURZA[1,2], J.-M. LONGPRÉ[1,2], R. LEDUC[1,2], M. BEHLKE[3], É. MARSAULT[1,2], P. SARRET[1,2]
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Abstract: The class A seven transmembrane domains receptor (7TMR) APJ is activated by its two endogenous ligands, apelin and Elabela. Apelin is a peptide neurohormone involved in water-intake balance, cardiovascular function and more recently, its shortest isoform, apelin-13, was demonstrated to exert potent analgesic effects following spinal or supra-spinal delivery. In the present study, we aimed at deciphering by which signaling pathways the apelin peptide exerted its antinociceptive action. For this purpose, a series of apelin-13 analogs incorporating unnatural amino acids in positions 12 and 13 were synthesized. Pro^{12} and Phe^{13} were respectively substituted by aminoisobutyric acid (Aib) and by the aromatic residues 1-Naphtylalanine (Nal) or 2-Nal. We first examined *in vitro* their ability to trigger different signaling pathways following binding to APJ, such as engagement of G-proteins $G\alpha_{i1}$, recruitment of β-arrestins 1 and 2, as well as efficiency to inhibit cAMP production. Then, the preference of the analogs to trigger a signaling pathway over another, referred to as biased signaling was quantified using the Black and Leff operational model. Our results revealed that all the tested compounds were less active than apelin-13 to inhibit forskolin-induced cAMP production with EC_{50} 10- to 20-fold higher than the native peptide. However, three analogs were 2- to 8-fold more potent than apelin-13 to recruit β-arrestin 2. These analogs exhibited a unique and conserved biased signaling profile towards β-arrestin 2 recruitment over inhibition of cAMP production with significant bias factors ranging from 35- to 83-fold in favor of the β-arrestin 2 recruitment. The antinociceptive activities of these newly synthesized compounds were then evaluated in the formalin-induced tonic pain model and in the CFA-induced chronic inflammatory pain paradigm in Sprague-Dawley rats. Interestingly, the apelin peptide analogs that were found to be more effective in reversing the formalin-evoked pain behaviors showed a strong bias towards β-arrestin 2 recruitment. We are currently exploring *in vivo* the effects of the selective knockdown of β-arrestins using DsiRNAs on the analgesic efficacy of these apelin peptides. Taken together, our results demonstrate that incorporation of unnatural amino acids at the C-terminal end of the apelin peptide impacts on the APJ receptor signaling and that the development of β-arrestin 2 biased APJ agonists may represent a promising strategy to identify more effective analgesic candidates.

Disclosures: É. Besserer-Offroy: None. **M. Lafrance:** None. **M. Dansereau:** None. **M. Ouirzane:** None. **N. Bode:** A. Employment/Salary (full or part-time):; Integrated DNA

Technologies. **A. Murza:** None. **J. Longpré:** None. **R. Leduc:** None. **M. Behlke:** A. Employment/Salary (full or part-time):; Integrated DNA Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Integrated DNA Technologies. **É. Marsault:** None. **P. Sarret:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.02/W16

Topic: D.03. Somatosensation: Pain

Support: MD Anderson Startup funds and a University of Texas System Rising STARs award (P.M.G.)

Title: Repurposing the Nrf2 activator dimethyl fumarate for treatment of neuropathic pain

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Abstract: Aim of Investigations: Currently available treatments for neuropathic pain have only have modest efficacy and have significant adverse effects, including abuse potential. As an alternative target for neuropathic pain, we focused on the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which is responsible for transcription of >200 antioxidant-related genes. We aimed to test whether activation of Nrf2 would resolve oxidative stress, hence improving mitochondrial function and attenuating neuroinflammation; both processes promote neuronal hyperexcitability that underlies neuropathic pain behaviors. Dimethyl fumarate, FDA- and EMA-approved for treatment of multiple sclerosis, was investigated as a putative Nrf2 activator.
Methods: Neuropathic pain was established with the spared nerve injury (SNI) model in male Sprague Dawley rats. Dimethyl fumarate/vehicle was orally administrated daily for 5 days, beginning 2 weeks after SNI/sham surgery (300 mg/kg/day). The von Frey test and a conflict-avoidance task were used to quantify nociceptive hypersensitivity. Immunohistochemistry and ELISA were used to assay Nrf2 translocation, levels of reactive oxygen species and antioxidants, and cytokines in ipsilateral L4/5 dorsal root ganglia (DRG). The Seahorse assay was used to evaluate mitochondria function in DRG neurons.
Results: Oral administration of dimethyl fumarate progressively reversed allodynia established by SNI. We further found that dimethyl fumarate treatment activated Nrf2 in DRG and restored redox homeostasis, including increased levels of glutathione and superoxide dismutase (SOD) activity, and reduced oxidative damage to RNA/DNA. Dimethyl fumarate treatment completely restored mitochondrial function. Furthermore, dimethyl fumarate attenuated levels of pro-

inflammatory mediators (IL-1β, IL-6, CCL2, and CCL3) and increased levels of anti-inflammatory cytokines (IL-4, IL-5, and IL-10).
Conclusions: Our results highlight the potential for dimethyl fumarate, a non-addictive anti-nociceptive drug, to be repurposed for disease-modifying treatment of neuropathic pain.

Disclosures: J. Li: None. **J. Ma:** None. **M.J. Lacagnina:** None. **A. Kavelaars:** None. **P.M. Grace:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.03/W17

Topic: D.03. Somatosensation: Pain

Support: NIH grant 1R01DE026806-01A1

Title: Artemin is overexpressed in oral cancer and induces oral cancer pain

Authors: *N. H. TU, E. CHEN, R. VEERAMACHANENI, A. BHATTACHARYA, R. KLARES, III, A. LOEB, P. C. BURKE, B. L. SCHMIDT, D. G. ALBERTSON
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Abstract: Oral cancer generates severe pain and the intensity increases with disease progression. The causes of oral cancer pain are not completely understood. Our working hypothesis proposes that the cancer secretes mediators that sensitize and activate primary afferent nociceptors in the microenvironment. In a study of the transcriptomes of oral cancers and contralateral normal oral tissues from patients with associated clinical information and pain status as measured by the University of California Oral Cancer Pain Questionnaire (UCSFOCPQ), we found artemin (*ARTN*), a member of the glial cell line-derived-neurotrophic factor (*GDNF*) family of proteins to be significantly overexpressed in oral cancers. Higher *ARTN* expression was present in patients reporting greater pain. To investigate whether *ARTN* expressed by the cancer contributes to oral cancer pain, we inoculated HSC-3, human oral squamous cell carcinoma cells (1×10^5 cells), into tongues of female $Foxn1^{nu}$ mice. Three days post injection human *ARTN* function blocking antibody (R&D systems human anti-*ARTN* monoclonal antibody MAB2589) or IgG control (R&D systems, 1-001-A) antibody (2.5 µg in 5 µL saline) was injected into the tongues two times per week (n=8 mice/group). We measured orofacial nociceptive behavior using a dolognawmeter or facial von Frey assay in two separate experiments. Mice were sacrificed at 24 - 30 days following injection of HSC-3 cells. Trigeminal ganglia were collected and acute neuron cell cultures were prepared to assess neuronal sensitivity by calcium imaging. We found that cancer mice receiving human anti *ARTN* function blocking antibody show significantly reduced nociceptive behavior measured by the dolognawmeter assay (percent change from

baseline) at 20 days (22.0 ± 51.8 vs 133.8 ± 85.5) and 24 days (32.0 ± 39.4 vs 118.0 ± 133.0) after HSC-3 cancer cell inoculation ($p<0.01$ and $p<0.05$, two-way ANOVA with Sidak post hoc analysis, respectively). The cancer mice treated with anti-*ARTN* antibody exhibited less facial nociceptive behavior at 24 days after HSC-3 inoculation (mean ± SEM, facial nociceptive score 2.2 ± 0.2 vs 3.4 ± 0.1, $p<0.01$, two-way ANOVA with Sidak post hoc analysis). A greater number of small (≤20 μm) neurons responded to 1 μM capsaicin (*Trpv1* agonist) in cultures from control animals compared to those from the *ARTN* antibody treated animals ($p=0.04$, Fisher's exact test) and the amplitude of response was greater in the control cultures ($\Delta F_{340/380}$ = 1.11 ± 0.10 vs 0.73 ± 0.09, $p=0.009$, unpaired t-test). These observations demonstrate that targeting *ARTN* from HSC-3 cells with a function blocking antibody attenuates cancer-induced nociceptive behavior and neuronal sensitivity.

Disclosures: N.H. Tu: None. **E. Chen:** None. **R. Veeramachaneni:** None. **A. Bhattacharya:** None. **R. Klares:** None. **A. Loeb:** None. **P.C. Burke:** None. **B.L. Schmidt:** None. **D.G. Albertson:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.04/W18

Topic: D.03. Somatosensation: Pain

Support: Korea Institute of Oriental Medicine (Daejeon, South Korea)
Chungnam National University (Daejeon, South Korea)

Title: Bee venom treatment alleviates scalding burn pain in mice

Authors: D.-W. KANG[1], S.-Y. KANG[2], J.-G. CHOI[1], T. KIM[1], C.-S. KIM[1], S. LEE[1], B. JEON[1], J. PARK[1], Y. RYU[2], *H.-W. KIM[1]
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Abstract: Despite the bee sting produces irritation and pain, it has been also used as a traditional therapy in Korea. This study was designed to investigate the effect of bee venom treatment on the burn injury-induced nociception in mice. In order to develop a burn injury model, right hind paw was temporarily immersed in hot water (65 degree Celsius, 2 second). Just after burn induction, subcutaneous injection of bee venom (0.01, 0.02 or 0.1 mg/kg) was started into the ipsilateral knee area once daily for 14 days. The von Frey test was performed to assess nociceptive response and altered walking parameters was evaluated by CatWalk automated gait analysis system. From 3 days after burn injury, tactile hypersensitivity was observed and sustained for 14 days after injury only in the affected paw. Gait parameters such as paw print

area and single stance were also significantly changed by burn injury. Repeated bee venom treatment at two higher doses used in this study (0.02 and 0.1 mg/kg) remarkably alleviated tactile hypersensitivity and recovered gait performances to similar level of acetaminophen (100 mg/kg, intraperitoneal, once daily) treated positive control group. These results suggest that the peripheral bee venom treatment may have the positive potency to treat burn injury-related pain.

Disclosures: D. Kang: None. **S. Kang:** None. **J. Choi:** None. **T. Kim:** None. **C. Kim:** None. **S. Lee:** None. **B. Jeon:** None. **J. Park:** None. **Y. Ryu:** None. **H. Kim:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.05/X1

Topic: D.03. Somatosensation: Pain

Support: Craig H. Neilsen Foundation Award #213959

Title: D1 and D3 receptor modulators as adjunct therapy for pain management after spinal cord injury

Authors: *H. M. RODGERS[1], J. YOW[1], E. EVANS[1], R. PATTON[1], S. CLEMENS[2], K. L. BREWER[1]
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Abstract: Chronic neuropathic pain is a common debilitating consequence of spinal cord injury (SCI). Current pharmaceutical treatments, such as opiates, are often unable to adequately manage SCI chronic pain and have serious risks, such as addiction. Thus, it is essential to develop new treatment strategies that improve analgesia while minimizing risks. An extensive overlap of dopamine and opioid signaling exists and we have shown previously that a D3 receptor (D3R) agonist can enhance morphine analgesia against a mechanical stimulus. Since D3Rs can form functional heteromers with D1Rs, the objective of this study was to determine whether a combination therapy of morphine with D1R or D3R modulators would provide superior analgesia for SCI chronic pain without increasing reward potential. Using a contusion model of SCI known to produce chronic pain behaviors (hyperalgesia and allodynia) we tested nociceptive responses (tail-flick for thermal hyperalgesia and von Frey for mechanical allodynia) of female Long Evans rats. Baseline thresholds were obtained prior to injury and re-tested after injury under the following drug conditions 1) saline, 2) morphine (2mg/kg) 3) morphine (2mg/kg) + SCH39166 (0.1mg/kg), 4) SCH39166 (0.1mg/kg) 5) morphine (2mg/kg) + pramipexole (0.1mg/kg) and 6) pramipexole (0.1mg/kg). Additionally, we assessed reward potential of each drug combination (Conditioned place preference). SCI decreased tail flick thresholds indicating

thermal hyperalgesia. Treatment with morphine created a bimodal distribution with 1/3 of SCI animals responding to morphine. Adjunct treatment with SCH39166, a D1R antagonist increased mechanical thresholds compared to saline, morphine and SCH39166 alone but only increased thermal thresholds in animals that did not respond to morphine alone. Adjunct treatment with morphine and the D3R agonist pramipexole increased both thermal and mechanical thresholds compared to saline, morphine or pramipexole alone. Conditioned place preference was not induced by either drug combination. The data demonstrate that in a model of SCI, adjunct therapy with dopamine modulators provides better analgesia than morphine alone. However, addition of the D3R agonist was more effective on both types of pain. Dopamine modulators as adjunct therapy may represent a potential clinical intervention for chronic neuropathic pain particularly in cases that are non-responsive to morphine alone.

Disclosures: H.M. Rodgers: None. **J. Yow:** None. **E. Evans:** None. **R. Patton:** None. **S. Clemens:** None. **K.L. Brewer:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.06/X2

Topic: D.03. Somatosensation: Pain

Support: Merit Review Award from the Department of Veterans Affairs to JEZ
Louisiana Board of Regents grant (ITRS-015B) to JEZ
Board of Regents Predoctoral Fellowship to AKF

Title: Treatment with novel endomorphin analog protects against latent sensitization and expedites recovery from chronic pain

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Abstract: Opioids are the gold standard for relief of moderate to severe pain, but in addition to well-known side effects, including abuse potential, opioids paradoxically cause pain sensitization over time, limiting their use. Morphine, for example, worsens and prolongs mechanical allodynia and thermal hyperalgesia after Complete Freund's Adjuvant (CFA) injection into a rat's hind paw after drug cessation [1]. ZH853 is a novel endomorphin analog that has reduced side effects, including abuse liability [2], and superior analgesia [3] compared to morphine. We tested whether chronic drug administration, before or after inflammatory pain, would induce sensitization of pain, as morphine does. Adult male Sprague-Dawley rats were implanted with intrathecal catheters and administered drug via osmotic minipump for 5 days. Inflammation was

induced by CFA injection to the left hind paw and sensitivity was measured with von Frey and Hargreaves testing. We also used the CatWalk XT to determine whether morphine and/or ZH853 made gait impairments worse than CFA alone. When all animals had recovered to baseline, naltrexone was used to probe whether latent sensitization had developed. We found that morphine prolonged and intensified hypersensitivity in both paradigms, while ZH853 reduced the total time and intensity of hypersensitivity, and protected against CFA-induced latent sensitization versus vehicle and morphine treatment. This study suggests that, unlike currently used opioids, ZH853 can treat chronic inflammatory pain effectively without causing further sensitization of the pain system.

1.Loram, L.C., et al., Prior exposure to repeated morphine potentiates mechanical allodynia induced by peripheral inflammation and neuropathy. Brain Behavior and Immunity, 2012. 26(8): p. 1256-1264.
2.Zadina, J.E., et al., Endomorphin analog analgesics with reduced abuse liability, respiratory depression, motor impairment, tolerance, and glial activation relative to morphine. Neuropharmacology, 2016. 105: p. 215-27.
3.Feehan, A.K., et al., Novel Endomorphin Analogs Are More Potent and Longer-Lasting Analgesics in Neuropathic, Inflammatory, Postoperative, and Visceral Pain Relative to Morphine. J Pain, 2017. 18(12): p. 1526-1541.

Disclosures: A.K. Feehan: None. **J.E. Zadina:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder for compound ZH853.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.07/X3

Topic: D.03. Somatosensation: Pain

Support: Maryland Stem Cell Foundation grant 2014-MSCRFI-0584
NIH Grant DE025137
NIH Grant NS019296
SYSU The Team-Building Project for Stem Cell Research (K00008)

Title: CCL5/CCR5 signalling in descending circuitry plays a role in bone marrow stromal cell-produced antihyperalgesia

Authors: W. GUO[1], J. YANG[1], S. IMAI[4,1], S. ZOU[1], H. LI[1,5], H. H. XU[2], K. D. MOUDGIL[6], R. DUBNER[1], F. WEI[1], *K. REN[3]
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Abstract: Our previous studies have found that bone marrow stromal cells (BMSCs), a major type of mesenchymal stromal cells, upregulate opioid receptors in the brain stem pain modulatory circuitry and attenuate pain hypersensitivity in animal models. The present work was undertaken to test the hypothesis that BMSCs produce pain relief through immune activation requiring chemokine signalling. Taking advantage of the observation that primary BMSCs produced pain relief while high passage BMSCs (≥20P) were ineffective, we compared gene transcription profiles of chemokine and their receptors between the primary and 20P-BMSCs with an Inflammatory Cytokines & Receptors RT^{2}Profiler^{TM}PCR Array (Qiagen). Fifty of 84 genes examined were expressed at a higher level (≥2-fold) in primary BMSCs, including CCL5 (RANTES), and its receptor CCR5. In rats with ligation injury of the masseter muscle tendon (TL), an antibody array (R&D Systems) revealed that the levels of CCL5 in the serum were also increased at 1 and 7 days following systemic infusion of primary BMSCs (1M cells). Further, immunostaining showed that peripheral blood monocytes (PBMCs) expressed both CCL5 and CCR5 and that treatment with BMSCs led to an increase in *Ccl5*mRNA in PBMCs. Expression of CCL5/CCR5 in both BMSCs and PBMCs suggests reciprocal interactions between infused BMSCs and host immune cells. As CCL5-CCR5 signalling has been shown to be involved in opioid receptor regulation, we examined the role of CCL5 signalling in descending circuitry in BMSC-produced pain attenuation. Mechanical nociception of the rat was assessed with von Frey filaments. EF_{50}(Effective Force50), the derived von Frey filament force (g) that produces a 50% response, was used as a measure of mechanical nociceptive sensitivity. Mechanical hyperalgesia as shown by a significant reduction of EF_{50} was induced in rats following TL, which was attenuated after the BMSC treatment. Antihyperalgesia was significantly reduced in TL rats receiving injection of met-RANTES (0.5 ng), a CCL5 inhibitor, and maraviroc (0.1 pmol), a CCR5 antagonist, into the rostral ventromedial medulla (RVM), the key structure of the brain stem pain modulatory circuitry. Consistently, western blot showed that BMSC-induced upregulation of mu-opioid receptors in the RVM was attenuated after intra-RVM maraviroc injection. These results suggest that the CCL5/CCR5 axis mediates peripheral BMSC-immune cell interactions and play a role in the descending circuitry in BMSC-produced antihyperalgesia.

Disclosures: W. Guo: None. **J. Yang:** None. **S. Imai:** None. **S. Zou:** None. **H. Li:** None. **H.H. Xu:** None. **K.D. Moudgil:** None. **R. Dubner:** None. **F. Wei:** None. **K. Ren:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.08/X4

Topic: D.03. Somatosensation: Pain

Support: Macquarie University Research Fellowship

Title: Characterization and modulation of human t-type calcium channels by synthetic cannabinoids *in vitro*

Authors: *C. BLADEN[1], S. MIRLOHI[1], M. SANTIAGO[1], M. LONGWORTH[2], M. KASSIOU[2], S. BANISTER[3], M. CONNOR[1]
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Abstract: T-type calcium channels ($Ca_V3.X$) are critical for many physiological processes, altering their activity contributes to disease states including cardiac arrhythmia, epilepsy and pain. Interestingly, clinical reports of some severe adverse reactions attributed to consumption of illicit Synthetic Cannabinoids (SCs), closely resemble the symptoms associated with disruption of T-type I_{Ca} function. It is known that other cannabinoid-based compounds can potently block and modulate T-type activity, therefore we screened a library of related SCs (Banister SD, et al., 2016) to identify whether misused SC compounds modulate human Ca_V3 channels *in vitro*. We used a combination of fluorometric (FLIPR) assays and patch clamp electrophysiology to screen a library of SCs for their ability to block or modulate T-type channels. Experiments used HEK293 Flp-In T-REx cells stably expressing $Ca_V3.1$, 3.2 or 3.3. Initial patch clamp screening of the SCs (10 µM) revealed 2 compounds that potently blocked the $Ca_v3.2$. One of these compounds, MDMB-CHMICA, has been implicated in many cases of severe poisoning, including up to 30 deaths. The other compound, AMB CHMINACA, is a less well described recreational drug. MDMB-CHMICA and AMB CHMINACA rapidly blocked $Ca_v3.2$ with $IC_{50's}$ of 1.5 ± 0.4 and 0.74 ± 0.3µM respectively. Neither SC affected the half activation or steady state inactivation potential of $Ca_v3.2$. AMB CHMINACA only showed a significant frequency-dependent block when I_{Ca} were evoked at 1 Hz, but not 0.2 or 0.5 Hz ($P < 0.05$ vs control). Slow inactivation block of $Ca_v3.2$ was assessed in presence and absence of drug using a 2 pulse protocol. Under these conditions, both SCs showed significant increase in channel block suggesting that they preferentially bind to this conformation of $Ca_v3.2$. These results are the first to show that some SCs can potently modulate T-type I_{Ca} in both a tonic and state dependent manner. FLIPR assays of $Ca_V3.X$ activity also showed strong inhibition of these I_{Ca} by most of the SCs tested. These findings are significant because they show that SCs modulate Ca_V3 channels in a manner distinct from tetrahydrocannabinol, the psychoactive component of cannabis. The severe adverse effects of MDMB-CHMICA and other SCs may be partly related to block of T-type I_{Ca}, as well as to their higher CB1 efficacy. Conversely, these findings also suggest that at the right dose, "illicit" SCs, like traditional cannabinoids, could be useful for modulating T-type channels for therapeutic applications. Banister SD, *et al.* (2016). *ACS Chem Neurosci* **7:** 1241-1254.

Disclosures: C. Bladen: None. **S. Mirlohi:** None. **M. Santiago:** None. **M. Longworth:** None. **M. Kassiou:** None. **S. Banister:** None. **M. Connor:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.09/X5

Topic: D.03. Somatosensation: Pain

Support: BK21 plus dental life science, South Korea
Korea Research Foundation, South Korea (2015R1A1A1A050275)

Title: click-chemistry based volatile albumin platform targeting M2 activated microglial cells

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Abstract: Microglia in M1 and M2 activation states play differential roles. M2 microglia are potential therapeutic target in many central nervous system diseases including neurodegenerative disease and brain cancer. We developed a platform targeting mannose receptor (CD206) positive M2 microglia by tagging mannose on albumin protein through ‘click chemistry', under physiologic condition that minimize protein denaturation from harsh reaction condition. Albumin was conjugated with DBCO-NHS and then with α-mannose-TEG-azide. The reaction product albumin-DBCO-azide was conjugated with Cy3/Cy5/Alexa647-azide for visualization. BV-2 cell line and primary cultured microglia from neonate mouse were used for in vitro validation of synthesized albumin platform. To activate these cells to M2 polarized state, interleukin-4 was treated on cells. To validate specificity and efficiency of albumin platform, immunocytochemistry and FACS was conducted after treating albumin platform on cells for specific periods. Up-regulation of M2 state marker genes in IL-4-treated BV-2 cell lines was demonstrated by real-time RT-PCR. Mannose/Alexa647 tagged albumin was applied for validating their selectivity. FACS and confocal microscopy imaging showed 60% more abundant fluorophore uptake in M2 state cells than in resting cells, which was successfully blocked by mannose and mannan polymer, respectively. These results suggest that mannose-tagged-albumin-based synthetic drug delivery platform is a potential therapeutic option for diseases that involves M2 microglial activation.

Disclosures: B. Lee: None. **J. Park:** None. **S. Oh:** None. **Y. Lee:** None. **G. Chung:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.10/X6

Topic: D.03. Somatosensation: Pain

Support: NIH-NCI grant R01CA142115
UC Center for Accelerated Innovation grant U54HL119893

Title: Targeting peripherally restricted CB1 receptors and endogenous cannabinoid systems for the treatment of cancer-induced bone pain while preventing chronic opioid-induced reward

Authors: *H. ZHANG[1], D. LUND[1], D. COLEMAN[1], R. DAVIDSON-KNAPP[1], H. CICCONE[1], W. STAATZ[1], M. IBRAHIM[1,2], T. LARGENT-MILNES[1], H. SELTZMAN[3], I. SPIGELMAN[4], T. VANDERAH[1]
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Abstract: Cancer-induced bone pain (CIBP) is a major complication affecting over 30% of cancer patients with bone metastasis. Due to the prevalence of CIBP and its disabling effects, opioids are now the major analgesics for the management of CIBP. However, the benefits of opioids when prescribed for CIBP are questionable due to severe side effects. The widespread use of opioids is associated with an increasing epidemic of opioid addictions and related overdose deaths. Therefore, the development of novel analgesic therapies attenuating opioid-induced reward are urgently needed. Recently, cannabinoids have emerged as attractive therapies for the treatment of chronic pain and drug-induced reward. In our studies, we, for the first time, found that activation of peripheral type 1 cannabinoid receptor (pCB1R) significantly alleviated spontaneous pain behaviors in a syngeneic murine model of CIBP. More importantly, the activation of pCB1R does not induce common side effects produced by cannabinoids and opioids, including motor impairment and enhanced bone degradation. Moreover, we investigated the role of endogenous cannabinoid systems in chronic opioid-induced reward. Our preliminary data indicate that systemic administration of a selective CB2 agonist can effectively mitigate chronic morphine-induced reward. Overall, our studies demonstrate that targeting peripheral CB1R or endogenous cannabinoid systems may be an effective way to manage CIBP and is a promising strategy to address the growing opioid epidemic.

Disclosures: H. Zhang: None. **D. Lund:** None. **D. Coleman:** None. **R. Davidson-Knapp:** None. **H. Ciccone:** None. **W. Staatz:** None. **M. Ibrahim:** None. **T. Largent-Milnes:** None. **H. Seltzman:** None. **I. Spigelman:** None. **T. Vanderah:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.11/X7

Topic: D.03. Somatosensation: Pain

Support: Boston Scientific Corporation
Duke Biomedical Engineering Department Second Year Fellowship

Title: Distributed network model of effects of spinal cord stimulation (SCS) on wide-dynamic range (WDR) neurons

Authors: *J. GILBERT[1], T. ZHANG[3], R. ESTELLER[3], W. M. GRILL[1,2]
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Abstract: SCS is a therapy for chronic pain but underlying mechanisms of action remain unclear and limit optimization of this therapy. Previously, a computational model of dorsal horn neurons was used to quantify the responses of WDR neurons - a proxy for pain intensity - to peripheral afferent activity and SCS (Zhang et al. 2014). However, the simplified center-surround receptive field (RF) connections in that model were likely insufficient to provide an accurate representation of the frequency dependence of SCS responses. We expanded this model to include heterogeneous excitatory and inhibitory RF interactions and quantified changes in WDR activity under representations of different pain conditions. The expanded model included high threshold excitatory and low threshold inhibitory surround inputs from multiple adjacent RFs. We increased the network size to ensure that activity in the center RFs was not influenced by edge-effect artifacts from the most distant surrounding RFs and validated the model by reproducing network responses to RF stimulation (Hillman and Wall 1969; Foreman et al. 1976). We used Monte Carlo simulations to produce 2000 network states representing different neuropathic pain conditions across a range of stimulation parameters and subsequently quantified the effect sizes of different model parameters and inputs. Analysis of the variance contributed by each network to the range of responses in the Monte Carlo simulations revealed SCS frequency, chloride reversal potential and the strength of surround GABAergic inputs as model parameters that contributed most to the network response. The importance of these parameters underscores the importance of various dorsal horn inhibitory mechanisms and targeting surround RFs for controlling SCS efficacy. Furthermore, there were strong interactions between these parameters and SCS frequency, indicating the need to account for disease progression to improve SCS efficacy and therapeutic longevity. These results contribute to our mechanistic understanding of SCS and may help identify stimulation parameters targeted to specific chronic pain conditions.

Disclosures: **J. Gilbert:** 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.; Boston Scientific. **T. Zhang:** A. Employment/Salary (full or part-time):; Boston Scientific Corporation. **R. Esteller:** A. Employment/Salary (full or part-time):; Boston Scientific Corporation. **W.M. Grill:** 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.; Boston Scientific Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Boston Scientific Corporation. F. Consulting Fees (e.g., advisory boards); Boston Scientific Corporation.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.12/X8

Topic: D.03. Somatosensation: Pain

Title: The HDAC2-YY1 complex epigenetically regulates spinal glutamate transporter activities: Implication for therapeutic target for chemotherapy-induced painful peripheral neuropathy

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common adverse effects of neurotoxic chemotherapy resulting in pain and decreased quality of life. Approximately 30 to 70% of patients receiving chemotherapy develop CIPN. Due to the lack of fully understanding of the mechanisms underlying CIPN, the current treatments are mainly empirical based on other neuropathic pain conditions rather than specifically targeting CIPN. Upregulation of histone deacetylase 2 (HDAC2) has been linked to impaired synaptic plasticity, which is well known to associate with the development of neuropathic pain. Here, we report that among the class I and II HDAC family, only HDAC2 was significantly upregulated in the spinal dorsal horn (SDH) of rat CIPN model following the long-lasting mechanical allodynia (over 28 days) induced by paclitaxel (cumulative does 8mg/kg, intraperitoneal injection). The enhanced expression of HDAC2 was mainly expressed in the spinal dorsal neurons but also observed in astrocytes. Both paclitaxel-induced mechanical allodynia and HDAC2 overexpression were inhibited by non-specific HDAC inhibitor valproic acid (VAP), HDAC2 inhibitor BRD6688, or knockdown HDAC2 by siRNA-HDAC2 (intrathecal injection). Notably, transcription factor Yin Yang 1 (YY1), a novel identified player in pain modulation, was found not only increased in

expression but also co-expressed with HDAC2 in the superficial dorsal horn following paclitaxel treatment and mechanical allodynia occurred. The interaction between HDAC2 and YY1 in CIPN was confirmed by co-immunoprecipitation (Co-IP), and their interaction was suppressed by BRD6688 or knockdown HDAC2 using siRNA-HDAC2. In the same animals developing painful neuropathy after paclitaxel, glutamate level detected by Gas chromatography-mass spectrometry (GC-MS) was markedly increased whereas excitatory amino acid transporter 2 (EAAT2) was significantly decreased in SDH compared to that in the vehicle treated group. YY1 often recruits HDAC as co-repressor to suppress gene expression. In glial cells, excessive glutamate induced YY1 binding to EAAT promoters leading to decreased EAAT activity. The current findings indicate that YY1, via recruiting HDAC2, may form a HDAC2-YY1 complex during CIPN development to tip the balance between glutamate release and reuptake, leading to painful hypersensitivity. Blocking HDAC2-YY1 interaction may restore this balance and relieve the symptoms of CIPN.

Disclosures: X. Wang: None. **P. Gu:** None. **J. Yu:** None. **C. Cheung:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.13/X9

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant 16K11679

Title: Daily intake of Japanese rice wine (sake) reduces masseter muscle nociceptive responses in the trigeminal subnucleus caudalis after psychophysical stress in the rats

Authors: *Y. NAKATANI[1], S. SHIMIZU[1], M. KUROSE[1], Y. KAKIHARA[2], M. SAEKI[1], K. YAMAMURA[1], R. TAKAGI[3], K. OKAMOTO[1]
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Abstract: Objective: Ample studies have provided the evidence on critical roles of chronic stress in the etiology of depression that is found to increase susceptibility to develop pain response and exacerbate existing pain. Evidence revealed that Japanese Rice Wine (Sake) had beneficial roles on the stress reduction such as psychological distress and pain. In this study we determined whether Sake had inhibitory effects on repeated stress-induced depression-like behavior and masseter muscle (MM) nociception in rats. Methods: Adult male Sprague-Dawley rats were used. Rats were subjected to the repeated forced swim stress (FST) or sham treatment (Sham) (10 min/Day) from Day -3 to -1, and immobility time (IT) during each FST was quantified as depression-like behaviors. Daily intraperiotoneal (i.p.) administration of Sake A or Sake B (300

mg/kg/ml as ethanol concentration; 15% ethanol) or 15% ethanol or saline was performed 10 min after each FST. At Day 0, rats were sacrificed at 2 hours after MM injury by formalin injection into the MM region to perform Fos immunohistochemistry. The number of Fos positive cells was counted in 3 areas of the trigeminal subnucleus caudalis (Vc) region, including the ventrolateral area of trigeminal interpolalis/Vc transition (vl-Vi/Vc), superficial and deep laminae at the caudal portion of Vc (caudal-Vc) regions in sham and FST each treatment groups. Result: FST significantly increased IT on Day -3 compared to Day -1 in vehicle-treated rats and Sake A and Sake B but not ethanol prevented increases in IT during FST compared to vehicle treatment. FST significantly increased Fos expression by MM injury in all regions compared to sham rats with vehicle. In FST rats, ethanol administration decreased the number of Fos positive cells significantly in all regions ipsilateral to MM injury, while both Sake showed significant reduction of Fos expression in all regions especially ipsilateral to MM injury. The inhibitory effect of sake on Fos expression was greater than that of ethanol. Both Sake and Ethanol had less effect on Fos expression in sham rats. **Conclusion:** Repeated exposures to FST enhanced depression-like behaviors and MM nociception, which could be inhibited by daily administration of sake just after each FST. These findings indicated that a certain dose of sake consumption could have preventive effects on psychological distress and pain responses.

Disclosures: S. Shimizu: None. **M. Kurose:** None. **Y. Kakihara:** None. **M. Saeki:** None. **K. Yamamura:** None. **R. Takagi:** None. **K. Okamoto:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.14/X10

Topic: D.03. Somatosensation: Pain

Support: SANPORC

Title: A potent anti-nociceptive effect after spinal subpial AAV9-medited GAD65 and VGAT gene delivery: A systematic study in neuropathic mice and adult pig

Authors: *T. TADOKORO, A. MIYANOHARA, O. PLATOSHYN, M. BRAVO-HERNÁNDEZ, S. MARSALA, M. MARSALA
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Abstract: Purpose: Peripheral nerve or spinal injury can cause neuropathic pain. Decrease in segmental GABAergic tone associated with peripheral or spinal injury has been postulated to play a role in the evolution and maintenance of neuropathic pain states. Accordingly several clinical studies have demonstrated a clinically relevant anti-nociceptive effect after treatment with GABA-mimetic compounds (such as gabapentin or tiagabine). While gene-therapy-based

approach to improve local spinal inhibitory tone would be a viable therapeutic strategy at present, no gene delivery method which would be relatively non-invasive, safe and effective in delivering gene of interest unilaterally into targeted spinal segment(s) and dorsal horn nociceptive neurons is available. By using a novel subpial gene delivery technique we studied the anti-nociceptive potency of spinal GAD65 and VGAT gene delivery in mouse neuropathic pain model. In addition, a dosing study to define a targeted viral dose to be used in perspective clinical trial was tested in adult naïve pig. **Method:** Mice with developed neuropathic pain (induced by partial unilateral sciatic nerve ligation) received 0.5 µl of mixed AAV9-UBI-GAD65 and -VGAT($1.2x10^{13}$ gc/ml, respectively) injected subpially targeting dorsal subpial space of L3-L5 segments. Before and after treatment animals were tested for i) tactile hypersensitivity, brush-evoked nociception, paw placement and open filed motor performance. Naïve adult pigs received progressively increased volumes of control AAV9-GFP injected subpially into L4-L6 segments. After survival (4-10 weeks weeks) the distribution of GAD65, VGAT or GFP fluorescence was analyzed in spinal cord sections using fluorescence microscopy. **Result:** i) Treated mice showed a complete reversal of nocicpetive responses which lasted for up to 10 weeks after treatment. Similarly, in contrast to control mice, a significant improvement in paw placement and open-field motor performace was seen in GAD65/VGAT-treated animals. ii) Immunofluorescence analysis showed a unilateral, dorsal horn-restricted upregulation of GAD65 and VGAT that was present in both inhibitory and excitatory interneurons. Comparable distribution of GFP fluorescence in adult pig was seen. **Conclusion**: The present study shows that subpial delivery of GAD65 and VGAT genes is safe and has a potent and long-lasting anti-nociceptive effect.

Disclosures: T. Tadokoro: None. **A. Miyanohara:** None. **O. Platoshyn:** None. **M. Bravo-Hernández:** None. **S. Marsala:** None. **M. Marsala:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.15/X11

Topic: D.03. Somatosensation: Pain

Support: Canadian Institutes of Health Research, Foundation Grant Program, 353649

Title: Therapeutic gene modulation of the CCR2 chemokine receptor confers analgesia and anti-proliferative activity in a rat model of cancer-induced bone pain

Authors: *E. MIDAVAINE[1], A. TRÉPANIER[1], M.-A. DANSEREAU[1], A. JACOBI[2], S. ROSE[2], M. BEHLKE[2], J.-M. LONGPRÉ[1], P. SARRET[1]
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Abstract: The lack of successful management of painful bone metastases in breast cancer patients underlines the urge for the development of novel analgesics. Indeed, patients dealing with metastatic bone cancer are profoundly impeded by intractable pain as opioid analgesics, the mainstay of pain therapy for bone cancer, show only limited analgesic efficacy. The chemokine CCL2 and its receptor CCR2 play a prominent role in tumor progression in the bone microenvironment, and increase the pain signal transmission within the spinal cord. The CCL2/CCR2 axis also initiates a vicious dialogue between tumor cells and bone-degrading osteoclasts, thus promoting tumor proliferation and intractable bone pain. The present study therefore aimed to investigate the inhibitory potential of a RNAi-based therapeutic approach targeting CCR2 to limit tumor expansion, reduce skeletal remodeling, and alleviate bone pain in a syngeneic breast cancer bone metastasis pain model. To this aim, 27-mer Dicer-substrate small interfering RNA (DsiRNA), targeting CCR2 were encapsulated in Neuro9 lipid nanoparticles. Analgesic efficacy of CCR2 knockdown was first validated in an acute pain model in which intrathecal (i.t.) delivery of anti-CCR2 DsiRNA prevented the CCL2-induced mechanical hypersensitivity compared to control-treated rats. In the bone cancer pain model consisting in injecting 30 000 MRMT-1 cells into the femur of Sprague-Dawley female rats, administration of anti-CCR2 DsiRNA (297 pmol/rat delivered i.t., d11 to d14) induced a complete reversal of the allodynic responses at the von Frey test at d14, compared to control-treated cancer-bearing rats. Dynamic weight-bearing analysis revealed a functional recovery in DsiRNA-treated animals as determined by an increase in weight-bearing on the affected limb as well as improvement in paw use during ambulation. Accordingly, bone cancer-induced paw retroflexion was also significantly reduced. In DsiRNA-treated rats, the crural nerves arising from the spinal cord segments L2-L4 exhibited a decreased in CCL2 and CGRP anterograde transport. *In vitro*, anti-CCR2 DsiRNA lacked significant effect on MRMT-1 (endogenously expressing CCR2) cell survival as assessed by MTT assay and DAPI cell cycle analysis using flow cytometry. However, chronic administration of anti-CCR2 DsiRNA from d11 to d14 in tumor-bearing animals reduced the tumor progression by 25%. In conclusion, CCR2 plays a prominent role in breast tumor-induced metastatic bone pain and its inhibition may limit the tumor burden and improve both bone health and pain management.

Disclosures: E. Midavaine: None. **A. Trépanier:** None. **M. Dansereau:** None. **A. Jacobi:** None. **S. Rose:** None. **M. Behlke:** None. **J. Longpré:** None. **P. Sarret:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.16/X12

Topic: D.03. Somatosensation: Pain

Title: Retrospective analysis of scrambler therapy in patients with chronic neuropathy

Authors: *N. PRAKASH[1], G. VARATKAR[2], R. VANDERBRINK[2], S. EGGLESTON[2], I. CHILIAN[2], A. LEITNER[2], J. HAYTER[2], K. VENKATARAMAN[2]
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Abstract: Background: Neuropathy has many causes, such diabetes, vitamin deficiency, or chemotherapy, but is often idiopathic. Neuropathy symptoms include pain, numbness, tingling, weakness, increased falling, and decreased ability to perform activities of daily living; all resulting in a negative impact on quality of life. Neuropathy not resolving within 3 months is deemed chronic neuropathy, and current treatment modalities include: physical therapy, pharmacologic therapy, behavioral medicine, neuromodulation, minimally-invasive and surgical interventions. Recognizing the limitations and hazards of long-term polypharmacy in aging patients, increasing emphasis has been placed on the non-pharmacologic options for management of chronic neuropathy. There remains a tremendous unmet need for an effective and curative intervention for chronic neuropathy. Currently there is great promise to meet this need with novel electro-therapeutic devices.
Methods: Patients with chronic neuropathy were referred to Physical Therapy at City of Hope for treatment with MC-5A Calmare® device (Calmare Therapeutics). Gabapentenoid medications were held 1 week prior to and during treatment. A modified Numeric Rating Scale (NRS) for pain was recorded before and after each treatment for each patient.
Results: Eight patients (3 females, 5 males) with ages ranging 43-80 with an average age of neuropathy onset of 57 years, and an average during of neuropathy of 6 years underwent 5-18 treatments. The average NRS was 5.63 before treatment and 3.13 after the 5th treatment. The average NRS improvement immediately before and after each treatment was 1.39.
Conclusion: Scrambler therapy is a promising electro-therapeutic device for reducing chronic neuropathic pain.

Disclosures: N. Prakash: A. Employment/Salary (full or part-time):; City of Hope Medical Group. **G. Varatkar:** A. Employment/Salary (full or part-time):; City of Hope National Cancer Center. **R. Vanderbrink:** A. Employment/Salary (full or part-time):; City of Hope National Cancer Center. **S. Eggleston:** A. Employment/Salary (full or part-time):; City of Hope National Cancer Center. **I. Chilian:** A. Employment/Salary (full or part-time):; City of Hope Medical Group. **A. Leitner:** A. Employment/Salary (full or part-time):; City of Hope Medical Group. **J. Hayter:** A. Employment/Salary (full or part-time):; City of Hope National Cancer Center. **K. Venkataraman:** A. Employment/Salary (full or part-time):; City of Hope Medical Group.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.17/X13

Topic: D.03. Somatosensation: Pain

Support: Boston Scientific Corporation
Duke Biomedical Engineering Department Second Year Fellowship

Title: A network model of nociceptive processing in the superficial dorsal horn: Validation and effects of spinal cord stimulation

Authors: *W. M. GRILL[1], J. GILBERT[1], T. ZHANG[2], R. ESTELLER[2]
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Abstract: Nerve and tissue damage causes changes in the state and activity of neurons in the dorsal horn and may lead to neuropathic pain. SCS is an effective therapeutic option for neuropathic pain but most animal and computational modeling studies investigating pain and SCS mechanisms have focused on the responses of deep dorsal horn wide-dynamic-range (WDR) neurons. However, loss of dorsal horn inhibitory control unmasks non-nociceptive Aβ inputs onto PKCγ neurons that feedforward to superficial dorsal horn (SDH) nociceptive-specific (NS) neurons, and this change potentially underlies hyperalgesia and allodynia, two features of many neuropathic pain conditions. Furthermore, accumulating experimental evidence indicates that NS neurons in the SDH also respond to SCS. We implemented a computational model of SDH neuronal circuitry to consolidate experimental data, examined the roles of feedforward excitation and different modes of inhibitory control in determining NS neuron activity, and predicted network responses to SCS. The network model included an excitatory pathway from a PKCγ neuron in lamina II/III to a lamina II glutamatergic excitatory interneuron to a NS neuron in lamina I. The excitatory pathway was gated by inhibitory interneurons with primarily glycinergic inhibition onto the PKCγ neuron and primarily GABAergic inhibition onto the glutamatergic and NS neurons, whose connections were established based on experimental recordings of synaptic responses (Takazawa et al. 2017). We validated the model by comparing network responses to corresponding data from mechanical and electrical stimulation (Lu et al. 2013). In addition, we delivered spike trains representing ramped mechanical inputs into the model to quantify shifts in activation threshold following loss of dorsal horn inhibition implemented through reducing glycinergic and GABAergic synaptic conductance and positively shifting the Cl^- reversal potential, and we replicated experimental observations of an excitatory shift in NS neuron responses following neuropathic injury (Lavertu et al. 2014). Finally, we used the model to predict NS neuron responses to SCS at different frequencies during simulated pinch inputs and found that SCS-generated inhibition did not completely suppress NS activity, potentially explaining why acute pain is not eliminated by SCS. This work synthesizes heterogeneous experimental recordings from superficial dorsal horn neurons into a computational model that replicates experimental responses and that can be used to make predictions about SDH neuronal responses to SCS under neuropathic pain conditions.

Disclosures: W.M. Grill: 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.; Boston Scientific Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Boston Scientific

Corporation. F. Consulting Fees (e.g., advisory boards); Boston Scientific Corporation. **J. Gilbert:** 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.; Boston Scientific Corporation. **T. Zhang:** A. Employment/Salary (full or part-time):; Boston Scientific Corporation. **R. Esteller:** A. Employment/Salary (full or part-time):; Boston Scientific Corporation.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.18/X14

Topic: D.03. Somatosensation: Pain

Support: Boston Scientific
NSF GRFP DGE-1650044

Title: Assessment of axonal recruitment with model-guided preclinical spinal cord stimulation in the *ex vivo* adult mouse spinal cord

Authors: *S. IDLETT[1,2], M. HALDER[1], J. N. QUEVEDO[3], T. ZHANG[4], N. BRILL[4], W. GU[4], M. MOFFITT[4], S. HOCHMAN[1]
[1]Emory Univ., Atlanta, GA; [2]Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA; [3]CINVESTAV del IPN, Mexico City, Mexico; [4]Boston Scientific Neuromodulation, Valencia, CA

Abstract: Dogma suggests that the identity of fibers recruited within clinically-therapeutic ranges of SCS are limited to Aβ axon collaterals in the dorsal column (DC) leading to pain modulation via gating by inhibitory interneurons thus, efforts to improve efficacy have historically focused to enhance selective targeting of these fibers. The extent at which other fiber populations and subsequent analgesia-inducing mechanism are engaged have not been thoroughly investigated.
Our objective was to characterize axonal recruitment with preclinical spinal cord stimulation (SCS) in the ex vivo adult spinal cord preparation
Methods: We developed an *ex vivo* adult mouse spinal cord preparation to assess recruitment following delivery of clinically-analogous stimuli determined by downscaling a finite element model of clinical SCS. Antidromic extracellular recordings were obtained from lumbar dorsal roots (DRs) to assess location-dependent recruitment of primary afferents with model-identified stimulation amplitudes. Relative recruitment thresholds for lumbar dorsal column (DC), Lissauer's Tract (LT) and DRs during monophasic bipolar SCS was also determined with model-identified stimulation distances (n=12).

Results: Multisegmental recruitment was observed. SCS amplitudes capable of recruiting Aβ fibers in DRs from distal spinal segments also recruited Aδ and C fibers in proximal segments. A fiber recruitment in lumbar segments also evoked synaptically-mediated dorsal root reflexes. Axons in DC were recruited at the lowest amplitude with the fastest conduction velocity, independent of stimulation distance and pulse duration. At 200μm above the spinal cord, the mean cathodic SCS amplitude for DC threshold was ~30 μA and subsequent recruitment of DRs and LT were 2.6 ($p<0.01$) and 4.4 ($p<0.0001$) times DC threshold amplitude, respectively. Determination of chronaxie and rheobase reveal significant differences in these properties for the first recruited populations of axons in the DC versus the DR ($p = 0.0312$).
Conclusions: Our findings provide further evidence that recruitment of DR /Aβ fibers may not be the source of discomfort-free analgesia associated with SCS, but instead a population of low-threshold axons in the dorsal column without axon collaterals in dorsal roots. These axons may represent postsynaptic dorsal column tract cells (PSDCs) projecting to brainstem gracile nuclei.

Disclosures: S. Idlett: None. **M. Halder:** None. **J.N. Quevedo:** None. **T. Zhang:** A. Employment/Salary (full or part-time):; Boston Scientific. **N. Brill:** A. Employment/Salary (full or part-time):; Boston Scientific. **W. Gu:** A. Employment/Salary (full or part-time):; Boston Scientific. **M. Moffitt:** A. Employment/Salary (full or part-time):; Boston Scientific. **S. Hochman:** 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.; Boston Scientific.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.19/Y1

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01-NS081118
NIH Grant R01-NS094206
NIH Grant P50-NS098573
NIH Grant U01-NS103569
NIH Grant P41-EB015894
MICROBRADAM
UEF - Brain Pool

Title: Orientation selective stimulation of dorsal root ganglia axons using computational models

Authors: L. R. MADDEN[1], J. P. SLOPSEMA[2], L. J. LEHTO[3], C. A. CUELLAR[4], I. A. LAVROV[5], S. MICHAELI[3], *M. D. JOHNSON[2]

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Abstract: Epidural electrical stimulation of the spinal cord has been shown clinically to have therapeutic effects for pain modulation and restoration of motor function after spinal cord injury. Epidural stimulation is thought to stimulate a large region of the spinal cord surrounding the active electrodes. Improvements can be made to provide more spatially selective activation tailored to the spinal cord anatomy. Previous research has shown that controlling the primary direction of an electric field can elicit orientation selective activation in the brain (Lehto et al., *JNE*, 2017). Here we applied this concept of orientation selectivity to the spinal cord using a computational model of epidural spinal cord stimulation. Anatomical slices of the lumbar and sacral segments of a rat spinal cord were segmented to construct a finite element model (FEM) using SolidWorks and COMSOL. The FEM, which contained four electrodes arranged in a diamond formation over the dorsal column, was coupled with multi-compartment dorsal root ganglia axon models in the NEURON programming environment. Stimulation was applied through 3 or 4-electrode configurations, which controlled the primary direction of the electric field (PDEF). The stimulation patterns consisted of biphasic square pulses with relative amplitude ratios amongst the electrode sites that followed phase-offset sinusoids, which generated rotation of the PDEF. For comparison, monopolar cathodes were rotated around the 3 and 4-contact arrangements. Stimulus thresholds for eliciting action potentials were found for modeled dorsal root ganglia axons. Modeled axons had the lowest activation thresholds for parallel PDEFs (using bipolar configurations) and for the most proximal single cathode (using monopolar configurations). Orientation-selectivity was quantified as the gain (maximum/minimum threshold) for each axon trajectory. Gains averaged at 8.6 ± 4.9 for 3-contact dipole stimulation, 10.2 ± 8.2 for 4-contact dipole stimulation, 4.7 ± 2.4 for 3-contact cathode rotation, and 14.3 ± 3.5 for 4-contact cathode rotation. Activation specificity, demonstrated by maximum gain, was higher for 4-contact over 3-contact configurations due in part to the stability of the center of rotation for 4-contact configurations. PDEF stimulation resulted in bidirectional threshold minimums and maximums, indicating that parallel electric fields can activate axons at similar thresholds. Together, orientation-selective stimulation shows promise for improving activation of axonal processes from the dorsal root ganglion to provide more precise neuromodulation for the treatment of pain and the restoration of movement.

Disclosures: L.R. Madden: None. **J.P. Slopsema:** None. **L.J. Lehto:** None. **C.A. Cuellar:** None. **I.A. Lavrov:** None. **S. Michaeli:** None. **M.D. Johnson:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.20/Y2

Topic: D.03. Somatosensation: Pain

Support: Boston Scientific Corporation

Title: The response of superficial dorsal neurons during kilohertz-frequency spinal cord stimulation

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Abstract: Conventional spinal cord stimulation (SCS) treat chronic pain through paresthesia-dependent mechanisms that require spatial overlap between the regions of pain and paresthesia. In contrast, kilohertz-frequency SCS (KHF-SCS) appears able to achieve paresthesia-free treatment of chronic pain. Although KHF-SCS can be clinically effective in pain control, the underlying mechanisms remain unclear. Previous single fiber recordings in anesthetized rats showed that dorsal column axons were neither activated nor blocked by KHF-SCS. We sought to quantify the activity of superficial dorsal horn neurons directly beneath the SCS electrode during the delivery of KHF-SCS. We conducted extracellular single-unit recording in healthy rats anesthetized with urethane during SCS at 50 Hz and 10 kHz at various intensities (20, 40 and 80 % motor threshold at corresponding frequency) for short durations (<30 s) during 0.33 Hz peripheral nerve electrical stimulation at 2x C-fiber threshold to characterize the effects of SCS on the acute nociceptive response. Of 14 neurons recorded between 0-350 μm from the surface, 3 were wide dynamic range (WDR) neurons and 11 were nociceptive-specific (NS) neurons. Among the NS neurons, the activity evoked by peripheral stimulation was suppressed in 45% of neurons, enhanced in 9% of neurons, and not statistically changed in 45% of neurons during both 50 Hz SCS applied at 80 % motor threshold and KHF-SCS applied at 40 % and 80 % motor threshold. Further analysis showed that both 50 Hz SCS and KHF-SCS significantly reduced C-fiber responses in the suppressed neurons. However, no apparent changes in activity were observed among NS or WDR neurons during 50 Hz SCS at 40 % or 20% motor threshold or during KHF-SCS applied at 20 % motor threshold. The results demonstrate heterogeneous effects of KHF-SCS, suggest that the stimulation amplitude required to suppress dorsal horn neuron activity depends on the applied SCS frequency, and contribute to understanding the underlying mechanisms and observed clinical effects of KHF-SCS.

Disclosures: **S. Kuo:** 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.; Boston Scientific Corporation. **T. Zhang:** A. Employment/Salary (full or part-time):; Neurobiology & Surgery. **R. Esteller:** A. Employment/Salary (full or part-time):; Boston Scientific Corporation. **M. Moffitt:** A. Employment/Salary (full or part-time):; Boston Scientific Corporation. **W.M. Grill:** 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.; Boston Scientific Corporation. E.

Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Boston Scientific Corporation. F. Consulting Fees (e.g., advisory boards); Boston Scientific Corporation.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.21/Y3

Topic: D.03. Somatosensation: Pain

Support: Department of Defense CDMRP Award W81XWH-15-1-0494
T32 Training Grant T32DA07234

Title: Biodistribution of AAV5 viral particles and target gene expression in aged mice

Authors: *K. R. PFLEPSEN[1], C. PETERSON[2], H. O. NGUYEN[1], K. F. KITTO[1], M. S. RIEDL[3], L. VULCHANOVA[5], G. L. WILCOX[6], C. A. FAIRBANKS[4]
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Abstract: The intrathecal delivery of AAV-based gene therapeutics is increasingly being investigated for clinical development of chronic analgesics or motor therapy. We and others have published studies on the biodistribution of such therapeutics in adolescent mouse populations based on expression patterns of reporter genes such as GFP or other fluorescent markers following gene transfer to various target tissues. As individuals age, the prevalence of pain conditions increases; therefore, we must consider changes of therapeutic distribution in aged populations when developing AAV therapies. However, there is limited information regarding the distribution of viral particles and target gene expression in aged mouse models following intrathecal injection. To address this question, we first evaluated the pattern of distribution of viral vector particles following intrathecal delivery of AAV5 in aged mice. Furthermore, we evaluated target gene expression and changes in hypersensitivity as a result of intrathecal injection of AAV5-CMV-hADC in aged mice following spared nerve injury. To evaluate particle distribution, conscious female ICR-CD1 mice (4 or 18-20 months old) were injected intrathecally with AAV5-ef1alpha-GFP (1.37 x 10(11) vector genomes in 10 microliters). Two hours post-injection, animals were sacrificed, and tissues of interest were immediately collected. Tissues were then examined using qPCR to detect the presence of viral DNA. To evaluate target gene expression in aged mice, we first induced peripheral hypersensitivity by spared nerve injury and then delivered AAV5-CMV-hADC (5.25 x 10(10) vector genomes per 5 microliters) intrathecally. Hindpaw hypersensitivity was evaluated weekly following injection using the von

Frey assay. Two and a half months following intrathecal injection, animals were sacrificed, and tissues of interest were collected by microdissection and evaluated by qPCR to detect the presence of the hADC gene. This research furthers our evaluation of AAV vectors and their distribution in an aged population for clinical translation.

Disclosures: K.R. Pflepsen: None. **C. Peterson:** None. **H.O. Nguyen:** None. **K.F. Kitto:** None. **M.S. Riedl:** None. **L. Vulchanova:** None. **G.L. Wilcox:** None. **C.A. Fairbanks:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.22/Y4

Topic: D.03. Somatosensation: Pain

Support: NIH R01 grant DE17794
NIH R01 grant DE22743
NIH R01 grants NS87988

Title: Anti-PD-1 monoclonal antibody Nivolumab protects against bone destruction and alleviates cancer pain in a mouse model of bone cancer

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Abstract: Programmed cell death ligand-1 (PD-L1) is typically produced by cancer cells and has been shown to suppress immunity through PD-1 receptor expressed on T cells. Emerging immune therapies such as anti-PD1 monoclonal antibodies have shown success in treating cancers such as melanoma, as well as lymphoma, lung cancer, ovarian cancer, and head and neck cancers. We recently demonstrated that PD-L1 inhibits acute and chronic pain by suppressing nociceptive neuron activity via PD-1. PD-L1 can also mask cancer pain in a melanoma model (Chen et al., Nat Neurosci, 2017). Since cancers often become painful after metastasis to bone tissue, we examined the role of PD-1 in a bone cancer pain model following inoculation of Lewis lung cancer cells (LLC) into femur bone cavity. Intravenous injections of nivolumab produced a rapid increase, within several hours after each injection, in mechanical and thermal pain sensitivity, due to possible activation of nociceptor terminals as we previously showed. However, nivolumab also produced sustained beneficial effects on cancer pain relief, days after each treatment. X-ray analysis revealed that femur bone destruction during cancer progression is also protected by nivolumab. Consistently, mice lacking *Pdcd1*, the gene encoding PD-1, exhibited lower baseline pain thresholds, as we previously demonstrated. However, bone cancer pain and bone destruction were also protected in KO mice. Our findings suggest that despite

transient increase in pain sensitivity, anti-PD-1 treatment may produce long-term benefits for cancer pain and bone protection due to possible suppression of tumor growth. This, anti-PD-1 monoclonal antibodies such as nivolumab may be used to treat bone cancer pain and protect bone in cancer patients.

References

Chen G, Kim YH, Li H, Luo H, Liu DL, Zhang ZJ, Lay M, Chang W, Zhang YQ, Ji RR (2017). PD-L1 inhibits acute and chronic pain by suppressing nociceptive neuron activity via PD-1. Nat Neurosci. 2017, Jul;20(7):917-926.

Disclosures: K. Wang: None. **S. Bang:** None. **R. Ji:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.23/Y5

Topic: D.03. Somatosensation: Pain

Support: NIH R01 AT009366

Title: Impacts of hymenolepis diminuta (helminth worm) colonization on chronic pain in male Sprague Dawley rats

Authors: *H. E. LIPPMAN[1], S. FULGHAM[2], S. BILBO[3], W. PARKER[4], S. MAIER[2], L. WATKINS[2]

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Abstract: Over the last century, members of post-industrial societies have experienced a significant depletion of the gut microbiome in terms of parasitic “old friends”. As a consequence, the ability of the remaining microbiota to modulate immune responses has been drastically limited. This lack of immunoregulation causes the immune system to be overactive by promoting inflammatory, T helper 1, immunity. It has been demonstrated that intestinal helminth worms such as *Hymenolepis diminuta*, are responsible for a shift from T helper 1 (Th1) cell immunity towards T helper 2 (Th2) cell immunity, which promotes an anti-inflammatory phenotype. Additionally, neuropathic pain is responsible for an upregulation of pro-inflammatory cytokines and a shift to Th1 immunity. It is possible that helminth worm therapy could serve as a treatment for neuropathic pain in the periphery and both neuropathic pain and cognitive dysfunction in the central nervous system through promotion of anti-inflammatory immune regulation.

We investigated the effects of *H. diminuta* on neuropathic pain development and cognition in male Sprague Dawley rats following chronic constriction injury (CCI) of the sciatic nerve. Rats

were colonized with a dose of 5 *Hymenolepid diminuta* cystercercoids (HDCs; larval stage), and the worms were allowed to mature for 6 weeks before CCI surgeries. Von Frey behavioral testing was used to quantify mechanical allodynia. Our results showed a significant improvement in allodynia in helminth-colonized rats over the course of five weeks following CCI. Fear conditioning behavior testing was used to quantify hippocampally-dependent learning and memory three weeks after CCI. Our results show that the helminth-colonized rats had significant improvement in contextual memory. Juvenile social exploration testing was use to assess social behavior; however, neither CCI surgery nor helminth colonization had an effect on social behavior. This poster will discuss the behavioral impacts of *H. diminuta* colonization on chronic pain development and cognition in rats that have received a CCI surgery, and it will consider the immune regulation that may be responsible for the observed behavioral shifts.

Disclosures: H.E. Lippman: None. **S. Fulgham:** None. **S. Bilbo:** None. **W. Parker:** None. **S. Maier:** None. **L. Watkins:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.24/Y6

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01 AT009366

Title: The effect of voluntary wheel running on activation of oxygen regulation transcription factors after chronic constriction injury

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Abstract: We have previously shown that 6 weeks of prior voluntary exercise attenuates the development of neuropathic pain and inflammatory cytokine signaling resulting from chronic constriction injury (CCI) of the sciatic nerve, but the mechanisms remain poorly understood. Dysregulation of oxygen redox status after peripheral nerve injury can promote neuropathic pain, as accumulation of reactive oxygen species (ROS) in the pain neuraxis can drive peripheral and central sensitization and neuroinflammation. Exercise may buffer redox imbalance after peripheral nerve injury, as it has been shown to modulate reactive oxygen species by upregulating antioxidant enzymes. We hypothesized that exercise preconditioning would attenuate ROS levels, correlating with resolution of the sciatic nerve injury, neuroinflammation, and neuropathic pain. Three key transcription factors interact to shape the cellular response to ROS: nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor kappa-light-chain-

enhancer of activated B cells (NFkb), and hypoxia-inducible factor (HIF). It is known that CCI results in increased gene expression of these three transcription factors in the dorsal lumbar spinal cord. We replicated these results in lumbar spinal cord at 3 weeks post CCI in male Sprague Dawley rats. Our results also show a significant upregulation of NFkB, Nrf2, and HIF1a gene expression in the sciatic injury site. Additionally, we investigated gene expression of the antioxidant enzymes involved in oxygen reduction (superoxide dismutase (SOD1 & SOD2), catalase, and glutathione), and found a significant increase of SOD2, catalase, and glutathione in the sciatic injury site and to a lesser extent in the dorsal lumbar spinal cord following CCI. The modulatory effects of 6 weeks of prior exercise on gene expression profile of antioxidants and transcription factors involved in redox status seen after CCI in the dorsal lumbar spinal cord, sciatic injury site, and DRG will be presented.

Disclosures: S.M. Fulgham: None. **J.B. Ball:** None. **S.F. Maier:** None. **L.R. Watkins:** None. **P.M. Grace:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.25/Y7

Topic: D.03. Somatosensation: Pain

Support: NIH Grant AT009366

Title: Voluntary wheel running protects against hippocampal dependent memory deficits caused by chronic constriction injury of the sciatic nerve

Authors: *J. BALL[1], S. GREEN-FULGHAM[1], M. R. FLESHNER[1], R. M. BARRIENTOS[1], N. PLATTNER[2], T. HEDESHIAN[2], S. F. MAIER[1], L. R. WATKINS[1], P. M. GRACE[3]
[1]Psychology/Neuroscience, [2]CU Boulder, Boulder, CO; [3]Critical Care and Resp. Care Res., Univ. of Texas MD Anderson, Houston, TX

Abstract: It has been shown that glial cells are activated in the lumbar spinal cord following chronic constriction injury (CCI) of the sciatic nerve. The resulting increase in inflammatory cytokines and activation of the NLRP3 inflammasome is correlated with increased central sensitization in the spinal cord, leading to chronic neuropathic pain. In the hippocampus however, prior work in the learning and memory field has shown that increases in inflammatory cytokines is correlated with impairment of hippocampus associated memory tasks. We have previously demonstrated that six weeks of voluntary wheel running that ceases prior to CCI, attenuates mechanical allodynia and decreases neuroimmune signaling in the lumbar spinal cord in male Sprague Dawley rats. We hypothesized that evidence of neuroinflammation would also be seen in the hippocampus following CCI, and that this would be attenuated by prior voluntary

exercise. This study investigated the changes in neuroimmune signaling following CCI in the hippocampus as well as the spinal cord resulting from prior voluntary exercise, and how these changes functionally related to improvements in behavioral tasks of hippocampus dependent memory, such as Object Place Recognition (OPR) and contextual fear conditioning. Six weeks of voluntary wheel running that ceased prior to CCI was found to significantly improve performance on hippocampus dependent memory behaviors compared to sedentary controls in rats with neuropathic pain. Our results also showed that interleukin-1beta protein and nitric oxide were attenuated in the contralateral dorsal hippocampus at day 10 after CCI in rats with prior voluntary exercise. Ongoing studies are investigating microglial activation and NLRP3 inflammasome expression in both hippocampus and dorsal lumbar spinal cord after CCI, and how prior exercise modulates the expression of these proteins.

Disclosures: J. Ball: None. **S. Green-Fulgham:** None. **M.R. Fleshner:** None. **R.M. Barrientos:** None. **N. Plattner:** None. **T. Hedeshian:** None. **S.F. Maier:** None. **L.R. Watkins:** None. **P.M. Grace:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.26/Y8

Topic: D.03. Somatosensation: Pain

Support: NIH R01 NS089530
University of Michigan Rackham Merit Fellowship Program

Title: Computational model of evoked potentials recorded during spinal cord stimulation for pain

Authors: *C. J. ANAYA[1,2], H. ZANDER[1,2], S. F. LEMPKA[1,2,3]
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Abstract: For the last several decades, spinal cord stimulation (SCS) has been a prevalent therapy for the treatment of refractory chronic pain. Despite widespread use, we still do not sufficiently understand its mechanisms of action. Evoked compound action potentials (ECAPs) recorded from inactive electrodes in an implanted SCS lead can be used to characterize the direct neuromodulatory effects of SCS and potentially improve the clinical outcomes of SCS. Therefore, we developed a computational model to investigate the underlying composition of SCS-induced ECAPs.We simulated ECAP recordings in a computational model containing two components: 1) a volume conductor finite element model (FEM), and 2) multi-compartment models of spinal cord axons. The FEM consisted of the gray and white matter of the spinal cord, surrounding cerebrospinal fluid, dura, epidural tissue, and vertebral column. We included an

explicit representation of an eight-electrode percutaneous lead implanted in the epidural tissue. We used the FEM to calculate the extracellular voltages generated by SCS and the ECAP recorded at each electrode. We populated the spinal cord with multi-compartment axon models using a fiber-size distribution based on human data. We determined the axonal response to SCS by coupling the 3D extracellular voltages to these axon models. We then used the theorem of reciprocity to estimate the voltages generated at the recording electrodes. We calculated the ECAPs recorded with conventional (i.e. 50 Hz) SCS at a range of amplitudes between the model-based sensory threshold (i.e. activation of 5% of dorsal column axons) and comfort threshold (i.e. 1.4 times sensory threshold). Our model ECAPs contained the expected triphasic shape with P1, N1, and P2 peaks and demonstrated a linear relationship between stimulating and recording amplitudes. At comfort threshold, the model-based P2-N1 amplitudes and conduction velocities corresponded with existing experimental data. Our results suggested that the ECAPs morphology and amplitude were dominated by the activation of axons with diameters ~7-10 μm in the dorsal aspect of the spinal cord.ECAPs during SCS can be used to investigate neural activation and corresponding SCS mechanisms of action. These ECAPs could provide a control signal to optimize stimulation parameters on a patient-specific basis. In this study, we developed a computational model of ECAPs during SCS to investigate the origin of these signals. Our results suggest that clinically-effective SCS may rely on the activation of a large number of axons within a narrow fiber diameter range located in the dorsal spinal cord.

Disclosures: C.J. Anaya: None. **H. Zander:** None. **S.F. Lempka:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.27/Y9

Topic: D.03. Somatosensation: Pain

Support: NIH R01 NS089530

Title: Role of tissue heterogeneity in computational models of epidural spinal cord stimulation

Authors: *H. ZANDER[1,2], S. F. LEMPKA[1,2,3]
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Abstract: Spinal cord stimulation (SCS) is a common neurostimulation technique to treat several neuropathic pain conditions that are refractory to conventional medical management. Despite widespread use, the mechanisms behind the therapeutic benefit of SCS are not fully known. Computational models provide a powerful tool to study SCS and its effects on the central nervous system. It is critical that these models contain sufficient detail to correlate model predictions with clinical effects. However, it is not clear what anatomical details must be

considered in computational models of SCS. Therefore, in this study, we developed computational models of various levels of complexity to determine which anatomical details affected the corresponding model-based predictions of neural activation.
We created a three-dimensional finite element model (FEM) of the lower thoracic epidural space and its surrounding anatomy. From this FEM, we calculated the extracellular voltages generated by SCS. Next, we applied these extracellular voltages to multicompartment cable models within the dorsal columns and dorsal rootlets to determine activation thresholds. To assess the importance of various anatomical features on the neural response to SCS, we generated FEMs of different levels of complexity that included detailed representation of the 3D vertebral column, intervertebral discs, dura, and explicit representation of the dorsal rootlets. We compared activation thresholds predicted with these detailed FEM's to the activation thresholds predicted by simplified cylindrical models commonly used in SCS modeling studies.
Our analysis showed that several anatomical details can affect the model predictions of neural activation by SCS. Explicit representation of the dorsal rootlet anatomy within the FEM only produced small differences in neural activation (~1-3%) relative to a simplified canonical model. However, the inclusion of an anatomically-realistic 3D vertebral column produced significant differences in activation thresholds (~1-20%) relative to a simplified model with a cylindrical bone domain. We also observed significant variability in activation thresholds that were attributed to the relative location of the stimulating electrode(s) with respect to the vertebrae and the foramina (~12-25%).
Our work demonstrates that certain anatomical details (e.g. 3D structure of the vertebrae and the relative location of the electrodes relative to the vertebrae and the foramina) may significantly affect the predicted neural response to SCS. Therefore, it is important to consider certain anatomical features when using computational models to study SCS for pain.

Disclosures: H. Zander: None. **S.F. Lempka:** None.

Poster

216. Treatments for Persistent Pain

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 216.28/Y10

Topic: D.03. Somatosensation: Pain

Support: NIH R01 NS089530

Title: Dorsal root ganglion stimulation for chronic pain: A computational analysis of neural activation

Authors: *R. D. GRAHAM[1], T. M. BRUNS[1,2], B. DUAN[3], S. F. LEMPKA[1,2,4]
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Abstract: Dorsal root ganglion stimulation (DRGS) is an FDA-approved therapy for chronic intractable pain of the lower limbs in patients with complex regional pain syndrome, and has been used off-label for a number of different pain etiologies (e.g. painful diabetic neuropathy, phantom limb pain, etc.). Unfortunately, not all patients receive sufficient pain relief from DRGS. At present, we do not have a clear understanding of the mechanisms of action of pain relief by DRGS. Understanding these mechanisms may inform the design of future stimulation technologies that improve clinical outcomes. In this work, we employed a computational approach to investigate the mechanisms of analgesia from DRGS. We constructed a volume conductor finite element model of an L5 human dorsal root ganglion (DRG), surrounding tissues, and a four-electrode lead implanted in the intraforaminal tissue. We modeled bipolar stimulation by applying the appropriate boundary conditions at the active and return electrodes. We also developed morphologically- and electrophysiologically-accurate multi-compartment models of mechanoreceptive Aβ-fibers and nociceptive C-fibers found in a DRG. To model DRGS, we interpolated the voltages generated by the stimulation onto each neuron compartment and recorded the neural response to stimulation. The sensory neuron models produced somatic action potential (AP) characteristics similar to those seen in experimental literature (e.g. AP height, duration, etc.). Clinical stimulation amplitudes (i.e. ≤1 mA) activated Aβ-fibers but not C-fibers. Anodic stimulation activated more cells when the active electrode was placed above the middle of the ganglion. Cathodic stimulation activated more cells when the active and return electrodes straddled the ganglion. When the Aβ-fibers generated spontaneous action potentials, a characteristic of tactile allodynia, electrical stimulation entrained neuron firing to regular intervals at the stimulation frequency. DRGS did not enhance low-pass filtering of noxious afferent signals at C-fiber T-junctions. Our results suggest that at clinical stimulation settings, DRGS is directly driving the activity of Aβ-fibers without modulating the activity of C-fibers. Therefore, a primary mechanism of DRGS-induced analgesia may be the activation of pain gating mechanisms within the spinal cord.

Disclosures: T.M. Bruns: None. **B. Duan:** None. **S.F. Lempka:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.01/Y11

Topic: D.05. Olfaction and Taste

Support: NIH/NIDCD T32 DC000044

Title: Neuronal characteristics of rat olfactory bulb dopamine neurons and their functional significance in signal gating

Authors: *K. S. KORSHUNOV, L. J. BLAKEMORE, P. Q. TROMBLEY
Florida State Univ., Tallahassee, FL

Abstract: The mammalian olfactory bulb (OB) transduces, processes, and discriminates billions of odor signals. This activity, crucial for survival of many mammalian species, is possible in part due to the OB's complex neuromodulatory circuitry. A major inhibitory, and partly excitatory, neuromodulator in the OB is dopamine (DA), located in the OB's glomerular layer (GL). Although much is known about the synaptic activity of OB DA neurons, their neuronal identity and electrophysiological/functional profile in the rat remain unclear. We studied these properties using the transgenic rat model, hTH-GFP. Of the three interneuron types present in the GL (periglomerular cells [PGCs], short-axon cells [SACs], and external-tufted cells [ETCs]), we believe these DA neurons may be PGCs and SACs, because they possess short (< 100 µm) and long (> 100 µm) processes consistent with being uniglomerular (PGCs) or multiglomerular (SACs). As these DA neurons do not express calretinin, they cannot be Type-2 PGCs (which do not receive olfactory nerve input). Whole-cell electrophysiological recordings indicate that these rat OB DA neurons do not produce spontaneous action potentials; this may represent a functional difference from mice, whose OB DA neurons do. To further characterize these DA neurons, we determined their membrane properties and cell sizes and compared these properties between neurons localized on top (closer to the olfactory nerve layer) and bottom (closer to the external plexiform layer) of their respective glomeruli. Functionally, when stimulated, all recorded neurons fired a single action potential, followed by a depolarization block throughout the stimulus duration. However, when stimulated with smaller currents, some neurons fired continuously throughout the stimulus duration. Thus, these neurons are likely gated by a low-pass filter. All OB DA neurons possess the hyperpolarization-activated non-specific cation h-current (I_H), which may contribute to their continuous spiking in response to small and short stimuli. By using ramp protocols (injecting increasing currents of varying amplitude and duration), we showed that the firing range of these neurons is longer when stimulated by shorter stimuli, potentially confirming the functional importance of their I_H. These neurons also displayed the transient A-type K^+ current (I_A), which likely sets their firing frequency (average of 22 Hz) when firing continuously. These results suggest that OB DA neurons may be two different cell types, that their properties may vary between rats and mice, and that these neurons may inhibit small, tonic signals, thus, increase the signal-to-noise ratio of odor processing.

Disclosures: K.S. Korshunov: None. **L.J. Blakemore:** None. **P.Q. Trombley:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.02/Y12

Topic: D.05. Olfaction and Taste

Support: Postdoctoral fellowship by the Deutsche Forschungsgemeinschaft (DFG) to T.A. (AC 304/1)
Wellcome Trust Investigator Award
The Francis Crick Institute
Medical Research Council (MC UP 1202/5)
Boeringer Ingelheim Fonds PhD scholarship to A.C.M.

Title: Perception and representation of temporally structured odor stimuli in the mouse olfactory bulb

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Abstract: Intensity fluctuations inherent to natural odour plumes are strongly modulated by the turbulent airflows in which they are carried. Odour plumes therefore hold rich temporal dynamics of odour concentration variation. As turbulence continually builds the structure of an odour plume, these dynamics contain information about the distance the plume has travelled as well as its source properties. It has, therefore, been hypothesised that animals could process the temporal dynamics of natural odour plumes in order to navigate and perform odour scene segmentation.
We used dual-energy photoionisation recording to determine the temporal features of odour plumes that are of potential behavioural salience during odour scene segmentation, finding that temporal correlation of odour concentrations reliably predicts whether odorants emerge from the same or different sources. To test whether mice are capable of using these temporal correlations to determine odour source separation, we developed a high-bandwidth odour delivery device capable of replicating many temporal features found in odour plumes. In conjunction with a high-throughput behavioural conditioning system (AutonoMouse) we trained mice (n=36) to discriminate between pairs of odours with a range of temporal correlations. Trained mice were capable of discriminating correlation structure at frequencies well over the sniff rate (>40 Hz). Examining reaction times during behaviour and disrupting correlation structure of the stimulus onset revealed that the animal's performance did not solely rely on the early part of the stimulus but that longer sampling time correlated with better performance.
The high-throughput nature of these behavioural experiments allowed us to determine the psychophysical limit of perception for temporal correlation between odours, and therefore to define an appropriate stimulus range to investigate olfactory bulb representation of these stimuli. In vivo Ca^{2+} imaging and extracellular recordings from mitral/tufted cells showed segregated responses depending on the correlation of odour stimuli with populations of 10s of neurons sufficient to accurately reach behavioural performance
We conclude that information of temporal correlations between odours is present in the output neurons of the olfactory bulb at sub-sniff resolution. Mice are capable of utilising this information in behaviour, suggesting that perception of temporal features of odour stimuli may

be a mechanism by which animals perform odour scene segmentation. Thus, olfaction is a high bandwidth sense with temporal structure containing information about olfactory space that is indeed accessible to mice.

Disclosures: T. Ackels: None. **A. Erskine:** None. **D. Dasgupta:** None. **I. Fukunaga:** None. **A.C. Marin:** None. **A.T. Schaefer:** None.

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Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.03/Y13

Topic: D.05. Olfaction and Taste

Support: Francis Crick Institute FC001153
UK Medical Research Council MC_UP_1202/5
T. M. is a Wellcome Trust Investigator WT096436AIA
A. T.S. is a Wellcome Trust Investigator 110174/Z/15/Z

Title: The 128nm architecture of the dorsal MOR174-9 mouse glomerular column

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Abstract: The glomerular column is one of the smallest neuronal circuits in the mammalian brain. Approximately 1800 columns lay side by side in the olfactory bulb, the first site for sensory integration in the olfactory system. Each glomerulus receives input from olfactory sensory neurons that express one specific odour receptor. The output of the column is mediated by dedicated projection neurons (mitral and tufted cells) which broadcast the sensed activity to higher brain areas.
The structure of the glomerular column is therefore informative on how this circuit encodes olfactory stimuli. We aim to resolve the architecture of the dorsal *MOR174-9* glomerular column by using targeted serial block-face electron microscopy (SBEM).
The location of any specific column varies across individuals; thus, a correlative light-to-electron microscopy approach is required. We targeted the dorsal *MOR174-9* glomerular column in adult mouse littermates by integrating 2-photon light microscopy, X-ray tomography and SBEM in an efficient, high-throughput workflow. Several samples from the same and from different mice

were processed simultaneously.
Volumes that fully contained the *MOR174-9* dorsal glomerulus and the adjacent glomeruli were imaged with SBEM at low resolution (64*64*128 nm^3). Mitral and tufted cells display an electron-light cytoplasm and their apical dendrites have large and constant diameters and a straight trajectory. Consequently, a good sampling of their cytoplasm is sufficient to allow for accurate tracing of their apical dendrites. In turn, datasets covering a volume of 0.75*0.75*0.5 mm^3 can be routinely obtained in 1-2 week-long imaging runs in a Merlin/3View2 SBEM.
We explored these datasets in 3D using webKnossos. We identified all neurites entering the glomerulus of interest that displayed a projection neuron-like appearance (cross-section consistently thicker than 1 µm and a cytoplasmic staining lighter than the surrounding neuropil). We identified all projection neurons sending their apical dendrites to the identified glomerulus and classified them into cell types based on commonly used histological features, such as the layer where their soma is located. Finally, we assessed the circuit's variability within the same animal (comparing between brain hemispheres) as well as between littermates.
Altogether, we report the variability of the architecture of a neural circuit in the mammalian brain.

Disclosures: C. Bosch Piñol: None. **T. Ackels:** None. **I. Whiteley:** None. **M. Berning:** None. **K.M. Boergens:** None. **M. Helmstaedter:** None. **K.L. Briggman:** None. **T.W. Margrie:** None. **A.T. Schaefer:** None.

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217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.04/Y14

Topic: D.05. Olfaction and Taste

Support: NIA R01-AG049937
NSF GRFP Grant No. DGE 1322106

Title: Adrenergic modulation of I_h in adult-born granule cells of the olfactory bulb

Authors: *R. HU, P. S. VILLAR, G. Z. DONG, R. C. ARANEDA
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Abstract: In the olfactory bulb (OB), the largest population of inhibitory neurons, the granule cells (GCs), undergo neurogenesis throughout life, but the mechanisms underlying their functional integration and survival remain poorly understood. Both developmental and adult neurogenesis are thought to rely on intrinsic and extrinsic activity-dependent mechanisms. Previously, we have shown that a hyperpolarization-activated cationic current (I_h) is present in GCs and contributes to electrical resonance and intrinsic excitability in these cells. Furthermore,

we showed that I_h is sensitive to intracellular concentrations of cAMP, suggesting that activation of metabotropic receptor mediated pathways can regulate this current. GCs are sensitive to top down regulation by neuromodulatory systems, including the noradrenergic system, which plays a major role in olfactory perception and learning. Therefore, we hypothesized that neuromodulation by noradrenaline (NA) can affect I_h in GCs to alter cell excitability and circuit function in adult born neurons. To label adult born GCs, we transduced an AAV-GFP by injection in the rostral migratory stream at P30. Two weeks post injection, I_h could be elicited in GFP labeled GCs with negative steps from −60 to –130 mV (−101 ± 13 pA, n = 12) and this current exhibited similar activation kinetics and voltage dependency as we previously described (tau = 37.6 ± 4.5 ms; V_{half} = –102 ± 2.4 mV; n = 12). Importantly, NA (10 µM) produced a ~25% decrease in I_h (0.76 ± 0.09 normalized current with respect to control, n = 3). This suppression of I_h by NA is mediated by activation of α_2-adrenoreceptors (AR) as application of clonidine (10 µM), an α_2-AR agonist, also reduced I_h (0.75 ± 0.08 normalized current, n = 4). In agreement with the reduction in I_h, activation of α_2-ARs produced an increase in GC excitability (500 ms square pulse, 20 – 100 pA; control, 7.6 ± 1.0 Hz, clonidine: 12.1 ± 2.4 Hz; n = 5). To further assess the functional role of α_2-AR regulation of I_h in GC excitability, we examined dendrodendritic inhibition onto mitral cells. Activation of α_2-ARs by clonidine enhanced dendrodendritic inhibition elicited by activation of mitral cells (charge transfer: control = −110 ± 17 pC, clonidine = −157 ± 25 pC, n = 10). Taken together, these results provide a mechanism by which α_2-AR modulation of I_h by NA regulates GC excitability during their critical window of integration in OB.

Disclosures: R. Hu: None. **P.S. Villar:** None. **G.Z. Dong:** None. **R.C. Araneda:** None.

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Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.05/Y15

Topic: D.05. Olfaction and Taste

Support: Simons Foundation Mathematical Modeling in Living Systems

Title: An anatomically-derived model of olfactory bulb connectivity for simulation of the effects of cortical feedback

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Abstract: The olfactory bulb receives both peripheral inputs from olfactory sensory neurons and centrifugal inputs from higher cortical structures. To better understand how the interplay between these two elements leads to dynamics, we developed a new model of the bulb's external

plexiform layer that incorporates detailed anatomical information about the distribution of synapses between mitral cells and granule cells. Using neurophysiological data concerning the reach and density of lateral dendrites of mitral cells, as well as the number of spines and their distribution on granule cells, we derived an equation that determines the probability of synapse between a mitral cell and a granule cell as a function of their separation. These results showed that the number of granule cells that are "shared" between two mitral cells (*i.e.* which connect to both mitral cells) decays substantially more slowly with distance between the mitral cells as compared with a previous estimate (Egger *et al* 2006). Our new estimate incorporates the branching of mitral cell lateral dendrites, which was not accounted for in previous work. We also therefore predict a longer range for effective lateral inhibition between mitral cells.
We then generated a network of thousands of mitral cells and tens of thousands of granule cells that is faithful to the constraints dictated by the olfactory bulb anatomy. Individual neurons were described using the Izhikevich model with parameters chosen to reproduce measured physiological characteristics of mitral and granule cells. The complete model reproduces known network response properties of the olfactory bulb. In ongoing work, we use this computational model to explore the effects on collective activity in the bulb of direct and granule cell-mediated cortical feedback to mitral cells. Specifically, we test whether cortical feedback can synchronize or de-synchronize groups of mitral cells at specific frequencies, a question that has important implications for how contextual information carried by the feedback changes sensory representations at the periphery and affects the transmission of this information to cortex.

Disclosures: D.E. Kersen: None. **G. Tavoni:** None. **V. Balasubramanian:** None.

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Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.06/Y16

Topic: D.05. Olfaction and Taste

Support: NIH Grant R00DC013305
Thomas Jefferson Fund, a program of FACE

Title: Sensory encoding of natural odor dynamics by mitral and tufted cells in the olfactory bulb

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Abstract: Studying sensory encoding in response to natural, complex stimuli has been important in understanding visual and auditory coding mechanisms, but the stochastic nature of odor plumes has made naturalistic stimuli difficult to quantify, and thus to study, in olfaction.

Therefore, the roles that spatial and temporal dynamics of natural plumes play in conveying olfactory information are not well understood, particularly in macrosmatic mammals such as mice. Since mice navigate in the same turbulent regime as many insects, it is reasonable to test whether mice might employ the same plume features used by insects, such as intermittency and concentration dynamics, to maintain accurate olfactory guided navigation and odor localization across differing environmental conditions. We tested whether the early olfactory system of mice encodes dynamic plume features by imaging neural activity in the main olfactory bulb (MOB) of awake, head-fixed mice (Thy1-GCaMP6f-GP 5.11) during plume-delivered odor presentations. We used customized, miniature sensors to record odor concentration and compared dorsal MOB fluorescence signals from mitral/tufted cells (MTs) to simultaneously-monitored odor fluctuations as mice received plume-delivered odors. Our data suggest that a subset of MTs encode turbulent fluctuations of odor concentration. This implies that plume dynamics could be processed in parallel with odor identity information to allow for rapidly adapting search behaviors in rodents.

Disclosures: S.M. Lewis: None. **J. Park:** None. **M.F. Tariq:** None. **A. Seminara:** None. **D.H. Gire:** None.

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Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.07/Y17

Topic: D.05. Olfaction and Taste

Support: NIH/NIBIB (P41-EB018783)
NIH/NICHD (R25-HD088157)
NIH/NIMH (P50-MH109429)
US Army Research Office (W911NF-14-1-0440)
Fondazione Neurone

Title: Electrophysiological evidence of lateralization in the olfactory system

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Abstract: The ability to distinguish unilateral odor stimuli is relatively unknown in humans, and can be improved by training. The neural correlates of this ability could serve as a basis for diagnostic and assistive applications, but suitable neural correlates have not yet been identified. In this study, we work towards this goal by investigating psychophysical and

electrophysiological human responses to unilateral odor stimuli delivered to the left and right nostril.
Specifically, we conducted two experiments in which 31 healthy young volunteers participated (age 24±4 years). In the first experiment, we divided the subjects by their ability to perform an unilateral odor detection task. To do this, the subjects completed a psychometric odor detection task, in which they were asked to specify the laterality of rose-like odor stimuli that were randomly presented in one of the nostrils. 17 of the 31 subjects correctly discriminate the side of stimulation, 14 did not. A Discriminant Function Analysis correctly classified 100% of the cases for both categories (chi-s[1]=57.556; $p<0.001$). In the second experiment, we used an olfactometer (MOL023-Bughard) to deliver 50 randomized, 250 ms long, unilateral odor stimuli, while we recorded EEG signals sampled at 512 Hz from 128 scalp locations. We then extracted odor-event-related potentials (oERPs) from the EEG signals after artifact rejection, filtering, and baseline correction.
In our analyses, we were interested in temporal and spatial neural correlates that are indicative of the two subject groups, i.e., the ability to distinguish unilateral odor stimuli. To accomplish this, we performed, on the grand average of oERP, three statistical tests between the two groups . The first test included a topographical analysis using global map dissimilarity (GMD). This revealed four time frames inside the epochs in which the topographical maps were different for the two subject groups. In the second test, we performed a spatial cluster analysis on the two grand averages, which identified a total of 17 topographies, 5 of which were shared between both groups. Finally, in the third test, we performed a local autoregressive average (LAuRA, 5000 solution points) algorithm to estimate the intracranial current distribution.
The results of these analyses show substantial differences between the two groups in all three statistical tests, which suggest the involvement of different brain structures in the processing of unilateral odor stimuli. This sheds light on the neural underpinnings of a relatively unknown human ability, and might lead to new diagnostic and assistive applications.

Disclosures: E. Iannilli: None. **T. Hummel:** None. **P. Brunner:** None. **G. Schalk:** None.

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Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.08/Y18

Topic: D.05. Olfaction and Taste

Support: NIH Grant DC013802

Title: Functional features of identical glomeruli in the medial/lateral maps in the mouse olfactory bulb

Authors: *T. SATO, R. HOMMA, S. NAGAYAMA
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Abstract: Axons of olfactory sensory neurons (OSNs) that express the same type of odorant receptor converge onto two glomeruli in the olfactory bulb (OB). One is located in the medial side and the other is in the lateral side of OB. Because these identical pairs of glomeruli are arranged symmetrically, it has been considered that there is a medial/lateral glomerular mirror maps in the OB. In contrast to the clear anatomical evidences, functional studies of these maps have not been conducted well because the majority of the medial glomeruli are located at the medial septum wall of the OB and difficult to access in intact brain. Recently, identical pairs of medial/lateral glomeruli that expressed trace amine-associated receptors (TAARs) are found both in the dorsal OB (Pacifico *et al*., *Cell Reports*, 2012 and Dewan *et al*., *Nature*, 2013). This finding stimulated us to compare their functional properties directly by simultaneous recording of them. In this study, the activity of these identical pairs of glomeruli are measured using *in vivo* wide-field calcium imaging technique with 125Hz temporal resolution. Two odorants, β-phenylethylamine and isopentylamine, were used to stimulate the TAARs glomeruli. For measuring neuronal activity in various types of neurons in the OB, we used Cre-dependent GCaMP3 expressing mice that were crossed with several types of Cre-driver mice (OSNs; OMP-Cre, GABAergic neurons; Gad2-Cre, dopaminergic neurons; DAT-Cre and mitral/tufted cells; Pcdh21-Cre). Contrary to our expectations, we could not find any differences in onset latency, rise time, decay time and peak amplitude of odor evoked activities between the pair of glomeruli in all examined mice. What we found was that medial glomerulus has significantly larger respiration-locked fluctuation in the postsynaptic neurons of Gad2-, DAT- and Pcdh21-GCaMP3 mice. But the differences were not observed in the presynaptic neurons of OMP-GCaMP3 mouse. Interestingly, this trend was also observed in resting condition in pre-stimulation period. However, it is more prominent during odor stimulation. These results were consistently observed in the all experiments using different odorant concentrations. Taken together, these findings raise the possibility that the medial maps in the postsynaptic neurons may contribute to the rhythm for odor information processing.

Disclosures: T. Sato: None. **R. Homma:** None. **S. Nagayama:** None.

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217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.09/Z1

Topic: D.05. Olfaction and Taste

Support: NIH F31DC017394
NSF Grant 1556207

Title: Spatial transcriptomics of olfactory receptors for high throughput mapping of olfactory bulb glomeruli

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Abstract: The formation of position-stereotyped, receptor-specific glomeruli in the olfactory bulb (OB) presents a complex wiring problem due to the expansive olfactory receptor (OR) repertoire and the expression of a single OR in olfactory sensory neurons scattered in the nasal epithelium. Identifying the glomeruli corresponding to a specific OR and overall organization of OR projections is critical to understanding how receptor signals are translated into specific spatio-temporal responses in the OB. Since 1994, tremendous efforts from the field have identified mouse OB glomeruli for ~3% of the 1100 ORs, primarily through in situ hybridization and transgenic reporter mice. The goal of this study is to generate a comprehensive map of mammalian OR glomeruli by applying a novel high-throughput approach that determines the OR identity of a glomerulus by sequencing low-abundance OR transcripts present in the axon termini of OSNs. We first identified the ORs present in the population of dorsal glomeruli viewed in functional imaging studies by dissecting this surface, synthesizing cDNA libraries, and enriching OR and trace amine-associated receptor (TAAR) transcripts using target capture probes. Differential expression analysis of the functional imaging sample and the remainder of the OB found 86 ORs and 11 TAARs to be enriched, with 94% of these ORs expressed in the dorsal olfactory epithelium and no TAARs enriched in the non-functional imaging sample. Spatial information for approximately 900 ORs was attained by targeted sequencing of 100 µm serial sections from individual OBs along the anterior-posterior, ventral-dorsal, and medial-lateral axes. We found reproducibly unique sets of OR transcripts enriched in each of the sections, suggesting OR identities of glomeruli contained in the section. A Bayesian-based reconstruction method will help determine the mirror-symmetric 3D spatial position of each OR's glomeruli from single-dimension transcriptomic data. Our anterior-posterior positional data will serve as a surrogate for OR basal activity, enabling us to rigorously evaluate the hypothesis that GPCR basal activity is a major determinant of OR axon targeting. Establishing an OR-to-OB map will provide a framework for integrating peripheral ligand-OR deorphanization assays with OB odor representations, a key new resource for understanding the olfactory code.

Disclosures: K. Zhu: None. **S.D. Burton:** None. **M. Wachowiak:** None. **H. Matsunami:** None.

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217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.10/Z2

Topic: D.05. Olfaction and Taste

Support: Wellcome Trust – India Alliance Intermediate fellowship IA/I/11/2500290

Title: Learning induced changes in network structure lead to reliable spatiotemporal representations of odors

Authors: *C. G. ASSISI, S. GARG
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Abstract: Olfactory circuits are a paradigmatic example of a system where specific spatiotemporal patterns (transient synchrony in ensembles of principal neurons and oscillations in population activity) have been attributed to odor identity and concentration. Local inhibition plays a key role in organizing spatiotemporal patterns of activity in the olfactory bulb. In fact, the ability to discriminate between similar odors can be enhanced by increasing the degree of inhibition of mitral cells by granule cells in the olfactory bulb. The goal of this study is to understand the relationship between the structure of an inhibitory network and the dynamics of its constituent neurons. Earlier studies have shown that inhibitory interactions between neurons may be represented in terms of the coloring* of the neuronal network. Neurons associated with the same colour tend to fire in approximate synchrony while those associated with different colors fire at different times. The coloring thus provides a simple rule that constrains the spatiotemporal patterns a network can generate. This relationship is easy to see in small or regular networks. However in more complex networks there are typically many ways to color a the network. In fact, determining a colouring, let alone all possible colourings, of an arbitrary network is thought to be an intractable problem. This combinatorial explosion of possibilities also implies that an inhibitory network can potentially generate a large number of spatiotemporal patterns, that is, encode a large number of odors. Some of these patterns may be learned by repeated exposure to the odor stimulus. How does odor learning modify the topology of the network that, in turn, converts an unreliable odor representation into a reliable one? Using a realistic conductance based model of the olfactory bulb, we show that odor learning, implemented as facilitation of inhibitory synapses, can generate a reliable representation of an odor. Further we use algorithms that detect modularity in random networks to show that the dynamics of an olfactory network can be correlated to the modular structure of the network. Inhibitory plasticity modifies the topology of the network in a manner that leads to asymmetries in network structure that generate spatiotemporal patterns that are resistant to noise.
* A colouring of a network is an partitioning that assigns different colours to nodes that are connected to each other. The minimal number of colours required to colour a network is called its chromatic number.

Disclosures: C.G. Assisi: None. **S. Garg:** None.

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Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.11/Z3

Topic: D.05. Olfaction and Taste

Support: NIH DC005259
NIH DC016133
NIH U01 NS099691
KIST 2E267190

Title: Defining the functions of olfactory bulb processing via comparison of input and output

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Abstract: Humans and other animals have the ability to recognize olfactory stimuli as the same across a range of concentrations, as well as the ability to segment novel olfactory stimuli from those in the background. It remains unclear where in the brain processing related to these kinds of perceptions is occurring. Recent work has suggested that the olfactory bulb, the brain structure that mediates the first stage of olfactory information processing is involved in generating perceptual concentration invariance. Here we asked whether the bulb also contributes to olfactory adaptation. Olfactory bulb glomeruli are regions of neuropil that contain input and output processes; olfactory receptor neuron nerve terminals (input) and mitral/tufted cell apical dendrites (output). Differences between the input and output of a brain region define the function(s) carried out by that region. We compared the activity signals from the input and output to repeated odor stimulation, which resulted in a decline in the output maps, while the input maps remained relatively stable. These results suggest that the mammalian olfactory bulb may also participate in the perception of sensory adaptation. Our imaging methods should also be useful for determining the input/output transformation in other regions of the mammalian brain.

Disclosures: D.A. Storace: None. **L.B. Cohen:** None.

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217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.12/Z4

Topic: D.05. Olfaction and Taste

Support: DFG; RO 4046/2-1

Title: Differential modulation of olfactory bulb activity by the basal forebrain

Authors: E. BÖHM, V. SCHWEDA, J. KOESLING, D. BRUNERT, *M. ROTHERMEL
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Abstract: The olfactory bulb (OB) receives neuromodulatory input from diverse areas whose role in shaping early olfactory processing remain unclear. One of the major neuromodulatory centers implicated in attentional modulation of sensory processing, the diagonal band of Broca (HDB), is composed of cholinergic, GABAergic as well as glutamatergic projection neurons. Here we used optogenetic tools to selectively activate or inhibit cholinergic or GABAergic HDB terminals at the level of the OB while recording OB mitral/tufted output neuron activity using multichannel electrophysiological recordings. An optogenetic activation of cholinergic fibers was shown to add an excitatory bias to OB output activity, that is independent of the strength of sensory input. A selective activation of GABAergic neuromodulatory fibers at the level of the OB significantly decreases the activity of mitral/tufted cells. Similar to the cholinergic data, no correlation between modulation strength and sensory input could be observed. Experiments performed using two inhibitory opsins expressed either in cholinergic or GABAergic HDB fibers so far revealed only weak modulation effects, potentially arguing for a weak baseline activity of HDB neurons in the anesthetized condition. These experiments demonstrate that: 1) A differential modulation of neuronal responses can not only be achieved by activating different top-downs system but can also be mediated via different neuronal populations of the same top-down area. 2) Despite recent reports pointing to a potential coexpression of cholinergic and GABAergic markers at the level of the OB, our data argue for a functionally distinct neuronal population. 3) The interplay between different neuronal HDB subpopulations might be important for the fine tuning of sensory information. 4) These modulations are likely to represent local effects mediated by neuromodulatory release at the level of the OB. Future experiments will investigate HDB stimulation effects also in the awake and behaving animal.

Disclosures: E. Böhm: None. **V. Schweda:** None. **J. Koesling:** None. **D. Brunert:** None. **M. Rothermel:** None.

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217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.13/Z5

Topic: D.05. Olfaction and Taste

Support: HFSP (RGP0015/2010)
SNF (310030B_152833/1, CRSII3_130470/1)
Novartis Research Foundation

Title: Dense reconstruction of network-level whitening operations in the olfactory bulb

Authors: *A. A. WANNER[1], R. W. FRIEDRICH[2]
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Abstract: In the olfactory bulb (OB), odors evoke distributed patterns of activity across glomeruli that are reorganized by networks of interneurons (INs). This reorganization results in multiple computations including a decorrelation and normalization of activity patterns across the output neurons, the mitral cells (MCs). To understand the mechanistic basis of these computations it is essential to analyze the relationship between function and structure of the underlying circuit. We combined in vivo multiphoton calcium imaging with dense circuit reconstruction from serial block-face electron microscopy stacks of the larval zebrafish OB (4.5 dpf). First, we measured and mapped the odor responses of >75% of the neurons in the OB. Next, we reconstructed the skeletons of all neurons in the OB (n>1000) and annotated all synapses on these neurons (n>500,000) resulting in the, to our knowledge, first wiring diagram of an entire vertebrate brain region at synaptic resolution. We found that whitening, i.e. the decorrelation and variance normalization of representations of two natural odor classes, amino acids and bile acids, occurs already at the early larval stage, before the emergence of granule cells. The reconstructed connectivity matrix allowed us to model the whitening operations in the OB on network level with single neuron resolution. These simulations suggest that both, decorrelation as well as variance normalization are mediated by specific, non-random connectivity patterns between MCs and INs. These results provide strong evidence that the connectivity between MCs and INs determines circuit function in the OB, and that the network is optimized, presumably by evolution, to process representations of natural odors.

Disclosures: A.A. Wanner: None. **R.W. Friedrich:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.14/Z6

Topic: D.05. Olfaction and Taste

Support: ERC Grant #616063
ISF Grant #224-17

Title: The role of adult born neurons in mitral cell odor coding

Authors: *H. SHANI NARKISS, A. VINOGRAD, G.-I. TASAKA, S. TERLETSKY, M. GROYSMAN, A. MIZRAHI
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Abstract: Adult born neurons (abNs) are continuously generated in the sub ventricular zone, from which they migrate to and integrate in the Olfactory Bulb (OB). The role of abNs in odor processing in the OB remains unknown because of technical limitations to reliably target these neurons with high efficiency for causal manipulations. Here we report the use of a newly developed Cre-reporter mouse (called TB) to study adult neurogenesis (Tasaka et al. 2018; Nature Communications 9(1), 871). We use this mouse with the Nestin-CreER2 driver for cellular labeling and genetic manipulation of abNs. As compared to the Rosa26 reporter, TB recombination was >2 fold higher as measured at any age after Tamoxifen induction (15, 30 and 60 days post injection, n=15 mice), thus showing highly efficient recombination in abNs with near zero levels of noise. Using this system, we induced recombination in abNs and expressed an inhibitory (Gi coupled) DREADD for silencing 30-60 days old abNs. To study the role of abNs on odor coding, we used *in vivo* two photon imaging to compare the responses of Mitral cells (MCs; expressing the calcium indicator GCamp6f via AAV5-CAMKII-GCamp6f) in a paired design - before and after silencing the abNs with CNO (5mg/kg). We imaged odor responses by MCs (N=339 MCs from n=10 experimental mice; N=389 cells from n=10 control mice) to a panel of 11 odors (6 monomolecular and 5 natural odors), expecting a dis-inhibitory effect on basic MC odor responses. Surprisingly, the exact opposite effect was consistently measured. On average, dis-inhibiting abNs induced an inhibitory effect on MC responses. Odor induced calcium responses decreased by approximately 20% in the experimental group (n≈2000 cell odor pairs, n=10 mice, t-test, p=10^-3), but remained stable in the control group (n≈2000 cell odor pairs, n=10 mice; t-test, p=0.8). Moreover, while excitatory odor-responses were inhibited, inhibitory odor-responses were strengthened and these results were observed in both anesthetized and awake mice. We are currently assessing the effects of silencing abNs on population codes by MCs. Taken together, these results underscore an unexpected excitatory effect of abNs on MC odor coding.

Disclosures: H. Shani Narkiss: None. **A. Vinograd:** None. **G. Tasaka:** None. **S. Terletsky:** None. **M. Groysman:** None. **A. Mizrahi:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.15/Z7

Topic: D.05. Olfaction and Taste

Support: NIH R01 DC013329
NSF GRFP DGE1144152
NIDCD NRSA F31 DC016482

Title: Development and refinement of functional properties of adult-born neurons in the olfactory bulb

Authors: *J. WALLACE, V. MURTHY
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Abstract: New neurons appear only in a few regions of the adult mammalian brain and become integrated into existing circuits. Despite extensive studies on adult neurogenesis, little is known about the functional development of individual neurons in their native environment in vivo and whether its regulation involves mechanisms similar or distinct from those operating in other brain regions during early postnatal development. We recently examined the functional life history of visualized adult-born granule cells (abGCs) in the olfactory bulb of mice using multiphoton imaging (Neuron 96:883-896). We found that abGCs can become responsive to odorants as soon as they arrive in the olfactory bulb. Tracking identified abGCs chronically over several weeks revealed that the robust and broadly-tuned responses of newly arrived abGCs gradually become weaker and more selective over a period of about 3 weeks. To address the cellular and molecular mechanisms involved in the functional refinement of abGCs, we have begun to examine the role of microglia. The ablation of microglia, which have been shown to play a role in synaptic refinement during development in other brain regions, reduces the odor responses of developing, but not preexisting GCs and alters their odor selectivity. In ongoing work, we investigate the role of microglia, and their interplay with abGCs, in complex olfactory behaviors.

Disclosures: J. Wallace: None. **V. Murthy:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.16/Z8

Topic: D.05. Olfaction and Taste

Support: NIH/BRAINI R21

Title: Calcium imaging of concentration change coding in the mouse olfactory bulb

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Abstract: All sensory modalities must track how stimuli change over time. To accomplish this, many neurons in sensory systems respond preferentially to dynamic stimuli, thus enhancing temporal contrast. Given the ethological importance of odor concentration change (ΔC) to tracking an odor, the olfactory system may also accentuate temporal changes. While dynamic stimulation is standard in studies of other sensory modalities, studies of mammalian olfaction have traditionally used square stimulus pulses of the same concentration. To provide dynamic odor stimuli, we developed an odor delivery system that can change odor concentration within the typical inhalation timeframe via air dilution manifold. This enables not just fast onset of the stimulus, but fast concentration changes on the timescale of individual sniffs. Importantly, these step-function stimuli reach steady state by the time the mouse begins to inhale, making them reproducible from trial to trial. Using electrophysiological recordings, we have previously shown that neurons of the mouse olfactory bulb explicitly encode ΔC. To understand the spatial distribution and morphological identity of ΔC sensitive neurons, we have performed calcium imaging, utilizing the ability of two photon imaging to reveal the spatial arrangement of imaged neurons. Using standard intersectional viral/transgenic techniques, we express GCaMP 6f in mitral and tufted cells of the olfactory bulb. We then image these neurons through chronically implanted windows on the dorsal surface of the bulb. Thus we can visualize ΔC-sensitive neurons, a putative cell type which may contribute to odor tracking.

Disclosures: M.A. Brown: None. **P.R. Parker:** None. **R. Shusterman:** None. **M. Smear:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.17/Z9

Topic: D.05. Olfaction and Taste

Support: NIH GRANT DC000566
NRSA 1F31DC016483-01A1

Title: Does the power of the local field potential in the olfactory bulb carry information on odorant concentration?

Authors: *J. LOSACCO, D. RESTREPO
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Abstract: Odor concentration, through its perceived intensity, can be used to localize food and avoid predators. Changes in concentration also change the quality of the odor, possibly to modulate salience. The cellular underpinnings of concentration encoding in the first relay of the olfactory system (the olfactory bulb) have been well-studied with respect to identifying pertinent cell types and basic physiology in the glomerular column. Mitral/tufted cells (M/T) are the primary projection neurons of the olfactory bulb (OB) and contribute to a gamma oscillation (35-95 Hz) in the LFP via granule cell-mitral cell reciprocal dendrodendritic interactions. M/T respond to increased odor concentration with reduced firing latency. However, markedly less is known about how the network of intact circuitry acts as a whole to convey stimulus strength to higher order regions of the brain.

Here, we implanted tetrodes into the mitral cell layer of the dorsomedial olfactory bulb of C57BL/6 mice and recorded LFP while they performed the behavioral go-no go task. This variant of the task uses different concentrations rather than odorant identities. Six half-log dilutions of isoamyl acetate in mineral oil were used, with the three highest (10%, 3.2%, and 1%) being rewarded and the three lowest (0.32%, 0.1%, and 0.032%) being unrewarded. To be rewarded, mice had to lick a water delivery tube for the high concentrations and refrain from licking for the low concentrations.

All five mice learned the task, surpassing the 80% performance threshold within three-four days of recording. The LFP was measured to study the dependence of oscillatory circuit activity on stimulus strength. We assayed the ability to discriminate between concentrations using the power of the LFP with a receiver operating characteristic analysis. For both naïve (performance 45-65%) and proficient (performance 80-100%) animals we found that the LFP power as able to discriminate between the rewarded and unrewarded stimuli but did not successfully differentiate concentrations with the same reward status. This was found for all bandwidths.

Disclosures: J. Losacco: None. **D. Restrepo:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.18/Z10

Topic: D.05. Olfaction and Taste

Support: NIH Grant1 R03 DC013997-01

Title: Serotonergic neurons in the *Drosophila* olfactory system have a combination of both top-down and bottom-up connectivity

Authors: *K. COATES[1], S. A. CALLE-SCHULER[2], J. S. LAURITZEN[2], B. N. MARTIK[1], L. WARNER[1], S. V. VALLA[1], F. LI[2], D. D. BOCK[2], A. M. DACKS[1]
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Abstract: Neuromodulation is a fundamental feature of the brain, enabling neural networks to flexibly respond to stimuli based on an animal's current needs. However, the nature of the input that drives activity of modulatory neurons has been particularly challenging to determine due to the large number and diverse nature of neurons within modulatory nuclei. In particular, the degree to which modulatory neurons are regulated in a "top-down" or "bottom-up" manner, is unclear. We therefore took a single cell resolution approach by reconstructing a pair of identified serotonergic neurons, the "CSDns", in the *Drosophila* olfactory system in a whole adult brain electron microscopy dataset. We determined the relative distribution of input and output across brain regions, and quantitatively assessed sources of synaptic input to these modulatory neurons. If the CSDns function in a "top-down" manner, we would expect processes in which the CSDns only receive input and other regions in which they only provide output. However, if they function in a "bottom-up" manner, we would expect that the CSDns will have a mixture of input and output within a given brain region. This was indeed the case, as the CSDns had mixed input and output within the contralateral antennal lobe, lateral horn, mushroom bodies and superior protocerebrum, suggesting that a large amount of CSDn activity occurs within the context of ongoing activity in their target network. However, the CSDns also had distinct "input islands" consisting of only post synaptic sites, suggesting that these sites represent significant regulatory domains for the CSDns. By reconstructing neurons upstream of the CSDns in these "input islands", we identified a previously uncharacterized population of neurons that form a multi-tiered feedforward network that converges upon the CSDns. These neurons span both brain hemispheres and, combined, provide a substantial amount of synaptic input to the CSDns. Thus, these modulatory neurons have both bottom-up interactions with their target network, yet also receive regulatory input from a small number of neurons within a distinct neuron class.

Disclosures: S.A. Calle-Schuler: None. **J.S. Lauritzen:** None. **B.N. Martik:** None. **L. Warner:** None. **S.V. Valla:** None. **F. Li:** None. **D.D. Bock:** None. **A.M. Dacks:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.19/Z11

Topic: D.05. Olfaction and Taste

Support: 5T32EB01485506
NeuroNexus Grant (#1707221).
NSF CAREER grant (#1453022)

Title: Differential processing through distinct neural ensembles in the *Drosophila* olfactory system

Authors: *D. LING, H. RONG[1], S. PARK[1], Y. BEN-SHAHAR[3], M. ANASTASIO[2], B. RAMAN[4]
[1]Biomed. Engin., Washington Univ. in St Louis, Saint Louis, MO; [2]Biomed. Engin., Washington Univ. in St Louis, St Louis, MO; [3]Biol., Washington Univ., Saint Louis, MO; [4]Biomed. Engin., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: The excitatory and inhibitory projection neurons (ePN and iPN, respectively) of the *Drosophila* antennal lobe receive and process sensory input from the antenna which they then relay to higher order brain centers such as the mushroom body (MB) and lateral horn (LH). Classically, the MB is thought to mediate associatively learned behaviors, while the LH facilitates innate behaviors. The ePNs are predominantly uniglomerular and project to both the LH and MB, whereas the iPNs are mostly multi-glomerular and send their outputs only to the LH. The functional role of these distinct pathways and how they process olfactory information is currently not well understood. To address this issue, we have begun light-sheet volumetric calcium-imaging of different stages of the olfactory system including sensory neurons, antennal lobe neurons, and MB neurons. Our preliminary data reveals that the sensory neuron input from the antenna has more discriminatory information, whereas ePN and iPN activities evoked by different odorants appear to be more correlated and become more similar as a result of processing within the antennal lobe. Currently, we are examining how well ePN and iPN activities predict the overall behavioral attraction or repulsion of the odorants.

Disclosures: H. Rong: None. **S. Park:** None. **Y. Ben-Shahar:** None. **M. Anastasio:** None. **B. Raman:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.20/Z12

Topic: D.05. Olfaction and Taste

Support: NSF DMS 1361145
Washington Research Foundation

Title: Modeling network connectivity for dopamine-mediated olfactory learning in mosquitos

Authors: K. JUNG, J. RIFFELL, *E. SHLIZERMAN
Univ. of Washington, Seattle, WA

Abstract: We study neural population coding of mosquitoes AL projection neurons subject to dopamine modulation. Projection neurons encode different stimuli via population fixed points in the response of Projection Neurons (PNs). Methods of dimension reduction, such as Optimal Exclusive Threshold Reduction (OETR), have been shown to be effective in the inference of low dimensional odor space which spans fixed points associated with monomolecular stimuli.
In our work, we apply the OETR method to multi-neuron recordings from mosquitoes PNs in three phases: before (S1), during (Dop), and after (S2) superfusion of dopamine over the brain of mosquitoes. We first test which stimuli produce separable fixed points, and once we found these, we construct a low dimensional odor space to map the fixed points and transients reaching them. We then examine the representation of the fixed points in different phases.
The trajectories of the fixed points in three different phases (S1, Dop, and S2) reveal that (i) superfusion of dopamine has longer-term effects on the AL encoding space, and that (ii) the degree of modulation differs from one odor to another. Particularly, neural responses to benzaldehyde show fixed point relocations in both Dop and S2 phases, while the fixed points associated with ammonia almost do not change their location in all three phases.
We employ a network model which infers the connectome of neurons in the AL from neural data and the odor space to investigate how dopamine modulation could rearrange neural connectivity in the AL. We solve the convex optimization problem in three different phases of dopamine superfusion (S1, Dop, and S2) and find the connectomes associated with each phase. Connectome analysis indicates that the distribution of connectivity matrices is being modified to accommodate the observed relocation of fixed points in the odor space. We, therefore, ask what are the changes the lateral inhibition from LN to PN is undergoing by fixing the connectivity within the LNs for all phases. We find that the distribution of lateral inhibition connections narrows in the transition from S1 to Dop and narrows further in the transition from Dop to S2. Taken together our results provide a first structural description of neural encoding modulation and possible anatomical changes associated with dopamine-mediated olfactory learning. These

results can be used to explore the connectivity patterns of dopamine neurons within the AL and their functionality with respect to learning.

Disclosures: K. Jung: None. **J. Riffell:** None. **E. Shlizerman:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.21/Z13

Topic: D.05. Olfaction and Taste

Title: Multiple neuromodulators influence odor coding via distinct mechanisms

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Abstract: Animals constantly adjust sensory processing to meet the ongoing demands of a dynamic internal and external environment. In the olfactory system, extrinsic modulatory neurons adjust odor coding within the context of ongoing activity in other brain regions, yet the consequences of integrating multiple modulatory inputs are not well understood. The antennal lobe (AL; the first olfactory neuropil) of the moth, *Manduca sexta* is innervated by widely projecting serotonergic and dopaminergic extrinsic neurons whose processes overlap extensively with both projection neurons (PNs) and local interneurons (LNs) across all glomeruli. Therefore, single PNs and LNs may be simultaneously influenced by both modulators. Using extracellular tetrode recordings, we asked do both modulators 1) target the same neurons, 2) affect the same temporal features of odor-evoked responses, and 3) alter olfactory coding via similar mechanisms. 5-HT alone increases response duration and odor-evoked firing rate of PNs, but does not affect a post-excitation inhibitory phase intrinsic to PNs ("I_2"). Although, DA alone also increases odor-evoked firing rate, it significantly shortens I_2, allowing PNs to recover to baseline quicker. This suggests that while both 5-HT and DA increase odor-evoked firing rate, they affect different temporal features of PN responses. In combination, 5-HT and DA increase odor evoked firing rate and decrease I_2, suggesting that modulatory effect of DA dominates when both modulators are integrated in a single neuron. In LNs, both 5-HT and DA alone increase post-inhibitory rebound excitation. However, their integrated effects are non-linear and subtractive, suggesting that both modulators may be targeting different and potentially opposing second messenger pathways. Overall, we find that most AL neurons integrate the influence of both 5-HT and DA, and while each modulator has similar effects on odor-evoked responses when applied alone, their integrated effects suggest each modulator alters olfactory coding via separate mechanisms.

Disclosures: K.M. Lizbinski: None. **A.M. Dacks:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.22/Z14

Topic: D.05. Olfaction and Taste

Support: ONR Grant#: N000141612426
NSF CAREER Award Grant #1453022

Title: Distinct ensembles encode opposing odor valences in the antennal lobe

Authors: *R. CHANDAK[1], B. RAMAN[2]
[1]Biomed. Engin., Washington Univ. in St. Louis, Saint Louis, MO; [2]Biomed. Engin., Washington Univ. in St. Louis, St Louis, MO

Abstract: Sensory stimuli evoke neural responses that map their identity, encode preferences, and guide behavior. Predicting and understanding how neural activities encode odor valences, which guide behaviors such as fleeing away from a predator or towards food, are open challenges in systems neuroscience. In this study, we used the locust (*Schistocerca americana*) olfactory system to examine this issue.

We began by examining neural recordings from excitatory projection neurons (PNs) in the locust antennal lobe that receive sensory input from olfactory receptor neurons in the antenna. Our results indicate that putatively attractive and repulsive odorants activate nearly distinct ensembles of PNs. For a given odor group, there still was sufficient information to distinguish and recognize individual stimuli. Taken together, these results indicate that there may be an organizational logic with which olfactory stimuli are encoded at the level of ensembles of neural activities in the antennal lobe.

In parallel, we are also systematically examining both innate and acquired behavioral preference of locusts to the same odor panel. Our preliminary results indicate that starved locusts could be conditioned to associate an odor with a food reward only when the odorant was innately attractive. Repulsive odors were not learnable. Interestingly, the offset of repulsive odors induced cross-learning for some attractants. Currently, we are examining how much of these behavioral preferences can be predicted from ensemble PN responses.

In sum, our results reveal that in the insect antennal lobe, unique ensembles of neurons may guide orthogonal behaviors (i.e., attraction vs repulsion). In particular, we see a binarization of odorants into attractive and repulsive categories with unique neural responses, behavioral outputs, and learnabilities.

Disclosures: R. Chandak: None. **B. Raman:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.23/Z15

Topic: D.05. Olfaction and Taste

Support: Office of Naval Research grant (N000141612426) to B. R.
NSF CAREER grant (#1453022) to B.R

Title: Encoding the expectation of a sensory stimulus

Authors: *L. ZHANG[1], A. B.-Y. CHEN[2], D. SAHA[2], B. RAMAN[2]
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Abstract: Most organisms possess an ability to differentiate unexpected or surprising sensory stimuli from those that are repeatedly encountered. How is this sensory computation performed? We examined this issue in the locust olfactory system. We found that odor-evoked responses in the antennal lobe (downstream to sensory neurons) systematically reduced upon repeated encounters of temporally discontinuous stimulus. Rather than confounding information about stimulus identity and intensity, neural representations were optimized to encode equivalent stimulus-specific information with fewer spikes. Further, spontaneous activity of the antennal lobe network also changed systematically and became negatively correlated with the response elicited by the repetitive stimulus (i.e. 'a negative image'). Notably, while response to the repetitive stimulus reduced, exposure to an unexpected/deviant cue generated undamped and even exaggerated spiking responses in several neurons. In sum, our results reveal how expectation regarding a stimulus is encoded in a neural circuit to allow response optimization and preferential filtering.

Disclosures: L. Zhang: None. **A.B. Chen:** None. **D. Saha:** None. **B. Raman:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.24/Z16

Topic: D.05. Olfaction and Taste

Support: NSF 1556337

Title: Novelty detection in early olfactory processing of the honeybee, apis melifera

Authors: *H. LEI[1], S. HANEY[2], C. M. JERNIGAN[1], X. GUO[3], C. COOK[1], M. BENZHANOV[4], B. SMITH[1]
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Abstract: As a form of nonassociative learning, sensory habituation to repeated inconsequential stimuli is a ubiquitous plasticity in animals' normal cognition. While filtering out such constant stimuli, animals are sensitized to respond to novel stimuli that may carry positive or negative value. The mushroom body output neurons in fruity flies - the 3rd-order central neurons in olfactory pathway - decrease response to repeated odor stimuli but increase response to novel odors. The basis supporting such novelty detection at the higher synaptic level is still not well understood. Here we show that in honeybees neural circuits at the early processing stage - the antennal lobe - are capable of adjusting neuronal responses so that the repeatedly exposed odor is weakly represented but novel odor is strongly contrasted. Modeling approach reveals that the circuit plasticity results from modification of GABAergic synapses within the network, expressed as local habituation and global sensitization.

Disclosures: S. Haney: None. **C.M. Jernigan:** None. **X. Guo:** None. **C. Cook:** None. **M. Benzhanov:** None. **B. Smith:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.25/Z17

Topic: D.05. Olfaction and Taste

Support: Human Frontier Science Program grant for Brian H Smith as co-PI.

Title: Glutamate-gated chloride channel receptors in the olfactory neuropils in the honey bee brain

Authors: *I. SINAKEVITCH[1], C. ARMENGAUD[2], B. H. SMITH[1]
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Abstract: Glutamate-gated chloride channels (GluCls) are members of the Cys-loop ligand-gated ion channel superfamily. In the honey bee, a single gene, *amel_glucl*, encoding multiple isoforms of a GluClalpha subunits, was previously investigated in the Armengaud lab [1, 2]. Here we report on studies of its distribution and possible functions in the antennal lobe and mushroom bodies, which are the functional analogs to the mammalian olfactory bulb and cortex,

respectively. We used antibodies against GluCl1 subunits to study its co-localization with the synaptic marker (anti-synapsin) and specific identified neurons using neural tracing techniques (neurobiotin) in the antennal lobe and mushroom bodies of the honey bee. In the antennal lobe, the anti-GluCl1 co-labels with uniglomerular projection neurons and does not co-localize with anti-synapsin. The data strongly suggest that glutamate is an important neuroactive molecule involved in inhibition of the uniglomerular projection neurons (uPNs) in the antennal lobe. The source of the glutamate in the antennal lobe is still under the investigation. The anti-GluCl1 also labels presynaptic terminals of uPNs in the calyx of the mushroom bodies (MBs). Moreover, the Kenyon cell dendrites in the MB olfactory calyx area (lip and basal ring) also express GluCl1 subunits. The subset of claw-type Kenyon cells also express GluCl1 subunit in the dendrites, cell bodies and axons in the gamma and lip area of the MB lobes. We concluded that GluCl channels are an important part of the olfactory processing center in the antennal lobes and MBs. Based on these results we propose a neuroanatomical model of the action of GluCl channels in olfactory processing. 1. El Hassani, A.K., et al., *Identification, localization and function of glutamate-gated chloride channel receptors in the honeybee brain.* Eur J Neurosci, 2012. **36**(4): p. 2409-20. 2. Demares, F., V., et al., *Expression and localization of glutamate-gated chloride channel variants in honeybee brain (Apis mellifera).* Insect Biochem Mol Biol, 2013. **43**(1): p. 115-24.

Disclosures: I. Sinakevitch: None. **C. Armengaud:** None. **B.H. Smith:** None.

Poster

217. Olfaction: Second Order Regions: Olfactory Bulb and Antennal Lobe

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 217.26/Z18

Topic: D.05. Olfaction and Taste

Title: Metamorphic development of the olfactory system in the red flour beetle (tribolium castaneum)

Authors: *B. TREBELS, S. DIPPEL[1], B. GÖTZ[1], C. KNOLL[1], M. UHL[1], E. A. WIMMER[2], J. SCHACHTNER[1]
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Abstract: Insects depend on their olfactory sense as a vital system. External cues are transformed through a rather complex pathway into internal information, which the animal can further process into various types of behavior. In holometabolous insects, like the red flour beetle *Tribolium castaneum*, the olfactory system is massively restructured during metamorphosis to match the adult requirements.
In the current study, we investigate the metamorphic development of the antennal olfactory sensory neurons (OSNs) and the antennal lobe (AL) in *T. castaneum*. The paired AL are the first

integration centers for the processing of antennal olfactory information (Dippel et al., 2016. BMC Biol 14:90). We correlated the AL development with the antennal OSN formation based on reporter expression of a partial *Orco Gal4/UAS-DsRed* line at different stages of metamorphic development. We found that the AL glomeruli are formed between 40% and 50% of total metamorphosis. Our data from the partial *Orco*-Gal4 line and immunohistochemical staining (IHC) against Orco indicate the reappearance of the antennal OSN and Orco expression, which disappeared in the pre-pupae, starting from 10% of total metamorphosis. These data suggest, similar to results found in *Drosophila melanogaster* (Jefferis et al., 2002. Curr Opin Neurobiol 12:80–86) that the larval OSN undergo programmed cell death and are replaced with new OSN between the pre-pupal stage and the first pupal stages of *T. castaneum.* However, unlike in *Drosophila,* expression of *Orco* reappears prior to the formation of the AL glomeruli. Currently we address the question whether the loss of the IHC and reporter signal in the prepupal stage is due to apoptosis of the larval OSN or loss of Orco expression. Therefore, we use the TUNEL assay to detect apoptosis and the thymidine analogue 5-ethyl-2'-desoxuridine (EdU) to label newborn neurons. In a second approach, we investigate the influence of Orco on the development of the antennal OSN during metamorphosis by performing a RNAi mediated systemic knockdown of *Orco* in the last larval stage (L6). Preliminary results show that fewer OSN reach the antennal lobes and less glomeruli are formed in the adult beetle. This indicates, in contrast to the fruit fly that Orco is required for the correct ingrowth of the OSN and the formation of the olfactory glomeruli, which is similar to recent results from ants (Yan et al., 2017. Cell 170:736-747.e9.; Trible et al., 2017. Cell 170:727-735.e10.).

Disclosures: S. Dippel: None. **B. Götz:** None. **C. Knoll:** None. **M. Uhl:** None. **E.A. Wimmer:** None. **J. Schachtner:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.01/AA1

Topic: D.05. Olfaction and Taste

Support: JSPS KAKENHI JP17H02088

Title: Ingesting/rejecting food may be determined in peripheral neurons in *Aplysia* buccal mass

Authors: *K. UMETA, T. YANAGI, Y. YOSHIMI
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Abstract: Taste is an important sense for determining whether the intaken food to be ingested or rejected for survival. A marine gastropod *Aplysia* has large neurons and shows clear taste preferences, which is modified by the experience and learning. We found sensory cells in S-

cluster of buccal ganglion responds to the hated taste faster (latency of *ca.* 2 s) than a preferred taste (latency of *ca.* 4 s). The difference of the latency is consistent with the fact that animals must respond more quickly to the disadvantageous information than advantageous one. However, it is unlikely that S-cluster sensory neurons, which is “input port” of the buccal ganglion, decide the latency with considering the taste preference. We hypothesized that the decision is made by the cerebral ganglion which controls important decision of behavior and connects with S-cluster neurons. The hypothesis was verified experimentally:
Buccal mass and buccal ganglion and cerebral ganglion was isolated with retaining the connection with nerve flux. The neurons in the ganglion were stained with fluorescent voltage sensitive dye (VSD,Di-4-ANEPPS) in the presence of tetraethyl ammonium (TEA) chloride to prolong action potential duration to be determined by voltage imaging. Subsequently, preferred taste (L-asparagine), hated taste (distilled water, L-aspartic acid), and non-taste (artificial seawater: ASW) were administered to radula portion. Then the responses of the fluorescent image were monitored after administration of preferred taste ($_{L}$-asparagine), hated taste (distilled water, $_{L}$-aspartic acids) or non-taste (artificial seawater: ASW) to radula inside the buccal mass. As a result, cerebral ganglion responded with same latency (*ca.* 1s) toward administrations of all fluids including ASW. The result indicates that neurons in cerebral ganglion respond to only touch sense of by administrated liquid thus it is unlikely that cerebral ganglion contributes to the decision of behavior responding to the tastes. Contrastively the VSD-stained BN-2 and BN-3 nerve bundles between the buccal mass and the buccal responded to the hated tastes with 2 s time lag but did to the preferred tastes with 4 s and indicated no response to ASW.
Those results indicated that ingestion or rejection of foods are determined by the taste at buccal mass but not at cerebral ganglion.

Disclosures: T. Yanagi: None. **Y. Yoshimi:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.02/AA2

Topic: D.05. Olfaction and Taste

Support: NIH R01DC006666
NIH F31DC015931

Title: Incidental taste experience enhances learning and changes firing-rate dynamics in gustatory cortex

Authors: *V. FLORES[1], J. WACHUTKA[2], D. LEVITAN[3], D. B. KATZ[4]
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Abstract: In conditioned taste aversion (CTA), an animal learns to avoid a particular taste that has been paired with malaise. Familiarity with future taste conditioned stimuli (CS) has long been known to reduce the strength of aversion learning. Recently, we have demonstrated that pre-exposure to "incidental" stimuli can influence later learning as well: specifically, pre-exposure to salty and sour tastes strengthen a later learned aversion to novel sucrose (Flores et al 2016); further work using immediate early gene expression (c-Fos) and optogenetics identified the gustatory cortex as a cite of enhanced learning-related neural activity caused by taste pre-exposure (TPE) - levels of CTA-associated c-Fos were higher in rats that had received TPE, but inhibition of GC activity during TPE eliminated both TPE's effect on future CTA learning and on learning-associated c-Fos. One potential interpretation of these results is that TPE changes the salience of the later-presented novel taste, thus enhancing its associability during CTA. Here, we explore this possibility, using (ensemble) single-neuron electrophysiology to determine how TPE changes GC firing rate dynamics in response to a novel CS before and after CTA. Parallel work unraveling the impact of TPE on other taste processing regions including the basolateral amygdala, central amygdala and hippocampus using c-Fos is guiding further electrophysiological experiments. Together, this work will both define an underlying neural circuit involved in TPE processing and further characterize the impact of TPE in GC neural activity.

Disclosures: V. Flores: None. **J. Wachutka:** None. **D. Levitan:** None. **D.B. Katz:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.03/AA3

Topic: D.05. Olfaction and Taste

Support: Intramural Grant Western University of Health Sciences 12356D
R01-RDC007628 NIDCD

Title: BDNF overexpression in transgenic mouse-lines preserves T1R3 and prevents taste disorder following chemotherapy

Authors: G. LUONG[1], L. G. PALACIOS[2], S. KEZIAN[2], A. TRAN[2], B. S. HENSON[1], C. A. NOSRAT[1], *I. VUKMANOVIC NOSRAT[1]
[1]Col. of Dent. Med., [2]Col. of Biomed. Sci., Western Univ. of Hlth. Sci., Pomona, CA

Abstract: Chemotherapy administered to patients for treatment of different kinds of cancers, has been shown to cause several side effects, such as impaired taste perception. Vismodegib is given to patients suffering from basal cell carcinoma (BCC) that is not amenable to surgical excision. BCC is the most common cancer and is caused by alterations in the Shh signaling pathway in the skin, predominantly mutations in Ptc, however mutations of Smo can also give rise to this

condition. As a result, the inhibition of signaling activity of Smo is lost, causing uncontrolled proliferation of basal cells. When Shh binds to Ptc in healthy basal cells, the inhibition of Smo is lost, and the activated Gli travels into the nucleus and activates proliferation. On the other hand, when Shh does not bind Pts, the pathway is inactive. The first FDA approved chemotherapy for treatment of BCC is vismodegib, which is an inhibitor of Smo and tumor shrinkage is observed in patients taking this drug. The Shh pathway is crucial in taste buds as the taste cells have a relatively short life span and need to be renewed continuously. Vismodegib treatment causes a decreased number of precursor cells in taste buds, and thereby cause a decreased number of type II cells encompassing the T1R3 receptor, which is a common subunit in the sweet (T1R2/T1R3) and umami (T1R1/T1R3) taste receptors. Thus, patients taking vismodegib lose normal taste sensation. Up to 55% of patients experience dysgeusia and many discontinue taking the drug. Treatment with neurotrophic factors to injured or atrophied organs has been shown to stimulate neuronal survival and functional improvement. Here we aim to show that overexpression of brain-derived neurotrophic factor (BDNF) in taste buds is able to prevent the side effects of chemotherapy. We used the two unique Gust-BDNF mouse-lines, as BDNF is the most potent neurotrophic factor in the gustatory system. We administered vismodegib orally for 10 weeks in an almond butter mixture, followed by taste preference evaluation using a 10mM sucrose solution. Thereafter, we used the T1R3 antibody to analyze the expression of the sweet/umami taste receptor. The T1R3 receptor showed a lower expression after the chemotherapy in both wild type and the BDNF overexpressing mice, however the decrease was less in Gust-BDNF mice. Additionally, the Gust-BDNF mice were able to detect sucrose after 10 weeks of chemotherapy, while the wild type mice were not, and the difference was significant for both of the mouse-lines. Preservation of the T1R3 receptor strengthens our hypothesis that BDNF overexpression is ascribable to preventing dysgeusia following chemotherapy.

Disclosures: G. Luong: None. **L.G. Palacios:** None. **S. Kezian:** None. **A. Tran:** None. **B.S. Henson:** None. **C.A. Nosrat:** None. **I. Vukmanovic Nosrat:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.04/AA4

Topic: D.05. Olfaction and Taste

Title: Wiring bitter taste with semaphorin signals

Authors: *L. J. MACPHERSON[1], H. LEE[2]
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Abstract: Animals depend on sensory cells in the oral cavity for the selection of food sources. Sweet, umami, and salty stimuli convey nutritional value, whereas bitter and sour inform the presence of toxic, unripe, or spoiled foods. The connectivity between taste receptor cells (TRCs) in the oral cavity and axons from their partner neurons in the gustatory ganglia must be correctly established in order to respond appropriately (attraction vs. aversion) to a taste stimulus. Notably, TRCs turn over rapidly throughout the lifetime of the animal. How do ganglion neurons recognize and wire to each new taste receptor cell? Specific guidance cues have recently been identified which coordinate this process for sweet and bitter TRCs. One of these cues, Semaphorin (Sema3A) is selectively expressed in bitter TRCs to promote connectivity with bitter-responsive gustatory ganglion neurons, ensuring fidelity and specificity of the bitter 'labeled line'. We now investigate the role of Sema3A receptors expressed by partner bitter ganglion neurons in completing the 'handshake' between TRCs and gustatory ganglion neurons at the periphery. Using Sema3A-receptor-Cre transgenic mice, we establish bona fide markers of bitter gustatory ganglion neurons, providing a crucial genetic handle on a functional population of peripheral gustatory neurons enabling future investigations into the connectivity of bitter taste circuits from the tongue to the brain.

Disclosures: L.J. Macpherson: None. **H. Lee:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.05/AA5

Topic: D.05. Olfaction and Taste

Support: NIH R01 DC006666

Title: Lithium chloride injection alters taste processing in the gustatory cortex

Authors: *B. T. STONE, J.-Y. LIN, N. MUKHERJEE, D. KATZ
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Abstract: Conditioned taste aversion (CTA) is a well-established learning paradigm whereby an association between a taste and paired effect (e.g. nausea) causes an animal to develop an avoidance behavior to the same stimulus at a later time point. A large literature addresses how toxicity by way of drug injection (commonly lithium chloride; LiCl) shapes aversive behavior, but few studies have delved into the nature of this powerful state itself. Here, we report the beginning of an investigation into how the spontaneous network state induced by LiCl specifically impacts taste processing, and how the activity underlying this affective state might support learning. Using extracellular (single-neuron and local field potentials; LFPs) recordings during a passive taste delivery task under two (LiCl-induced sickness and Neutral) conditions, I

have shown an evolution of LiCl-related network activity (i.e., spectral properties of local field potential firing) in which rhythmic activity in the 7-12Hz range emerges at 12 minutes post injection and vanishes 6 minutes later. I then probed the nature of the interaction between affective state and coding within the rat gustatory cortex (GC). I found that LiCl-induced sickness, in comparison to encoding an array of tastes under a neutral (healthy) state, altered discriminability efficacy within the much-studied "identity epoch" and protracted modulations in low-frequency (7-12Hz and 13-30Hz) LFPs during processing of novel taste stimuli. These cellular and network profiles were maintained when the same tastes were presented again 2 days later, further substantiating an affective state-dependent encoding processes that recursively appears as a product of associative learning.

Disclosures: B.T. Stone: None. **J. Lin:** None. **N. Mukherjee:** None. **D. Katz:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.06/AA6

Topic: D.05. Olfaction and Taste

Support: NIDCD R01 DC006914 to PMD

Title: Optogenetic stimulation of gabaergic neurons in the nucleus of the solitary tract of the tat enhances taste information and retards taste-related learning

Authors: *J. D. SAMMONS[1], C. E. BASS[2], J. D. VICTOR[3], P. M. DI LORENZO[1]
[1]Psychology, Binghamton Univ., Binghamton, NY; [2]3435 Main St., Univ. At Buffalo SUNY, Buffalo, NY; [3]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: The first central nucleus in the taste system, the nucleus of the solitary tract (NTS), contains a heterogeneous mix of neuronal subtypes. The functional role of each subtype in taste information propagation is unknown. Here, we used optogenetic tools to study how selective excitation of GABAergic terminals in the NTS affects taste responses in awake, freely licking rats. Further, the effects of GABA excitation on taste discrimination learning in a Go no-Go (GnG) paradigm were examined. Viruses restricting ChR2-EYFP expression to GABAergic neurons using a GAD1 promoter were infused unilaterally into the NTS. Following 2-4 wks recovery, an optrode (optical fiber with 8-16 tungsten microwires) was implanted into the taste-responsive NTS. After recovery, rats were presented with an array of taste stimuli under moderate water deprivation. Rats were given trials of 5 consecutive licks of a tastant (0.1 M NaCl, 0.1 M sucrose, 0.1/0.01 M MSG/IMP, 0.01 M citric acid, 0.001 M quinine, 0.1 M KCl, 0.1 M NH4Cl, or artificial saliva) separated by 5 rinse licks on a VR5 schedule. Each taste stimulus lick triggered a 1s train of laser light (25 Hz of 473 at 8-10 mW) in a random half of the trials.

After ~2 wks of taste-only recording, rats were switched to a GnG paradigm. A single cue stimulus lick (0.1 M NaCl, 0.1/.01 M MSG/IMP or 0.1 M KCl in separate sessions) was followed by 5 dry licks, 3 licks of a test stimulus (0.1 M NaCl, 0.1/0.01 M MSG/IMP, or 0.1 M KCl) and a 1 s timeout. If cue and test stimuli matched, continued licking produced a 3-lick 0.5 M sucrose reward. If they differed, the rat was required to withhold licking for 1 s or be punished by 3 licks of 2 mM quinine and a 5 s timeout. In a random half of each trial type, each test lick triggered 1 s of optical stimulation. The data show that GABAergic stimulation increased information conveyed by NTS taste neurons (n = 80 of 140 total cells) and sometimes produced taste responses in neurons that were previously non-taste-responsive (n=20). GABAergic stimulation also had a varied but coupled effect on lick coherence and taste tuning of NTS neurons. In some neurons, lick coherence was reduced and tuning was broadened. In others, especially in cells with short-duration taste responses, lick coherence was increased and tuning was narrowed. Additionally, GABAergic stimulation retarded GnG performance in the majority of animals (3/5). Overall, results suggest that enhancement of GABAergic activity in the NTS may improve information conveyed about taste quality by individual neurons, but may scramble the taste-related information sent upstream by the population, resulting in degraded taste discrimination performance.

Disclosures: J.D. Sammons: None. **C.E. Bass:** None. **J.D. Victor:** None. **P.M. Di Lorenzo:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.07/AA7

Topic: D.05. Olfaction and Taste

Support: JSPS KAKENHI JP15H01587
RIKEN (MIH) Research Foundation

Title: Effects of d/l-valine on the taste circuit in the perinatal period

Authors: *A. ARATA[1], K. NAKAYAMA[2], C. YOSHIDA[3], S. MOROKUMA[4], Y. TAKESHIMA[2]
[1]Hyogo Col. of Med., Nishinomiya, Japan; [2]Dept. of Pediatrics, Hyogo Col. of Med., Nishinomiya, Hyogo, Japan; [3]Dept. of Cardiol., Steel Mem. Hirohata Hosp., Hirohata, Himeji, Japan; [4]Dept. of Helth Science, Grad. Sch. of Med. Sci., Kyushu Univ., Higashi-ku, Fukuoka, Japan

Abstract: Sense of taste on the surface of the tongue and sent to the brain can feel sweetness, sourness, saltiness, bitterness and umami. At first the gustatory nerve connects to the solitary

tract nucleus, and toward reticular formation; secondly, connects to parabrachial nucleus and reaches taste area in cortex. We produced isolated brainstem-spinal cord intact tongue preparation including solitary tract nucleus, parabrachial nucleus, and facial nucleus to analyze taste circuit keeping sensory-motor connection. We examined the effects of sweet amino acid D-valine and bitter amino acid L-valine on tongue movement focused on perinatal period (the embryonic day 16 (E16)-the postnatal day 3 (P3)). The tongue movement was recorded by bipolar-tungsten electrode inserted to tongue muscle in vitro preparation, and we also examined the behavior concerning taste in vivo P0-P3 rats; that was counted mouth movement as mastication. The tongue movement was irregular, and D/L valine effects were invisible in E16. Then the tongue movement detected clearly, and the effects of D/L valine were seen in E18. Application of D-valine to tongue increased tongue movement, but L-valine inhibited tongue movement or showed long delayed effect in P0-3 rat. When sucrose was applied into the in vitro preparation, tongue movement was increased after 3 minutes from the application. Application of D-valine to tongue increased tongue movement after 2-3minutes from application, but L-valine inhibited tongue movement or showed long delayed effect in postnatal 0-2-day-old rat. D-Valine and L-Valine distinguished each reception. In the circuit, the pons was required to the effect of Valine recognition because without pons has no effect of tongue movement with Valine application. These results suggested that D/L-Valine were detected with the sense of taste as different taste reception using pontine circuit. In behavioral study, rat pups tend to drink D-valine, but they avoided to drink L-valine. The differences of D/L valine were detected clearly. This avoidance behavior in P3 rat was stronger than that in P2. These results suggested that D/L-valine might have different certain taste receptors and the hate memory of bitter taste would be established in P2-P3 rats.

Disclosures: A. Arata: None. **K. Nakayama:** None. **C. Yoshida:** None. **S. Morokuma:** None. **Y. Takeshima:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.08/AA8

Topic: D.05. Olfaction and Taste

Support: NIDCD R01-DC013770

Title: Inhibitory modulation of thalamocortical input to rat primary gustatory cortex

Authors: *M. HALEY, A. FONTANINI, A. MAFFEI
SUNY at Stony Brook, Stony Brook, NY

Abstract: Sensory information is transmitted to primary sensory cortices via subcortical ascending pathways from sensory thalamic nuclei. In the gustatory system, a prominent projection from gustatory thalamus, the parvicellular region of ventroposteromedial nucleus of the thalamus (VPMpc), carries information about tastes to primary gustatory cortex (GC). Although numerous studies have examined the properties of thalamocortical inputs to other primary sensory cortices, such as visual or somatosensory cortex, there has been a paucity of studies investigating thalamocortical projections to gustatory cortex. Here, we combine whole cell recordings in acute GC slices with optogenetic activation of VPMpc axon terminal fields to investigate the synaptic properties, targets, and distribution of thalamic input to GC. Our data indicates that differently from other sensory systems, thalamocortical input to GC is broadly distributed across cortical layers. Similar to other sensory thalamocortical projections, VPMpc projections target both excitatory neurons and fast-spiking, parvalbumin-expressing, GABAergic neurons in GC. Short-term dynamics of VPMpc-GC synapses differ between the two cell types, demonstrating stronger short-term depression onto inhibitory neurons. To investigate how feedforward inhibition recruited by VPMpc afferents affects thalamocortical transmission, we examined VPMpc-GC synaptic properties and short-term dynamics in the presence of GABA-A and GABA-B agonists and antagonists. Bath application of picrotoxin or CPG-52342, to block GABA-A and GABA-B transmission respectively, increased the amplitude of VPMpc-GC postsynaptic currents (EPSCs), and increased the likelihood of VPMpc elicited spikes in current clamp. Differently, muscimol significantly decreased the amplitude of VPMpc-GC EPSCs. Together these results suggest a prominent role for thalamocortical modulation by inhibition in gustatory cortex.

Disclosures: M. Haley: None. **A. Fontanini:** None. **A. Maffei:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.09/AA9

Topic: D.05. Olfaction and Taste

Support: NIH Grant DC04846

Title: Foliate taste bud volume is retained following adult chorda tympani nerve injury in rats

Authors: *K. L. APA, S. I. SOLLARS
Univ. of Nebraska at Omaha, Omaha, NE

Abstract: The gustatory system includes a complex network of interacting receptor cells and nerves, which detect and transmit taste information. The anterior two-thirds of the tongue contains fungiform papillae that house a single taste bud each. The back of the tongue has

bilateral foliate papillae typically consisting of six trenches per side, which we categorized as anterior, middle, and posterior (2 trenches each), that are lined with numerous taste buds. The chorda tympani (CT) taste nerve innervates both fungiform and foliate taste buds (particularly in the anterior trenches). Along with CT support, the foliates make additional synaptic connections with the glossopharyngeal taste nerve, notably in both the middle and posterior trenches. When the CT is cut (CTX) in adult (> 40 days of age) rats, the nerve regenerates as evidenced by a transient reduction in fungiform taste buds and then a return similar to controls. To investigate whether the same was true for foliate taste buds, the current study examined foliate taste bud volume following CTX. Rats received unilateral CTX at 65 days of age and were sacrificed 50 days later. Tongue tissue was sectioned at 10µm using a cryostat and stained with hematoxylin and eosin for taste bud visualization. Foliate taste bud perimeter tracings were done using the computer program Neurolucida (MBF Bioscience). Foliate taste bud volume was calculated by multiplying the summed perimeter tracings across sections by section thickness, and was compared between the intact and transected sides, and within each trench category. An ANOVA revealed differences in taste bud volume between trenches ($p < .05$), and no difference in overall taste bud volume between the intact and transected sides ($p > .1$), suggesting that, similar to fungiform taste buds, foliate taste bud volume is not permanently reduced after adult CTX. Surprisingly, planned comparisons indicate larger volumes on the transected compared to the intact posterior trenches ($p < .05$). We present data that suggests 50 days after adult CTX taste buds are present in the foliate papillae, indicating the possibility of either regeneration or foliate taste bud maintenance in the absence of CT support.

Disclosures: K.L. Apa: None. **S.I. Sollars:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.10/AA10

Topic: D.05. Olfaction and Taste

Support: CSULB Small Faculty Grant 2017

Title: Responses to sweetened fat in male and female rats classified as sucralose avoiders or sucralose preferers

Authors: *A. GOULD, Y. TREESUKOSOL
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Abstract: Sucralose is an artificial sweetener known as the commercially marketed calorie-free additive, Splenda. When presented water and sucralose in a two-bottle preference test, as sucralose concentration increase, some rats show preference (sucralose preferers SP) and some

show avoidance (sucralose avoiders SA). Previous reports have demonstrated associations of sucralose acceptance with intake of sweet, bitter or creamy substances. In the current study, male (n=16) and female (n=16) Sprague-Dawley rats were categorized as either SP or SA using a series of two-bottle preference tests with water and ascending concentrations of sucralose (0.0001-2 g/L). It has been previously reported that the SP/SA profile is evident only in female rats but here we observe SP and SA profiles in both sexes. Next, to assess whether the SP/SA profile would predict binge eating behavior, animals were placed on a binge-access schedule. Rats were given 30-min access to chow (3.43 kcal/g) and sweetened fat-shortening (8.6 kcal/g; sucrose and Crisco) following 23-hour food deprivation twice a week. Across these 30-min sessions, SP and SA rats did not significantly differ in intake of the sweetened fat-shortening nor in intake of standard chow. In contrast, while sweetened fat-shortening intake did not significantly differ by sex, male rats ate significantly more of the chow than female rats during these 30-min sessions. Taken together, these findings suggest sucralose acceptance does not predict intake of palatable diets in this binge eating paradigm. Next, we are measuring ad libitum intake of chow and sweetened fat in a separate cohort of SA and SP rats to compare responses to these stimuli.

Disclosures: A. Gould: None. **Y. Treesukosol:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.11/AA11

Topic: D.05. Olfaction and Taste

Support: NIH Grant DC006666
NIH Grant DC016706

Title: Brief perturbation of amygdala-cortical projections alters palatability coding in gustatory cortex

Authors: *J.-Y. LIN, N. MUKHERJEE, D. KATZ
Brandeis Univ., Waltham, MA

Abstract: Taste stimuli contain both chemical (taste identity, for instance sweet and salty) and hedonic value (taste palatability) information. Reflecting the complexity of tastes, gustatory cortex (GC), GC single-unit taste responses convey a time series of information—first about taste identity (e.g., sweet, bitter; Epoch 1: ~0.2-0.7s post-delivery) and then taste palatability (Epoch 2: ~0.8-1.5s post-delivery). We have hypothesized that the dynamic nature of this coding reflects the fact that GC integrates information from multiple subcortical nuclei, and that in particular the emergence of palatability-related information in GC specifically requires

temporally-restricted inputs from basolateral amygdala (BLA). Previous work (Piette, et al., 2012) broadly confirmed the importance of BLA in cortical palatability coding; to more rigorously test our hypothesis, we examined whether taste-related GC firing could be altered by brief, targeted optogenetic perturbation limited to BLA-GC projections. We first infected BLA of adult female Long Evans rats with AAV-ArchT; four weeks later, we implanted 1) unilateral or bilateral multi-electrode bundles with optical fibers ('optotrodes') in the GC and 2) intra-oral cannula (IOC) for taste delivery. With this preparation, we were able to specifically silence BLA-GC projections (sparing both BLA and GC somae) while presenting 0.1M NaCl, 0.3M Sucrose, 0.1M Citric Acid and 1mM Quinine-HCl. We found that optogenetic inhibition of BLA-GC projections had bidirectional effects on GC taste responses. Single unit responses were dramatically altered, but the effect was specifically restricted to the epoch of palatability-related firing; taste identity firing remains unaffected by the inactivation. This pattern of results is consistent with the hypothesis that relative to other inputs, BLA preferentially provides palatability information to GC. Future directions will involve experiments that aim to examine the impact of this brief, targeted optogenetic inactivation on taste-guided behavior.

Disclosures: J. Lin: None. **N. Mukherjee:** None. **D. Katz:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.12/BB1

Topic: D.05. Olfaction and Taste

Support: NIH/NIDCD R01DC015234
NIH/NIDCD R21DC016714

Title: Neural correlates of goal-directed decision making in the gustatory cortex of mice

Authors: *K. CHEN, R. VINCIS, L. A. CZARNECKI, A. FONTANINI
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Abstract: It is generally believed that primary sensory cortices exclusively represent basic sensory information. However, recent evidence points to these areas as regions capable of high levels of integration. The gustatory cortex (GC) is well known for its multiple functionalities including chemosensory processing and learning, multi-sensory integration, and food-cue association. The multifaceted nature of GC, suggests that it may be involved in computing complex cognitive variables associated with consummatory decision as well. Here we use behavioral training, chemogenetic manipulation and electrophysiological recordings to test the hypothesis that GC can process decisions, goals and outcomes in a perceptual decision-making task.

We designed a taste-based, two-alternative choice task where mice are trained to discriminate between four tastants of two categories (sweets: sucrose S, maltose M; bitter: sucrose octacetate O, quinine Q) delivered at a central spout. Animals report taste identity on lateral spouts by licking either left or right for water reward after a delay period. One taste of each category is rewarded on each lateral spout (S & Q - reward left; M & O - reward right), leaving animals unable to simply rely on quality (sweet vs bitter) or hedonics (palatable vs aversive) for their decisions. Bilateral chemogenetic inactivation of GC negatively affected task performance (25% reduction).
We implanted moveable tetrodes in GC and recorded neural activity in well trained mice. Analysis of single unit activity revealed that GC neurons can encode planning, spatial goals and reward outcome of the taste discrimination task. Specifically, 43% of neurons in GC reflect intention to lick right or left during the delay period (planning), 48% of neurons represent licking right or left (spatial goal) and 40% of neurons represent correct or erroneous choice (reward outcome).
Overall our results show GC involvement in all the steps of a taste-based perceptual decision. These data suggest that GC may directly drive and shape decisions important for consummatory behaviors.

Disclosures: K. Chen: None. **R. Vincis:** None. **L.A. Czarnecki:** None. **A. Fontanini:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.13/DP09/BB2

Topic: D.05. Olfaction and Taste

Support: NIH NIDCD R21 DC015202
NIH NIDCD R01 DC016833

Title: Spatial organization of awake taste responses in mouse gustatory cortex using miniature head-mounted microscopes

Authors: *S. M. STASZKO, L. LU, J. D. BOUGHTER, M. L. FLETCHER
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Abstract: Previous literature has yielded mixed results on the spatial organization of taste coding in gustatory cortex (GC). One recent study utilizing in-vivo 2-photon (2P) calcium imaging described both sucrose and quinine “hot spots” occupying different spatial regions of GC along the anterior-posterior axis, suggesting the spatial separation of taste coding based on hedonic quality (Chen et al., 2011). However, recent 2P imaging work in our laboratory revealed no spatial organization of taste responses in the region of gustatory cortex analyzed, similar to

previous findings reported in both rodents and humans (Fletcher et al., 2017; Accolla et al., 2007; Schoenfeld et al., 2004). One major limitation of previous rodent imaging studies is that they were performed in anesthetized animals. Recent work in our laboratory utilizes miniature head mounted microscopes (miniscopes) to image awake, in-vivo taste responses of cortical neurons in multiple regions of mouse GC. The goal of this research is to determine cortical responses to taste stimuli and the spatial organization of those responses in awake mouse GC. AAV1.Syn.GCaMP6f is stereotaxically injected into the gustatory cortex of C57BL/6J mice in different regions along the anterior-posterior axis including central GC (AP +1.5mm, ML +3.3mm, DV -2.1 mm) and posterior GC (AP -0.3 mm, ML +3.85 mm, DV -1.8mm). After recovery, a 0.5mm x 4mm gradient index (GRIN) lens is implanted at the cortical region and layer of interest, allowing for the visualization of cells through the miniscope. Animals received multiple trials of 0.5 M sucrose, 0.3 M sodium chloride, 0.02 M citric acid, 0.01 M quinine, an umami mixture (1.0 M monopotassium glutamate and 0.1 M inosine 5'-monophosphate), water, and artificial saliva within a single day. These stimuli were then randomly repeated for a total of 5 experimental days to allow for within and across-day repeatability analyses.
Data will be collected from different cortical layers as well as different regions along the anterior-posterior axis of GC. Spatial organization of taste responses in awake GC will be analyzed individually for each region by examining the percent of neurons within the region responding to a given taste as well as best-taste responses to each stimulus (what percentage of neurons respond best to a given stimulus). Broadness of tuning will be analyzed using both entropy and noise-to-signal calculations. Principal component analysis will be used to examine the organization of population responses in awake GC. Together, this data will describe the spatial organization of taste in awake mouse GC.

Disclosures: S.M. Staszko: None. **L. Lu:** None. **J.D. Boughter:** None. **M.L. Fletcher:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.14/BB3

Topic: D.05. Olfaction and Taste

Support: NIDCD R01 DC6013904

Title: Effect of weight-loss following in obese rats; diet composition and food preferences

Authors: *T. NGUYEN, M. S. WEISS, P. M. DI LORENZO
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Abstract: Obesity, a health concern currently affecting over 30% of adults in the United States, is primarily caused by a chronic surplus of calories from foods dense in fats and sugars. Often

during attempts to lose weight, many individuals experience weight gain following an initial weight loss, otherwise known as yo-yo dieting or weight cycling. Here, we investigated how changes in diet composition following weight gain affected the weight, body composition, and behavioral preferences in rats with diet-induced obesity. Sprague-Dawley rats were placed on a 45% high fat diet (HFD) for 10 weeks, and then split into two groups. One group received *ad libitum* standard lab chow diet (HFD-SC; Purina 5001) and the other group was pair-fed an amount of equal caloric value of the HFD (HFD-PF). Experimental groups were compared to age matched rats on SC with no experience with HFD (Control). Rats were scanned via dual-energy X-ray absorptiometry (DXA) every 4 weeks to determine body composition. 10 weeks after the diet change, HFD-PF rats had significantly high body fat (28.6±3.8%) than HFD-SC rats (18.1%±1.6, $F(1, 60) = 7.9$; $p < 0.01$). Control rats were had significantly less body fat than both groups (12.7% ± 0.2). To assess changes in food preference in these two groups, we conducted a 48-hr access test using Ensure, a food source high in sugar and fat while also measuring food consumption. Two concentrations of Ensure were used: 25% and 50%, diluted with water. Both water and Ensure were available for 48 hrs in the home cage, with the bottle placement rotated after 24 hrs. All rats had clear preference for Ensure with both concentrations (> 90% preference). Amount consumed (in kCal) was normalized by body weight in all groups. Both HFD-SC and HFD-PF rats ingested significantly less total calories from food + Ensure normalized by body weight than lean controls for when presented with both concentrations of Ensure ($F(2, 21) = 19.53$, $p < 0.05$). When normalized for body weight, HFD-PF rats consumed less calories from Ensure than both HFD-SC and lean controls ($F(2, 21) = 4.995$, $p< 0.05$). HFD-SC rats consume more calories from Ensure than both HFD-PF and controls ($F(2, 21) = 3.81$, $p < 0.05$), perhaps due to an increased salience toward sweet-fat taste from their previous history with a palatable diet. Although, all groups of animals groups have >90% preference for Ensure over water, animals on HFD-PF and HFD-SC do not compensate for caloric consumption with subsequent food intake like the lean animals.

Disclosures: T. Nguyen: None. **M.S. Weiss:** None. **P.M. Di Lorenzo:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.15/BB4

Topic: D.05. Olfaction and Taste

Support: Productos Medix 3247
CONACyt Grants Fronteras de la Ciencia 63 y Problemas Nacionales 464

Title: Sucrose’s palatability in the Lateral Hypothalamus is encoded by GABAergic and non-GABAergic neurons

Authors: *M. HERNANDEZ LUNA[1], M. VILLAVICENCIO[2], J. LUIS-ISLAS[3], A. HERNÁNDEZ-COSS[4], R. GUTIERREZ[2]
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Abstract: The prevalence of overweight and obesity has scaled in the last decades. One culprit of this epidemic is the overconsumption of sucrose, which due to its high palatability (hedonic value) promotes its intake beyond homeostatic need. Palatability is the affective evaluation of a tastant. In rats, it is measured by an increase in lick rate elicited by increasing sucrose's concentration. The Lateral Hypothalamic Area (LHA) has been established as an important node on the feeding circuit. Extracellular recordings on rats revealed that LHA neurons respond to palatable tastantses. Although, LHA contains a heterogeneous population of neurons. Recently it has been reported that the LHA^{GABA} promotes appetitive and consummatory behaviors, regardless of the caloric content or biological relevance of the consumed stimuli. However, it remains unclear which LHA neuron types are involved in encoding sucrose's palatability. We hypothesized that a subpopulation of LHA^{GABA} neurons encode the oromotor palatability responses elicited by sucrose. To address this issue, we used transgenic mice (Vgat-ires-Cre) that express channelrhodopsin-2 (ChR2) on LHA^{GABA} neurons. Employing extracellular optrode recordings, we examined single unit LHA responses in these subjects performing a Brief Access Taste Test (BATT). After the task, we used optogenetic tagging to identify LHA^{GABA} neurons. In BATT, a trial consists of a reward period of 4s where the subject can lick the sipper to be rewarded with a different sucrose concentration (0, 1.5, 3, 10, 18 or 32 wt/vol %) on each trial. The average number of licks per second (lick rate) and the size of the bouts (bursts of rhythmic licks separated by a pause ≥0.5 s) were used as direct measures of palatability. An increase in lick rate and a larger bout size were observed as the sucrose concentration increased. We found two populations of neurons with distinct sucrose palatability-related responses, one that increased and other that decreased their firing rate as the sucrose's palatability increased. We also found that a portion of these palatability-related neurons were LHA^{GABA} neurons. Moreover, another subset of palatability-related neurons was inhibited by photostimulation, indicating that they were non-GABAergic neurons, but they also belong to the same the circuitry modulated by the photostimulation of LHA^{GABA} neurons. Finally, we also found a subpopulation of non-GABAergic LHA neurons (i.e non-responsive to photostimulation) also tracked the hedonic value of sucrose. We concluded that a heterogeneous population of GABAergic and non-GABAergic neurons in LHA encode palatability information.

Disclosures: M. Hernandez Luna: None. **M. Villavicencio:** None. **J. Luis-Islas:** None. **A. Hernández-Coss:** None. **R. Gutierrez:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.16/BB5

Topic: D.05. Olfaction and Taste

Support: NIH/NIDCD Grant R01DC012543
NIH/NIDCD Grant R01DC015234

Title: Elemental and configural representations of multimodal associative cues in the gustatory cortex of alert mice

Authors: *L. A. CZARNECKI, A. FONTANINI
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Abstract: The gustatory cortex (GC) has been shown to respond to crossmodal cues predictive of taste. Much of this work has focused on predictors of a single sensory modality, whereas naturalistic food predictive cues are often composed of multiple sensory modalities. How GC processes these multimodal cues remains largely unknown. Here, we investigate if GC processes a multimodal cue configurally (as a unique entity, not merely the sum of its elements) or elementally (as a simple sum of its components). To do so, a paradigm was used in which an odor (isoamylacetate, 4ppm) and tone (2kHz, 75 dB) were simultaneously presented to headfixed mice for 2 seconds. At the termination of this compound presentation, mice had 5 seconds to make 5 dry licks to a fixed spout for a drop of sucrose (200mM). After animals responded to at least 75% of trials for three consecutive days, they received a test day consisting of 10 unreinforced presentations of the tone alone, odor alone, as well as the previously learned compound. Animals made licks to almost 80% of compound and odor alone presentations, but to less than 10% of tone alone presentations, indicating a robust overshadowing of tones by odors. Animals made, on average, 8 licks to the compound presentation, 4 licks to the odor and less than 1 lick to the tone. This suggests that while the compound and odor have equal ability to elicit a behavioral response, the magnitude of that response is not equal. Interestingly, in mice implanted with 8 moveable tetrodes in GC, we saw a similar physiological response pattern. Analysis of single unit activity revealed that half of responsive neurons were evoked by both the presentation of the compound as well as the presentation of the odor. Only 9% of neurons were responsive to the compound and the tone. Subsets of neurons were sensitive to individual elements (22% to the odor and 4% to the tone). Conversely, 17% of neurons responded uniquely to the compound but to neither element. These data show a large overlap, both in behavior and in single unit activity, between the compound and odor stimuli. This suggests preservation of some individual features, but also the existence of a representation unique to the learned compound

cue, indicating a mixed elemental/configural strategy of multimodal cue representation to instruct licking.

Disclosures: L.A. Czarnecki: None. **A. Fontanini:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.17/BB6

Topic: D.05. Olfaction and Taste

Support: NIDCD R01 DC006914

Title: Spiking of taste neurons in the nucleus of the solitary tract is modulated by theta oscillations

Authors: *A. DENMAN-BRICE, P. DI LORENZO
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Abstract: Subsets of neurons at all levels of the rodent taste system fire in phase with the lick cycle during bouts of licking, and in some structures this relationship is task dependent. Synchronization of lick-coherent neural activity across taste areas in the brain presents a possible mechanism for information transfer between structures, and may be driven by rhythmic subthreshold synaptic inputs, which can be measured as local field potential (LFP) oscillations. Neurons in the nucleus of the solitary tract (NTS), the first central relay nucleus in the taste system, display diverse rhythmic firing patterns tied to licking. It is unknown whether this activity is influenced by synchronous subthreshold inputs, and whether it is related to processing of taste information. We investigated whether NTS neurons showed evidence of synchronization with LFP oscillations, and if so what properties those neurons possessed. We analyzed single unit and local field potential (LFP) signals recorded from freely moving rats with 8- or 16-channel microwire electrodes implanted in the NTS. During these recording sessions subjects licked at a computer-controlled lickspout, which dispensed taste solutions (or a neutral control stimulus) with neutral rinses between trials. A total of 177 isolated single units with concurrent LFP recordings were used in the analysis. LFP signals contained spontaneous oscillatory activity in the theta range even when subjects were not licking, and during licking this activity became entrained to the lick cycle. Some neurons fired in synchrony with spontaneous theta oscillations, and a majority of these preferentially fired at the trough of the spontaneous theta rhythm. However, neurons that preferentially fired at the trough of the spontaneous theta oscillation displayed diverse firing patterns within the lick cycle during licking. We analyzed neurons' spike trains to detect temporally coded information about taste quality, and found that neurons whose firing was modulated by theta oscillations during licking encoded more taste information than

non-theta modulated neurons. The strength of a neuron's phase locking to the lick cycle, however, was not correlated with how much taste information the neuron encoded. We also found that a subgroup of cells were able to differentiate presentation of a neutral stimulus during a trial from presentation of the same neutral stimulus during an inter-trial rinse, but typically could not differentiate between neutral stimulus trials and other stimulus trials. These results suggest that LFP oscillations in NTS neurons are important to the processing of taste information, and may reflect the state of NTS taste circuitry.

Disclosures: A. Denman-Brice: None. **P. Di Lorenzo:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.18/BB7

Topic: D.05. Olfaction and Taste

Support: NIH R01DC004574

Title: Electrophysiological responses to sugars and amino acids in the nucleus of the solitary tract of type 1 taste receptor double knockout mice

Authors: *K. BALASUBRAMANIAN[1], G. D. BLONDE[2], A. C. SPECTOR[2], S. P. TRAVERS[1]
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Abstract: The tastes of sugars and amino acids are signaled by distinct heterodimers of the Type 1 taste receptor proteins that share a common subunit (sugars: T1R2+T1R3; L-amino acids: T1R1+T1R3). However, mice with deletion of one subunit (T1R3) exhibit residual neural responses, suggesting a role for the remaining subunit or T1R-independent mechanisms. Moreover, behavioral experiments indicate that mice lacking both the T1R1 and T1R3 subunits can detect high concentrations of umami compounds. To clarify T1R residual responses, we recorded from single neurons (n=144) in the 1st-order central taste relay, the rostral nucleus of the solitary tract, in T1R double knock-out mice (T1R dbl KO): T1R2+T1R3 (KO23) or T1R1+T1R3 (KO13) and wild type (WT) strains (C57BL/6 and 129X1/SvJ). Stimuli [mM Conc.] were representatives for standard taste qualities (sucrose [100], NaCl [100], citric acid [10], cycloheximide [.01] + quinine [3] and umami (MSG [100 & 600] +amiloride [.1] + IMP [2.5]), additional monosaccharides (glucose and fructose [1000]) and amino acids (MSG +/- amiloride, glycine, and L-lysine [all 600]). As previously shown for T1R3 KO's, residual responses to saccharides occurred in T1R dbl KO mice. However, particularly for glucose, these tended to be more frequent in KO13 *vs* KO23 mice (23% vs 8%) suggesting the T1R2 subunit

can maintain some responsiveness to sugars. Nevertheless, each mono- and disaccharide elicited responses 5-29X larger in WT mice (P's<.006) and neurons with preferential sensitivity to sweet (and/or umami) stimuli were observed almost exclusively in WT mice (84%, P=.003). These changes markedly decreased the distinctiveness of across-neuron patterns to sugars in the T1R dbl KO mice, with higher across-neuron correlations between sugars and non-sweet stimuli (r= +0.02 $\pm$ 0.026 WT, +0.42 $\pm$ 0.046 dbl KO, P<.0005). Changes in amino acid responses were more subtle, suggestive of T1-independent mechanisms. In fact, amino acid responses were not significantly smaller in T1R dbl KO's, although 100mM umami was 4X as effective in WT mice and umami synergism was largely missing in dbl KO's but prominent in WT mice (P =0.004). These data appear consistent with the abilities of KO13 mice to detect higher umami concentrations but are puzzling because behavioral discrimination of MSG (+ amiloride) requires IMP but neural responses to MSG + amiloride in the T1R dbl KO's are just as large without this cyclic nucleotide. Indeed, the relatively robust responses to MSG + amiloride in both WT and dbl KO mice in the absence of behavioral discrimination suggests that this neural activity is not routed to circuits underlying sensory-discriminative function.

Disclosures: K. Balasubramanian: None. **G.D. Blonde:** None. **A.C. Spector:** None. **S.P. Travers:** None.

Poster

218. Taste

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 218.19/BB8

Topic: D.05. Olfaction and Taste

Support: NIDCD RO1 DC006914 to PMD.

Title: Electrophysiological responses to food and feeding in the nucleus of the solitary tract in the rat

Authors: *S. PILATO[1], P. DI LORENZO[2]
[2]Psychology: Behavioral Neurosci., [1]Binghamton Univ., Vestal, NY

Abstract: In previous work we have shown that odors presented with taste stimuli can modify neural responses to taste in the nucleus of the solitary tract (NTS) of the rat. These results suggest that neurons in the NTS might respond optimally to stimuli that combine multiple chemosensory modalities, i.e. food. Here, we describe the response of NTS neurons recorded as a rat approaches and consumes various foods. We will test the hypothesis that thee response will be stimulus specific in each neuron. Subjects were Sprague Dawley rats (N = 4) that had a drivable 16 channel microwire assembly implanted into the rostral NTS. After completion of the electrode implantation surgery and post-operative recovery, rats were food deprived and placed

in an operant chamber (Med Associates; Fairfax, VT). The chamber contained seven wells arranged linearly near the floor of one end of the chamber. Different foods filled some of the wells; the identity and placement of foods were randomized daily. Foods were chosen that were emblematic of the "basic" taste qualities. These included: dark chocolate (90% cacao; bitter), cheese (fat), banana (sweet), Cheerios (sweet), milk chocolate chips (sweet), Granny Smith apples (sour), salted peanuts (salty), and shiitake mushrooms (umami). A Cineplex Behavioral Research System (Plexon, Inc) was positioned outside of an observation window for simultaneous acquisition of neural and video data. For each recording session (30 min), rats could approach and choose from any of the available foods. Videos were scored offline for consummatory behaviors by 4 different raters. Thus far, eight of 10 neurons responded to both well entry (with or without subsequent eating) and eating-related behaviors. Neural responses were stimulus specific and were similar to neural NTS responses to prototypical tastants in temporal envelope and duration. Well entry responses may be evoked by food-related odors and/or may reflect instructions originating in higher-order structures. Analyses of temporal coding of taste in 6 neurons showed that 5 neurons conveyed a significant amount of information about differences across food stimuli. On average, spike trains evoked by eating conveyed more information about food compared with spike trains evoked by well entry. In all, preliminary results suggest that NTS neurons may be closely tied to appetitive as well as consummatory responses.
Funded by NIDCD grant RO1 DC006914 to PMD.

Disclosures: S. Pilato: None. **P. Di Lorenzo:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.01/BB9

Topic: D.07. Vision

Support: IARPA Microns
Allen Institute founders Paul G. Allen and Jodi Allen

Title: Sample preparation for high throughput functional connectomics using calcium imaging and transmission electron microscopy

Authors: *J. BUCHANAN[1], M. M. TAKENO[2], A. L. BODOR[3], D. J. BUMBARGER[4], A. A. BLECKERT[3], M. FROUDARAKIS[5], J. REIMER[5], A. S. TOLIAS[5], R. REID[2], N. M. DA COSTA[3]
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Abstract: Mapping the wiring diagram of the neocortex constrains models of computation by the structural components of the brain. Electron microscopy (EM) remains the gold standard to identify these components since it has adequate resolution to identify thin wires of micro connectivity. Here, we describe an EM pipeline to scale up technology to collect petascale sized datasets containing a full local cortical microcircuit in mouse visual cortex. We supplement datasets with functional studies of neurons whose calcium activity has been imaged *in vivo.*
We previously prepared 100 μm^3 of mouse cortex and aim to increase sample volume 1000x. Larger volumes (1 mm^3) are needed to map local connections of a mouse cortical microcircuit. Preparation of 1mm^3 and larger specimens by EM presents technical challenges. The foremost problem is osmium tetroxide (OsO^4) penetration.
After *in vivo* 2P and 3P imaging of calcium signals in neurons and mapping of vasculature, mice were prepared for correlative, high resolution TEMCA imaging of serial sections from the same area. The goal was to scale up to 1mm^3 cube of imaged brain and prepare high contrast samples for high throughput imaging.
Sample preparation required the previously imaged ROI to be exactly placed in resin blocks. Detailed fiducial marking using blood vessel patterns and meticulous block trimming was imperative. After perfusion, the imaged area was marked with dye prior to vibratome cutting to ensure placement in the slice. Finally, the blood vessel pattern was overlaid to map out exact position of the ROI in resin blocks.
High contrast samples were necessary for thin sectioning, imaging and automatic image segmentation. Thus, vibratome slices were processed using a precision designed staining protocol. This protocol utilized multiple rounds of Os staining combined with amplification to highlight membranes. Increased time and addition of solvents was required to increase Os penetration. Applications of the heavy metals lead nitrate and uranyl acetate were added *en bloc* to avoid on section staining.
We prepared 8 mice for analysis by TEM for quality of tissue fixation, stain penetration and block hardness. Blocks containing the ROI were imaged by Micro-CT to evaluate staining and Os penetration. Final sample choice considered stain penetration, ultrastructure, contrast, ROI placement and physiological data. The best samples were registered with ROI fiducial marks and trimmed for collection of 25K serial sections using an ATUM (automatic tape collection ultramicrotome).
In summary, we have pushed the limits of sample size for EM, both for Os staining and sectioning to collect 1mm^3 data set of previously imaged brain tissue.

Disclosures: J. Buchanan: None. **M.M. Takeno:** None. **A.L. Bodor:** None. **D.J. Bumbarger:** None. **A.A. Bleckert:** None. **M. Froudarakis:** None. **J. Reimer:** None. **A.S. Tolias:** None. **R. Reid:** None. **N.M. da Costa:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.02/BB10

Topic: D.07. Vision

Support: NEI R01-EY018847
NEI P30-EY002520-33
NEI T32- EY07001-37
NIDA R01DA028525
NIMH F30-MH088228
D16PC00003 (IARPA)

Title: Accuracy of sensory information does not saturate for large neuronal populations

Authors: *R. J. COTTON[1], A. S. ECKER[2], E. FROUDARAKIS[3], P. BERENS[5], M. BETHGE[6], P. SAGGAU[7], A. S. TOLIAS[4]
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Abstract: How effectively does the brain encode information across large numbers of neurons? Many models predict that shared variability (‘noise correlations’) will cause information to saturate for even moderately sized population, although empirical evidence in this regime is severely lacking. We studied this prediction using a novel 3D high-speed *in vivo* two-photon microscope to record nearly all of the hundreds of neurons in a small volume of the mouse primary visual cortex. We presented full field grating with five closely spaced orientations and measured how encoded information grows with population size.
Contrary to numerous predictions, we find that information continues to increase for population sizes of several hundred neurons with little sign of saturation. In addition, a decoder ignoring correlations between neurons can still decode the majority of the information in the population. The growth of information with population size is well described by an equation motivated by models of information limiting correlations, with the magnitude of these information limiting correlations a consistent and small value across numerous anesthetized and awake animals. Finally, we find the empiric correlation structure is consistent with numerous eigenvectors weakly aligned to the population tuning, $f(\theta)$, which can give rise to similar growth.
Our results suggest that sensory neural populations represent information in a truly distributed manner and pooling of neural activity within local circuits may be much more effective than

previously anticipated. The representation in early sensory areas does not appear to be impaired substantially by shared sensory noise.

Disclosures: R.J. Cotton: None. **A.S. Ecker:** None. **E. Froudarakis:** None. **P. Berens:** None. **M. Bethge:** None. **P. Saggau:** None. **A.S. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.03/BB11

Topic: D.07. Vision

Support: D16PC00003

Title: Differential surround influence on V1 neuronal responses dependent on presence of center stimuli

Authors: *J. FU, F. H. SINZ, S. SHEN, X. S. PITKOW, A. S. TOLIAS
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Abstract: Activities of pyramidal neurons in primary visual cortex (V1) are modulated by visual stimuli presented outside their classical receptive field (CRF). This phenomenon is referred to as surround modulation. The interaction between stimulus features in the CRF and the modulatory influence from the surround are thought to be nonlinear, yet the functional and computational consequences of this interaction remains controversial. Previous studies have reported the surround modulation to be either excitatory or inhibitory, depending on the stimulus properties within the CRF. Our goal is to understand how surround stimuli modulate the encoding of a center stimulus by characterizing neuronal response properties with independently controlled center and surround stimuli, and putting the resulting center-surround interaction in the context of Bayesian inference using probabilistic models.
We first focused on characterizing surround modulation with commonly used stimuli and criteria. We recorded activities of transgenically labelled, GCaMP6s positive pyramidal neurons in layer 2/3 of mouse V1 using 2-photon imaging. The aggregated receptive field of a population of neurons were estimated with random-dot stimuli. To isolate the effect of the surround, we measured size tuning response curves with drifting grating stimuli that were either restricted to the CRF (center stimuli) or restricted to the surround (surround stimuli). Consistent with previous studies, pyramidal neurons in mouse V1 were selective for sizes of visual stimuli and the preferred size increases as stimuli contrast decreases. We also found neurons that were reliably excited by surround stimuli, even though their preferred stimulus size was less than the inner radii of the surround stimuli. Interestingly, those neurons did not necessarily prefer the same orientation or direction in the CRF as in the surround.

The results seem counter-intuitive given what has been reported on surround modulation. The effect of the surround has been commonly described as a modulatory force on the response to the center, and the strongest modulatory strength occurs when the surround is congruent. Cavanaugh and colleagues have reported similar excitatory surround effects in macaque V1. They propose a functional model with independent center and surround mechanisms that can quantitatively explain surround excitation. However, the mechanism for surround preference and its relation to center preference is unclear. We seek to extend their model to account for the difference between center and surround preferences. Building the functional model will inform us of computational relevance of the excitatory surround.

Disclosures: J. Fu: None. **F.H. Sinz:** None. **S. Shen:** None. **X.S. Pitkow:** None. **A.S. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.04/BB12

Topic: D.07. Vision

Support: iARPA via DoI/IBC D16PC0005

Title: Analyzing inhibitory connectivity onto pyramidal cells in a densely reconstructed volume of visual cortex

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Abstract: The relation between feature selectivity and synaptic connectivity of neurons in mouse primary visual cortex (V1) has been researched intensively in recent years. Excitatory and inhibitory synaptic inputs to V1 simple cells are tuned to the same preferred orientation (Liu et al., 2011). Although inhibitory input is broader, this might seem incompatible with the report that inhibitory connectivity onto pyramidal cells is dense and non-selective (Packer and Yuste, 2011). More recently, evidence for stronger connectivity from parvalbumin-positive interneurons to pyramidal neurons with similar visual preferences has been reported (Znamenskiy et al., bioRxiv, 2018).

We measured the visual responses of pyramidal neurons by calcium imaging in vivo, and then reconstructed synaptic connections from inhibitory interneurons, based on 3D EM images of mouse V1 (millions of cubic microns). We analyze pairs of pyramidal cells that receive synapses from the same inhibitory axon. Our dense reconstruction allows us to study thousands of inhibitory axons fragments that pass through our EM reconstructed volume but raises the difficulty of identifying the types of interneurons to which they belong. To automate the classification of inhibitory axons we developed computational methods for semantic segmentation of cells (axon, dendrite, spine heads, soma) and morphological distinctions between cell types (eg. basket, chandelier cells). We present our methods as well as a structure-function analysis of inhibitory inputs onto pyramidal cells in our dataset.

Disclosures: S. Dorkenwald: None. **A. Bodor:** None. **T. Nick:** None. **A. Wilson:** None. **T. Macrina:** None. **A. Bae:** None. **A. Bleckert:** None. **D. Bumbarger:** None. **D. Buniatyan:** None. **E. Froudarakis:** None. **D. Ih:** None. **C. Jordan:** None. **N. Kemnitz:** None. **K. Lee:** None. **R. Lu:** None. **S. Popovych:** None. **W. Silversmith:** None. **I. Tartavull:** None. **W. Wong:** None. **J. Wu:** None. **J. Zung:** None. **J. Reimer:** None. **C.R. Reid:** None. **A.S. Tolias:** None. **N. da Costa:** None. **H.S. Seung:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.05/BB13

Topic: D.07. Vision

Support: D16PC00003 (IARPA)

Title: Connectivity and function of two cortical feedback circuits

Authors: *S. SHEN, X. JIANG, F. SCALA, J. REIMER, J. FU, P. FAHEY, F. SINZ, A. TOLIAS
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Abstract: Cell-type specific connectivity in the local circuitry of the mammalian neocortex shares a canonical rule, while it still remains elusive whether top-down feedback connections also follow a similar circuitry. We combined multiple whole-cell recordings with optogenetics to examine the connectivity and function of two feedback pathways in adult mice. One pathway is from the lateromedial area (LM) to the primary visual cortex (V1), and the other is from the vibrissal primary motor cortex (vM1) to the vibrissal primary somatosensory cortex (vS1). We found that these two pathways are different in both the connectivity profile and functions. LM provided strong monosynaptic excitation to Layer 23 parvalbumin (PV) and somatostatin (SOM) expressing interneurons and weaker input to all other cell types across different layers, while the

major target of vM1 in vS1 is vasoactive intestinal polypeptide (VIP) expressing interneurons. Consistently, LM to V1 feedback sharpened the temporal pattern of V1 pyramidal cells, while vM1 to vS1 feedback enhanced the activity of vS1 pyramidal cells, sometimes with bursts of firing. Our results suggest the existence of two functional modules of feedback pathways in the mouse neocortex, which might execute completely different top-down neural modulations.

Disclosures: S. Shen: None. **X. Jiang:** None. **F. Scala:** None. **J. Reimer:** None. **J. Fu:** None. **P. Fahey:** None. **F. Sinz:** None. **A. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.06/BB14

Topic: D.07. Vision

Support: D16PC00003 (IARPA)

Title: Stimuli for fast mapping of feature tuning in mouse visual cortex

Authors: *D. YATSENKO[1], P. G. FAHEY[2], E. FROUDARAKIS[2], J. REIMER[2], E. Y. WALKER[2], F. H. SINZ[3], E. COBOS[3], A. S. TOLIAS[2]
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Abstract: Basic characterization of neurons' visual responses commonly includes linear receptive fields and tuning for feature orientation, direction of motion, spatial frequency, and temporal frequency. Even for similar correlation structure, the ability of different visual stimuli to drive strong and reliable activity in neurons is an empirical question as the visual system is sensitive to higher-order statistics of the stimulus.
We designed and evaluated synthetic stimuli for fast measurement of visual response properties. The first stimulus, *"Monet",* comprises pink noise with periods of coherent feature orientation and motion while preserving the same spatial correlation structure as the conventional pink noise across the stimulus ensemble. The second stimulus, *"Trippy",* encodes movies as $v = \cos(f)$ where f is a phase movie generated as dynamic random noise with low spatial and temporal bandwidth and sufficiently high amplitude to ensure representation of all relevant spatial and temporal frequencies. The *Trippy* stimulus features elongated curved contours while still having compact spatiotemporal autocorrelations, allowing RF computation by simple spike-triggered averaging. Both stimuli allow computing tuning for orientation, direction of motion, and (for Trippy) spatiotemporal frequencies. By correlating responses between repeated presentations of identical conditions, we measured the strength and reliability of responses to quantify the overall stimulus drive. We found that the Monet stimulus significantly exceeded the reliability of conventional pink noise stimuli while Trippy produced nearly double the drive of Monet,

although it did not reach the reliability of dynamic naturalistic stimuli. As a result, a combination of the two stimuli can assess all basic stimulus response properties from a 15-minute recording even when used in two-photon recordings from thousands of cells simultaneously.
This presentation demonstrates the stimuli, explains how to perform the analysis, and summarizes results from two-photon recordings.

Disclosures: D. Yatsenko: None. **P.G. Fahey:** None. **E. Froudarakis:** None. **J. Reimer:** None. **E.Y. Walker:** None. **F.H. Sinz:** None. **E. Cobos:** None. **A.S. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.07/BB15

Topic: D.07. Vision

Support: D16PC00003 (IARPA)
F30MH112312

Title: Dense volume functional calcium imaging in mouse visual cortex

Authors: *P. FAHEY[1], J. REIMER[1], E. FROUDARAKIS[1], E. COBOS[1], F. H. SINZ[1], D. YATSENKO[1], T. MUHAMMAD[1], A. S. TOLIAS[1,2]
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Abstract: As new optical imaging technologies and transgenic mouse resources become available, *in vivo* functional calcium imaging is now possible at scales and depths that were previously prohibitive. As part of the multi-institution MICrONS (Machine Intelligence from Cortical Networks) project, we undertook to perform functional calcium imaging in all neurons in a roughly one cubic millimeter volume spanning mouse primary visual cortex and higher visual areas.
A 90 minute visual stimulus was designed to balance parametric and natural movie clips for an efficient exploration of feature selectivity and cortical representation of natural inputs. After placing a cranial window over right visual cortex, the stimulus was shown to the left eye of awake, head-mounted GCaMP6-expressing mice while we imaged at 6.3 Hz in four 1200 x 1100 µm fields, averaging over 5000 neurons per scan distributed across the 600 µm volume depth. Additional behavioral recordings included treadmill rotation, ultrasonic audio, and videos of the face and body to record changes in the pupil, whiskers, and posture.
Experimental constraints necessitated imaging across several days, requiring daily data quality control and scan registration into a structural imaging stack to confirm precise field-of-view placement for full volume coverage of over 65,000 to 100,000 neurons per mouse. To efficiently

process such large quantities of data within a day, we developed a streamlined analysis pipeline including raster and motion correction, as well as cell body segmentation and spike rate inference from the fluorescence signals. We monitored the data quality using a combination of basic signal quality measures and the reliability and feature selectivity on the raw scans in repeated presentations of parametric and natural movie stimuli. Altogether, we collected over 1.5 million neuron-hours of imaging across 12 mice, one of which will be selected for EM and dense reconstruction at the Allen Institute for Brain Science and Princeton University, respectively. In addition to the inherent value of such a large and comprehensive dataset, we believe the general approach for dense functional imaging developed in this effort will be valuable as datasets of this scale become increasingly more common.

Disclosures: P. Fahey: None. **J. Reimer:** None. **E. Froudarakis:** None. **E. Cobos:** None. **F.H. Sinz:** None. **D. Yatsenko:** None. **T. Muhammad:** None. **A.S. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.08/BB16

Topic: D.07. Vision

Support: IARPA D16PC00004

Title: Automated high-throughput transmission electron microscope imaging pipeline for connectomics

Authors: *W. YIN, ESQ, D. BRITTAIN, J. BORSETH, M. SCOTT, D. WILLIAMS, J. PERKINS, D. CASTELLI, N. DA COSTA, C. REID
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Electron microscopy is the gold standard for structural studies identifying micro connectivity in the brain. We have built a pipeline to scale this technology to enable the acquisition of petascale datasets containing local cortical microcircuits. We have chosen to implement a platform for distributed high throughput electron microscopy composed of multiple transmission electron microscopes (TEMs), which will image in parallel different sections from the same block of tissue. TEM imaging has one of the highest signal to noise ratios and offers high speed, high resolution and cost-effective imaging of conventionally processed tissue.
Our design is based on the original Transmission Electron Microscopy with Camera Array system (Bock et a, 2011, Lee et al, 2016). We have customized high-throughput multi-scope imaging pipeline by modifying JEOL-1200EXII microscope with faster cameras and a novel nanopositioner and sample handling system. The key hardware modifications include: (1) An extended column and custom electron-sensitive scintillator that produce a 10-fold increase in the

field-of-view with negligible impact on spatial resolution;(2) A commercially available large-format CMOS camera outfitted with a low distortion lens that reduces image acquisition time to 50-150ms with low field distortion; and (3) A fast nano-positioning sample stage that offers fast, high-fidelity raster imaging of large tissue sections . The acquisition software has been designed for continuous autonomous imaging and adaptable to advances in sensor technology that might further increase throughput.
The current burst imaging rate is 300 Mpixel/s (image acquisition only) per microscope and effective imaging rate is 50 Mpixel/s (Imaging, step-and-settle time, QC and post processing). This brings the combined burst acquisition rate of the pipeline to 1800 Mpixel/s and the effective rate to 300 Mpixel/s with five microscopes running acquisition in parallel (at a voxel size of 4 x 4 x 40 nm). It is worth noting that this rates can easily be surpassed, and we recently teste a 50 Mpixel camera that increase the effective rate of a single microscope to 125 Mpixel/s. The microscope imaging rates were reached while acquiring thousands of 1×1 mm^2 montages (~10000 tiles) to exercise the imaging pipeline for our target volumes: 1 mm^3 of neocortex. To image the 1 mm^3 block, 25,000 thin slices of tissue sections will be imagined in parallel across different microscopes.

Disclosures: W. Yin: None. **D. Brittain:** None. **J. Borseth:** None. **M. Scott:** None. **D. Williams:** None. **J. Perkins:** None. **D. Castelli:** None. **N. da Costa:** None. **C. Reid:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.09/BB17

Topic: D.07. Vision

Support: D16PC00003

Title: Deciphering the wiring diagram of layer 4 neuronal circuit of visual cortex of adult mice at the level of morphologically defined cell types

Authors: *F. SCALA[1], S. SHEN[1], S. PAPADOPOULOS[1], S. LATURNUS[2], J. CASTRO[1], P. BERENS[3], X. JIANG[1], A. S. TOLIAS[1]
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Abstract: Understanding how brain regions compute their input-output function requires knowing the cellular sub-populations and their local and long-range connectivity. Sensory cortices of mammals organize as a stereotypical, six layer structure, with Layer 4 (L4) receiving most of the inputs from the thalamus thus representing the first level of cortical processing of sensory information. Despite the importance of L4 in sensory cortices, a complete census of cell

types and their wiring diagram in mature neocortex, remains to be elucidated. In this study, we used multiple simultaneous whole-cell recordings combined with morphological recovery on the primary visual cortex (V1) of adult mouse, to systematically profile the L4 neuronal circuits at the level of major cell types and their connections. We identified seven types of γ-aminobutyric acid-releasing (GABAergic) interneurons, including basket cells, Martinoti cells, neurogliaform cells, all of which could be readily discriminated by their morphological and electrophysiological features. The analysis of the intra-laminar connectivity between pyramidal-, basket-, and Martinotti-cells, reveals cell type-specific connectivity motifs, providing information on the structural and functional organization of L4 in the visual cortex of adult mice. Notably, the comparison between visual- and somatosensory-cortex revealed remarkable differences in major cell types and their connectivity principles, arguing against a canonical circuits across brain regions. Overall, these results pave the way for future studies on L4 neocortex, with the intent to understand how cortical networks orchestrate their activity to process information.

Disclosures: F. Scala: None. **S. Shen:** None. **S. Papadopoulos:** None. **S. Laturnus:** None. **J. Castro:** None. **P. Berens:** None. **X. Jiang:** None. **A.S. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.10/CC1

Topic: D.07. Vision

Support: IARPA D16PC00003
DARPA D17PC00162

Title: DataJoint: A framework for scientific data pipelines

Authors: *J. REIMER[1], D. YATSENKO[1], E. Y. WALKER[1], F. H. SINZ[2], C. TURNER[1], A. S. TOLIAS[1]
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Abstract: As neuroscience data becomes larger, more multi-modal, and complex, many scientists struggle with ad-hoc strategies and workflows for collaboration and data sharing. Much discussion has focused on sharing data after they have been collected and processed. However, in complex collaborative projects, principled data management must begin early in the process as large and intricate datasets from diverse instrumentation are precisely aligned, annotated, and organized for flexible access by multiple agents. A *data pipeline* is collection of tools, resources, and processes for entry, acquisition, processing, querying, navigation, and monitoring of shared data with provisions for efficiency and data integrity.
DataJoint is a free, open-source framework designed for custom data pipelines in science labs.

With interfaces in MATLAB and Python and multiple data hosting options, it enables the definition of shared data pipelines for collaborative work within a lab or across multiple labs, without limitations to particular acquisition systems or data modalities. Explicit referential constraints within the pipeline communicate the structure of the pipeline and guide the workflow. DataJoint's uniform process for defining computations allows large groups to work efficiently together and to deploy distributed computations with minimal effort. DataJoint presents a clean data model to the research scientist, allowing division of labor between data engineers and domain experts. Relevant resources resources are provided at http://datajoint.io

Disclosures: D. Yatsenko: None. **E.Y. Walker:** None. **F.H. Sinz:** None. **C. Turner:** None. **A.S. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.11/CC2

Topic: D.07. Vision

Support: IARPA Contract D16PC0005
NIMH Grant T32MH065214

Title: Pyramidal-to-interneuron connectivity rules in mouse primary visual cortex deciphered by combining calcium imaging and 3D electron microscopy

Authors: *A. M. WILSON[1], S. DORKENWALD[1], T. MACRINA[1], N. TURNER[1], J. A. BAE[1], D. IH[1], C. JORDAN[1], N. KEMNITZ[1], K. LEE[1,2], R. LU[1], S. POPOVYCH[1], W. SILVERSMITH[1], I. TARTAVULL[1], W. WONG[1], J. WU[1], J. ZUNG[1], E. FROUDARAKIS[3,4], A. BLECKERT[5], A. BODOR[5], D. BUMBARGER[5], J. REIMER[3,4], A. S. TOLIAS[3,4,7], N. M. DA COSTA[5], R. REID[6], H. SEUNG[1]
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Abstract: Mouse primary visual cortex (V1) has emerged as an important model system for relating the feature selectivity of sensory neurons to their synaptic connectivity. Some inhibitory interneurons respond selectively to particular stimulus orientations, but the mechanism of orientation selectivity is controversial. Kerlin et al. (2010) found that orientation tuning of interneurons is weaker than for pyramidal neurons. They conjectured that interneurons indiscriminately receive connections from all neighboring pyramidal neurons, and therefore the preferred orientation of an interneuron should be the one that happens to be overrepresented in the diverse preferred orientations of neighboring pyramidal neurons. Bock et al. (2011)

subsequently found evidence for the hypothesized indiscriminate connectivity. Recently, calcium imaging in vivo followed by synaptic physiology in brain slices indicates that parvalbumin-positive (PV) interneurons receive stronger connections from pyramidal neurons with similar visual preferences (Znamenskiy et al. 2018). This is consistent with the report that some PV interneurons (Runyan et al. 2010) are sharply tuned to stimulus orientation. It remains unclear whether the connections are stronger because they involve more synapses or stronger synapses. Furthermore, other interneuron types have not yet been investigated. We observed the visual responses of pyramidal neurons by calcium imaging in vivo, and then reconstructed synaptic connections to neighboring inhibitory interneurons, based on 3D electron microscopy (EM) images of mouse V1 (millions of cubic microns in layer 2-3). We quantified similarity of visual preferences for pyramidal cells presynaptic to the same interneuron, and related this to connection strength estimated by synapse number and size. Using this information we comment on whether pyramidal inputs to an interneuron are significantly biased in their visual preferences, and whether this bias is likely due to number of synapses or individual synapse strengths, for a number of different interneuron types.

Disclosures: A.M. Wilson: None. **S. Dorkenwald:** None. **T. Macrina:** None. **N. Turner:** None. **J.A. Bae:** None. **D. Ih:** None. **C. Jordan:** None. **N. Kemnitz:** None. **K. Lee:** None. **R. Lu:** None. **S. Popovych:** None. **W. Silversmith:** None. **I. Tartavull:** None. **W. Wong:** None. **J. Wu:** None. **J. Zung:** None. **E. Froudarakis:** None. **A. Bleckert:** None. **A. Bodor:** None. **D. Bumbarger:** None. **J. Reimer:** None. **A.S. Tolias:** None. **N.M. da Costa:** None. **R. Reid:** None. **H. Seung:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.12/CC3

Topic: D.07. Vision

Support: IARPA DoI/IBC (D16PC00005)

Title: An automated anatomical reconstruction system for petascale connectomics

Authors: *N. L. TURNER[1], J. BAE[1], D. BUNIATYAN[1], S. DORKENWALD[1], N. KEMNITZ[1], D. IH[1], K. LEE[1], R. LU[1], T. MACRINA[1], S. POPOVYCH[1], W. SILVERSMITH[1], I. TARTAVULL[1], J. WU[1], W. WONG[1], J. ZUNG[1], E. FROUDARAKIS[2], P. FAHEY[2], J. REIMER[3], A. L. BODOR[4], A. A. BLECKERT[4], D. J. BUMBARGER[5], N. M. DA COSTA[4], A. S. TOLIAS[3], R. REID[5], H. SEUNG[1]
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Abstract: Connectomics uses electron microscopy (EM) to study the fine structure of neuronal arbors and their connectivity at nanoscale resolution. Recent efforts in EM connectomics predominantly use manual skeleton tracing (Kornfeld et al. 2017, Schmidt et al. 2017, Lee et al. 2016), yet reconstructing larger volumes require automated methods which are both efficient and accurate. We've developed a scalable approach for automated neural circuit reconstruction. We plan to scale this effort up to a $1mm^3$ reconstruction of mouse visual cortex. Here, we describe the anatomical reconstruction pipeline in detail.

Our reconstruction begins by aligning a cohesive 3D volume from EM image tiles. This is achieved using Alembic, a customized implementation of elastic models based on correspondences generated by normalized cross correlation (Saalfeld et al. 2012). We then train convolutional neural networks to detect cell boundaries and synaptic clefts within the aligned 3D image (Lee et al. 2017). After applying the cell boundary detector over the entire dataset, the image is over-segmented using a modified watershed algorithm (Zlateski & Seung 2015), and the resulting segments are agglomerated to produce larger regions of a cell's morphology. The voxelwise synaptic cleft predictions are segmented using connected components, and filtered by size. The connectivity between segments is then inferred by a convolutional network using each predicted cleft as an attentional signal.

We deploy each of these methods over hundreds of machines in the cloud, managed by a few key software systems. These include (1) Air-Tasks, a container management system based on Apache Airflow, (2) CloudVolume, a customized data cutout service, and (3) Igneous, a set of tasks for creation of image hierarchies and meshing for visualization in Neuroglancer.

In collaboration with Baylor College of Medicine and the Allen Institute for Brain Science, we've successfully applied this approach to a 196 x 130 x 40 μm^3 volume, and associated the reconstructed cells with 2-photon imaging data of the same volume. Our agglomerated regions capture whole dendritic shafts, with most spines intact. We also observe synapse detection at greater than 90% precision and recall by multiple evaluation schemes. We also estimate that proofreading this volume finds validated edges of the connectivity graph at least 5x faster than manual skeleton tracing (Boergens et al., 2017; Lee et al 2016).

Disclosures: N.L. Turner: None. **J. Bae:** None. **D. Buniatyan:** None. **S. Dorkenwald:** None. **N. Kemnitz:** None. **D. Ih:** None. **K. Lee:** None. **R. Lu:** None. **T. Macrina:** None. **S. Popovych:** None. **W. Silversmith:** None. **I. Tartavull:** None. **J. Wu:** None. **W. Wong:** None. **J. Zung:** None. **E. Froudarakis:** None. **P. Fahey:** None. **J. Reimer:** None. **A.L. Bodor:** None. **A.A. Bleckert:** None. **D.J. Bumbarger:** None. **N.M. da Costa:** None. **A.S. Tolias:** None. **R. Reid:** None. **H. Seung:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.13/CC4

Topic: D.07. Vision

Support: IARPA via DoI/IBC contract number D16PC0005

Title: Comparing the connectivity fraction for axo-dendritic contacts with pyramidal neuron spiny dendrites and interneuron nonspiny dendrites in mouse V1

Authors: *T. MACRINA[1], N. TURNER[1], R. LU[1], D. IH[1], K. LEE[1], J. WU[1], S. POPOVYCH[1], W. SILVERSMITH[1], N. KEMNITZ[1], W. WONG[1], C. JORDAN[1], I. TARTAVULL[2], J. ZUNG[1], D. BUNIATYAN[1], S. DORKENWALD[1], J. A. BAE[1], D. BUMBARGER[3], A. BLECKERT[3], N. DA COSTA[3], R. C. REID[3], H. S. SEUNG[1]
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Abstract: Peters' Rule is the idea that synaptic connectivity between cell types can be predicted statistically from the availability of axons and dendrites in the neuropil. When Peters' Rule holds, it is useful for estimating synaptic connectivity from overlap between arbors. When Peters' Rule is violated, it defines the baseline connectivity from which deviations indicate specificity of connections. Here we use a strategy employed by Mishchenko et al. (2010), using the the "connectivity fraction" to investigate Peters rule. Defining the connectivity fraction as the percentage of axo-dendritic contacts that are synapses, they showed that axonal contacts with dendritic spines of hippocampal CA1 pyramidal neurons had a connectivity fraction of 20%. Here we analyze the connectivity fraction for axonal contacts with dendrites of neocortical pyramidal neurons, as well as with inhibitory interneurons. We further breakdown the connectivity fraction by contacts with dendritic spine heads, spine necks, and shafts of pyramidal neurons. Our analysis was performed using a million cubic micron volume of mouse visual cortex that was imaged by serial section transmission electron microscopy. Neurites were reconstructed and synapses were detected automatically using 3D convolutional networks.

Disclosures: T. Macrina: None. **N. Turner:** None. **R. Lu:** None. **D. Ih:** None. **K. Lee:** None. **J. Wu:** None. **S. Popovych:** None. **W. Silversmith:** None. **N. Kemnitz:** None. **W. Wong:** None. **C. Jordan:** None. **I. Tartavull:** None. **J. Zung:** None. **D. Buniatyan:** None. **S. Dorkenwald:** None. **J.A. Bae:** None. **D. Bumbarger:** None. **A. Bleckert:** None. **N. da Costa:** None. **R.C. Reid:** None. **H.S. Seung:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.14/CC5

Topic: D.07. Vision

Support: IARPA D16PC00003

Title: In silico characterization of non-linear response properties of cortical neurons using maximally exciting images

Authors: *F. H. SINZ[1], E. Y. WALKER[1], E. FROUDARAKIS[1], P. G. FAHEY[1], A. S. ECKER[2], E. M. COBOS[1], J. REIMER[1], A. S. TOLIAS[1]
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Abstract: To understand stimulus representations in visual cortex, we need models that faithfully predict neural activity in response to natural input and methods to categorize their computations. Recently, novel predictive models based on deep neural networks have set a new standard in predicting the activity of cortical neurons to natural stimuli over traditional methods such as linear-nonlinear (LN) models. This powerful new system identification approach promises new insights into the ongoing non-linear signal processing in primary visual cortex through analysis of the predictive model and subsequent testing of the insights in physiological experiments.
However, while linear operations are easily summarized by a linear filter on the image, non-linear functions in high dimension are much harder to characterize. Here, we use visualization techniques from deep learning to obtain most exciting images (MEI) for neurons in the predictive deep network model. For each neuron, we start with a white noise image and perform gradient ascent on the image to maximize the target neuron's predicted response. To overcome the known issue of high-frequency noise introduced by this method, we precondition the gradient at each iteration with low pass filtering. Furthermore, we use Gaussian filtering with progressively decreasing filter scale on the image to optimize the image in a coarse to fine manner. When this generation procedure is applied to a LN model, the resulting MEI is equivalent to the smoothened receptive field (RF). Interestingly, for the deep network models we find that the MEIs are notably distinct from RFs. This suggests that the non-linearity captured by the deep learning model is more complex than a simple non-linearity applied after a linear filter bank. We consistently find the MEIs to drive predicted neurons in the deep network model more strongly than contrast and luminance matched RFs, even when tested in other models determined by different initializations and variations of the deep network architecture but with comparable prediction performances. This suggests that the MEIs capture nonlinear response properties in the data that extends beyond the particular choice of the model.

Disclosures: F.H. Sinz: None. **E.Y. Walker:** None. **E. Froudarakis:** None. **P.G. Fahey:** None. **A.S. Ecker:** None. **E.M. Cobos:** None. **J. Reimer:** None. **A.S. Tolias:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.15/CC6

Topic: D.07. Vision

Support: Human Brain Project 7202070

Title: Optogenetic silencing of V1 neural activity during figure-ground segregation

Authors: *L. KIRCHBERGER[1], H. E. VAN BEEST[1], S. MUKHERJEE[1], U. H. SCHNABEL[1], M. W. SELF[1], P. R. ROELFSEMA[1,2,3]
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Abstract: When inspecting a visual scene, it seems effortless for us to identify shapes, objects and surfaces. The segregation of objects from their surround is an important step in this process. Neurons in primary visual cortex (V1) enhance their activity if it is elicited by figures compared to when it is elicited by a background. The difference in activity is referred to as figure-ground modulation (FGM). Interestingly, FGM is not present in the early response of V1 neurons after about 40 ms, which is driven by feedforward input from the retina, but arises quite late after stimulus onset (~100 ms), suggesting that it may be the result of recurrent interactions between V1 and higher visual areas. Here we used optogenetics to test whether FGM in mouse V1 is necessary for figure perception. We trained head-fixed mice on a two-alternative forced choice task. We expressed the inhibitory opsin GtACR2 in V1 pyramidal neurons of both hemispheres so that we could temporarily inhibit them with blue light. The mice indicated the position of a figure, which differed from the background in either contrast (contrast detection), orientation or phase (figure-ground), by licking the corresponding side. We inhibited V1 activity at different times after the onset of the visual stimulus to establish the minimum V1 processing time necessary to reliably report the figure position and whether it depends on the necessity of figure-ground segregation. When the stimulus was defined by contrast, the mice were able to perform the task even when processing times were reduced to ~70 ms after stimulus onset. As V1 neurons have a response latency of ~50 ms, the actual necessary V1 activity is only ~20 ms, indicating that early, feedforward information is sufficient to perceive this type of figure. Notably, some mice could perform above chance even when V1 was inhibited for the entire duration of the stimulus, suggesting residual performance without V1. However, the tasks demanding figure-ground segregation relied on late V1 activity. In these tasks, the accuracy of the mice reached its asymptote only when we allowed for at least 150 ms of processing time. These results provide direct evidence that sustained neural activity in V1 is necessary for the detection of a figure on a complex background, giving new insights into how the brain processes

more complex visual stimuli. Further experiments are necessary to identify the origin of sustained V1 activity.

Disclosures: L. Kirchberger: None. **H.E. Van Beest:** None. **S. Mukherjee:** None. **U.H. Schnabel:** None. **M.W. Self:** None. **P.R. Roelfsema:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.16/CC7

Topic: D.07. Vision

Support: Erasmus Mundus NeuroTime fellowship
ERC Grant 339490

Title: The role of interneurons during figure-ground perception in mouse visual cortex

Authors: *S. MUKHERJEE[1], U. H. SCHNABEL[1], H. E. VAN BEEST[1], L. KIRCHBERGER[1], M. W. SELF[1], P. R. ROELFSEMA[1,2,3]
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Abstract: Visual perception and image segmentation rely on multiple hierarchical areas of the visual cortex. Neurons in lower visual areas, such as primary visual cortex (V1), code for simple features and drive neurons coding for more complex features in higher areas, which in turn, feedback to modulate V1 activity. Here we asked how the V1 microcircuit integrates feedback during the processing of figure-ground displays, where a figure stands out from the background based on a difference in stimulus orientation. A figure elicits a stronger response of V1 neurons than the background, a difference that is called Figure-Ground Modulation(FGM). We suspected that excitatory and the different inhibitory cell classes might play specific roles in FGM and focused on a well-established sub-division of interneurons into vasoactive intestinal peptide (VIP), somatostatin (SST) and parvalbumin (PV) cells. We studied the role of these different neuronal subclasses using two-photon calcium imaging during figure-ground perception. We observed robust FGM with multiple types of figure-ground displays, implying that it is a robust phenomenon. The excitatory neuronal population in V1 responded more strongly to figures than to backgrounds, implying that V1 outputs a stronger signal for figures. VIP cells also enhanced their activity if the figure fell on their receptive field compared to the ground. By contrast, the SST cells were more active during the background condition, in accordance with previous work suggesting that SST neurons are responsible for the suppression of activity elicited by homogeneous image regions.Our results, taken together, suggest that feedback from neurons in

higher visual areas that represent the figure might activate VIP neurons in V1, which in turn, inhibit SST neurons thereby disinhibiting the excitatory neurons, resulting in enhanced firing of the excitatory neurons in V1. As a result, the V1 representation of the figure is labeled with stronger activity. In favour of this hypothesis, we also found a stronger figure representation in excitatory neurons in lateral and medial higher visual areas. Feedback axons from these higher visual areas show a topographic arrangement over V1, which could support such a selective feedback signal for generating FGM in V1. Our results provide a mechanistic, cellular understanding of how the V1 microcircuit is able to parse image elements and group them together for a coherent percept.

Disclosures: S. Mukherjee: None. **U.H. Schnabel:** None. **H.E. Van Beest:** None. **L. Kirchberger:** None. **M.W. Self:** None. **P.R. Roelfsema:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.17/CC8

Topic: D.07. Vision

Support: ERC Grant 339490
HBP 7202070

Title: Active figure-ground segregation and its neuronal correlates throughout the mouse cortex

Authors: *H. E. VAN BEEST[1], U. H. SCHNABEL[1], S. MUKHERJEE[1], L. KIRCHBERGER[1], M. W. SELF[1], P. R. ROELFSEMA[1,2,3]
[1]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Academic Med. Ctr., Amsterdam, Netherlands; [3]Ctr. for Neurogenomics and Cognitive Res., VU Univ., Amsterdam, Netherlands

Abstract: An important question in visual neuroscience is how an object is segregated from the background. Cells at early stages of the visual hierarchy receive inputs from a small region of the retina, known as their receptive field (RF). Despite this, activity of cells at these early stages can be modulated by contextual visual information from far outside the RF. An example of such a contextual effect is figure-ground modulation (FGM), in which the activity of a neuron in the primary visual cortex (V1) is enhanced when its receptive field falls on a figure-area of a stimulus, rather than on a background. FGM occurs irrespective of the feedforward input to the neuron in V1, and it usually starts after the initial visual response onset to the stimulus (after 100ms). This has led to the idea that FGM in V1 is inherited from feedback projections coming from higher visual areas, which have larger receptive fields. Although this modulation was first observed in monkeys, it has recently been shown by our lab that a similar modulation can be found in mouse V1. The mouse-model provides many new technological possibilities, such as

recording from specific cell-populations on a large scale, which makes it possible to identify cortical areas in which FGM occurs. In this study, we imaged activity from excitatory cells in superficial layers of the entire cortex through a clear-skull in awake Thy1-GCaMP6 mice. First, we identified visual areas V1, LM, AL, RL, AM and PM as regions in which a passively shown figure elicited more activity than a background, suggesting that FGM is broadly represented across many visual areas. Next, we trained mice to perform a figure-detection task, to investigate the global activation of different brain regions when a complex figure is perceived and used to guide a specific action; a lick-response on the side of the figure counted as a correct response. As expected, 100ms after stimulus onset, a figure elicited more activity than a background in visual areas. In addition, the side the figure was presented seemed to modulate this difference. In more frontal regions, the difference between figure and ground seemed less relevant; activity in those regions was more dependent on the side to which the animal would respond. These results provide insight into the network of brain areas involved in figure-segregation, and how this signal is transformed into an action. In other work of our lab, we investigated whether FGM in visual area V1 is necessary to perform the task, and how different interneurons are involved in FGM. These studies together will help us understand the role of global and local interactions across the brain during performance of a complex visual task.

Disclosures: H.E. Van Beest: None. **U.H. Schnabel:** None. **S. Mukherjee:** None. **L. Kirchberger:** None. **M.W. Self:** None. **P.R. Roelfsema:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.18/CC9

Topic: D.07. Vision

Support: 604102, Human Brain Project
339490, ERC

Title: A fovea-like representation of space in mouse visual cortex

Authors: *M. W. SELF[1], H. E. VAN BEEST[1], L. KIRCHBERGER[1], S. MUKHERJEE[1], U. H. SCHNABEL[1], P. R. ROELFSEMA[1,2,3]
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Abstract: The mouse visual system differs from that of primates in that mice lack a fovea, the region of the retina with greatly enhanced photoreceptor density in comparison to the periphery. This has implications for the use of the mouse as a model for the human visual system, for example, mice do not need to move their eyes to bring interesting objects into the fovea for

detailed analysis. Previous studies however, have suggested that the photoreceptor density of the mouse retina is not entirely uniform and that the representation of space in mouse visual cortex may be enlarged for particular regions of the visual scene. Here we investigated the representation of space in mouse visual cortex through the use of population receptive field (pRF) mapping through the intact skull of mice expressing the genetically encoded calcium indicator GCaMP. pRF mapping allows estimates to be made of both the position and size of the aggregate receptive fields at a point in cortex. Surprisingly we found that mouse primary visual cortex (V1) contains a region in which pRF sizes were considerably smaller, superficially resembling the foveal representation of space in primate V1. Receptive fields in this region, located in front of, and slightly above the mouse (azimuth 0 degrees, elevation 20 degrees), were approximately half the size of those in regions representing more peripheral parts of space. This spatial basis could also be observed in the neighboring higher visual areas: LM, RL and AL as the region of high resolution was centered on the border of V1 and the lateral visual areas. We investigated the source of this organization further using both 2-photon imaging and electrophysiological recordings to access the receptive fields of individual cells in V1 and surrounding areas. The results suggest a previously unsuspected similarity in the representation of space between mice and humans which may improve our ability to translate mouse visual research to the human.

Disclosures: M.W. Self: None. **H.E. Van Beest:** None. **L. Kirchberger:** None. **S. Mukherjee:** None. **U.H. Schnabel:** None. **P.R. Roelfsema:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.19/CC10

Topic: D.07. Vision

Support: NIH 5T32EY024234
NIH R01 EY019743
NIH R01 EY026812
NIH U01 NS099702
NSF IOS 1355075
NSF EAGER 1649923
Ella & Georg Ehrnrooth Foundation

Title: Temporal dynamics of the effect of optogenetic inactivation of V2 feedback on V1 responses

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Abstract: Top-down cortico-cortical feedback (FB) is hypothesized to contribute to numerous cognitive and perceptual phenomena. Using optogenetic inactivation of feedback terminals and laminar array recordings, we (Nurminen et al., 2018) recently demonstrated that FB projections from the second visual area (V2) to primary visual cortex (V1) play a critical role in regulating response amplitude and receptive field (RF) size in marmoset V1. The timing of these effects remains an open question. Thus, we followed up on our prior results by investigating the temporal dynamics of the effects of selective inactivation of V2-to-V1 FB on V1 visual responses. We used the inhibitory opsin ArchT to silence V2-to-V1 FB, by co-injecting AAV9-CaMKII.Cre and AAV9.CAG.Flex.Arch.eGFP into V2 of 5 marmosets we drove selective expression of ArchT in V2 neurons. Four weeks after injections, we performed linear array recordings in V1 under sufentanil anesthesia. To activate ArchT, we applied focal surface photostimulation (stim) to V1 within an ~1mm radius around the array. We measured size tuning to either full contrast (4/5 animals) or 50% contrast (1/5) drifting sinusoidal gratings with and without FB inactivation. To examine the time course of FB inactivation effects we compared the firing rate in control and stim trials in 100ms windows stepped every 10ms from 100ms pre/post visual stimulus onset; focusing on responses to stimuli either matched to the RF size (rf) or extending into the proximal surround (prox). Cells exhibited a diversity of temporal response difference profiles. To examine population effects, we first normalized window times to each unit's visual onset latency before averaging. On average, the change in response amplitude during photostimulation began rapidly but peaked earlier in the rf (~50ms following visual response onset) compared to the prox (~150ms following visual response onset) condition. To ensure that these differences in mean firing rate were robust, and not driven by undersampling across trials or time, we also computed receiver operating characteristic (ROC) curves from the distributions of responses to rf and near stimuli during control and stim trials in each window. Here, we observed similar differences in the time at which the average area under the ROC curves peaked for the rf and near conditions, suggesting differences were indeed robust. These results suggest that feedback effects are dependent on stimulus parameters and RF size changes following feedback inactivation should follow the aforementioned dynamics - a result borne out by preliminary analysis. We are examining a network model of visual cortex to identify putative circuit mechanisms.

Disclosures: A.M. Clark: None. **L. Nurminen:** None. **A. Angelucci:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.20/CC11

Topic: D.07. Vision

Support: NIH Grants R01 EY019743
NIH Grant R01 EY026812
NIH Grant U01 NS099702
NSF Grant IOS-1355075
NSF Grant EAGER 1649923
Research to Prevent Blindness

Title: Parallel feedback pathways between macaque visual areas V2 and V1

Authors: *S. F. TA'AFUA[1], F. FEDERER[2], S. MERLIN[3], A. ANGELUCCI[2]
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Abstract: In macaque visual cortex, visual information travels along feedforward connections from lower- to higher-order areas, where it is processed both hierarchically and in parallel. Neuronal receptive fields in higher visual areas become progressively larger and tuned to increasingly complex visual stimulus features, with multiple parallel circuits processing different aspects of visual information (e.g. form, motion, etc.). For example, in primary visual cortex (V1), cells in cytochrome oxidase (CO) blob compartments project predominantly to V2 CO thin stripes, while those in V1 interblobs project to V2 CO thick and pale stripes (Sincich and Horton 2002; Federer et al. 2009, 2013). V1, in turn, receives a dense network of feedback (FB) projections from higher-order areas, whose anatomy and function is less well understood. For example, it remains unknown whether FB connections from V2-to-V1 segregate within CO compartments (Angelucci et al., 2002; Shmuel et al. 2005), like the feedforward V1-to-V2 pathways, or contact multiple CO compartments in a diffuse and unspecific fashion (Stettler et al. 2002). This is because previous anatomical studies of FB connections lacked sensitive anatomical tracers capable of labeling V2-to-V1 axons unambiguously, without also labeling the reciprocal feedforward V1-to-V2 projections.
Here we have investigated the anatomical organization of V2-to-V1 FB connections in macaque using AAV9 vectors of fluorescent proteins that allow unambiguous anterograde labeling of FB axons. Viral injections (n=19) were targeted to specific V2 CO stripes identified *in vivo* using intrinsic signal optical imaging in 4 animals. After 5-7 weeks the brains were sectioned parallel to the imaging plane to identify CO compartments, or sagittally to identify cortical layers. The density of labeled FB axons resulting from each injection was quantified with respect to both CO compartments and cortical layers in V1.
We found that V2 FB to V1 shows laminar and CO-compartment specificity. All stripe types sent denser FB projections to V1 layers (L) 1/2A, 5B, and 6B, and sparser projections to L2B/3. FB projections to L4B were evident after injections in thick stripes, but sparse or absent after injections in other stripe types. In all layers of V1, FB axons terminated in columnar patches. The density of labeled V2 FB axon terminals was highest in V1 interblobs after injections in thick and pale stripes, but in CO blobs after injections in thin stripes. We conclude that V2-to-V1 FB form parallel pathways, just like the reciprocal feedforward projections, and specifically target the same layers and compartments from which feedforward projections to V2 originate.

Disclosures: S.F. Ta'afua: None. **F. Federer:** None. **S. Merlin:** None. **A. Angelucci:** None.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.21/CC12

Topic: D.07. Vision

Support: NIH grants R01 EY019743, R01 EY026812 and U01 NS099702
NSF Grants IOS-1355075 and EAGER 1649923
Research to prevent blindness grant

Title: Orientation organization of feedforward connections from V1 to V2 in macaque visual cortex

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Abstract: A crucial step in visual object recognition is the computation of object contours, which relies on the ability of visual system neurons to extract information on the orientation of edges. In the primate visual system, the analysis of edge orientation begins with the emergence of orientation selectivity in V1 cells (Hubel & Wiesel, 1968), and continues in V2 thick and pale stripes, where cells respond to more complex contours, such as elongated edges, angles and curves (Heider et al. 2000; Hedge & Van Essen 2000; Ito & Komatsu 2004; Anzai et al. 2007). Feedforward models treat these complex V2 responses as arising from linear convergence of orientation selective inputs from V1. However, despite decades of research on the anatomy and function of areas V1 and V2, it is still unknown how V2 cells and columns pool V1 inputs, and how the latter contribute to generating the visual responses of V2 neurons. To address this question, we have examined the orientation-organization of V1 inputs to V2, using combined optical imaging (OI) and tracer injections.
Small injections of the retrograde tracer CTB conjugated to fluorescent Alexa-488, 555, or 647 dyes were targeted to single orientation domains in V2 thick or pale stripes, identified *in vivo* using intrinsic signal OI in 5 macaque monkeys. After the injection, imaging for orientation and retinotopy was continued for an additional 4-6 days. The brain was sectioned parallel to the imaging plane, and labeled V1 cells and V2 injection sites were imaged on a confocal microscope and aligned to the functional maps using surface vasculature. We mapped the retinotopic location and orientation preference (OP) of labeled V1 cells and V2 injection sites based on their location on the retinotopic and orientation maps, respectively.
We found that the distribution of OPs of labeled V1 cells peaks at the OP (±30°) of the V2

injection site, and that the field of V1 labeled cells is elongated along an axis in visual space matching the OP at the V2 injected site. This result suggests that V1-to V2 inputs may integrate collinear line segments into elongated contours. However, mapping both the retinotopic location and OP of each V1 labeled cells demonstrated a more complex spatial distribution of oriented line segments, which included both collinear/cocircular and parallel structure. This orientation organization is reminiscent of the statistics of the geometric relationship between oriented edges in natural images (Geisler et al 2001). Our results suggest that converging V1 inputs contribute to generating the more complex receptive fields of V2 neurons, and that the connectivity between V1 and V2 is optimized to extract contours from natural images.

Disclosures: M.S. Hassanpour: A. Employment/Salary (full or part-time):; Department of Ophthalmology and Visual Science, Moran Eye Institute, University of Utah. Other; NIH grants R01 EY019743, R01 EY026812 and U01 NS099702, NSF Grants IOS-1355075 and EAGER 1649923, Research to Prevent Blindness. **S. Merlin:** A. Employment/Salary (full or part-time):; Department of Ophthalmology and Visual Science, Moran Eye Institute, University of Utah, School of Science and Health, Western Sydney University. **L. Nurminen:** A. Employment/Salary (full or part-time):; Department of Ophthalmology and Visual Science, Moran Eye Institute, University of Utah. **F. Federer:** A. Employment/Salary (full or part-time):; Department of Ophthalmology and Visual Science, Moran Eye Institute, University of Utah. **A. Angelucci:** A. Employment/Salary (full or part-time):; Department of Ophthalmology and Visual Science, Moran Eye Institute, University of Utah.

Poster

219. Visual Cortex: Functional Architecture and Circuits I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 219.22/CC13

Topic: D.07. Vision

Support: NIH Grant R01 EY019743
NIH Grant R01 EY026812
NIH Grant U01 NS099702
NSF Grant IOS-1355075
NSF Grant EAGER 1649923
RPB

Title: A direct feedback-to-feedforward circuit for fast feedback modulation of incoming feedforward signals

Authors: *C. SIU[1], S. MERLIN[2], F. FEDERER[1], A. ANGELUCCI[1]
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Abstract: In the primate visual system, visual information ascends from the primary visual cortex (V1) to hierarchically higher areas where increasingly complex stimulus features are processed. This incoming feedforward (FF) signals can be modulated by top-down influences, which are likely mediated by feedback (FB) connections from higher to lower areas. We have recently shown, in primates, that FB connections from the secondary visual area (V2) modulate the receptive field size and response amplitude of V1 neurons (Nurminen et al. Nat. Comm. 2018), and that this modulation is fast, occurring shortly after visual response onset (Clark et al., SFN 2018). These results suggest that FB can rapidly influence the transfer of information from V1 to extrastriate cortex, possibly by making direct synaptic contacts with forward projecting V1 neurons. We tested this hypothesis using a novel viral-labeling technique, termed TRIO (TRacing Inputs and Outputs), that labels direct presynaptic inputs to specific projection neurons (Callaway & Luo 2015, Kim 2016). We performed TRIO in macaque monkey visual cortex to label monosynaptic inputs to V1 neurons sending forward projections to V2. Guided by *in vivo* optical imaging, we injected a retrograde canine adenovirus (CAV2-Cre) into V2, and two anterograde Cre-dependent AAV9 vectors at retinotopically matched V1 sites, one carrying the genes for the avian TVA receptor and mCherry (AAV9-flex-TVA-mCherry), the other the rabies virus glycoprotein (AAV9-flex-oG). The combination of Cre-dependent AAV9 and Cre-expressing CAV2 vectors ensured gene expression can only occur in cells that project from V1 to V2 injection sites. We then injected, a G-deleted rabies virus pseudotyped with the TVA complimentary envelope protein, EnvA, carrying GFP. This labeled V1 projection neurons with mCherry and GFP (yellow cells); moreover, due to the presence of oG in these cells, the virus also labeled presynaptic neurons with GFP (green cells). Brains were sectioned tangentially, fluorescent label imaged and then reacted for cytochrome oxidase to identify the layer and compartment of fluorescent-labeled cells. We found that V2-projecting V1 neurons receive direct presynpatic inputs from both distant neurons within V1 and FB-projecting neurons in V2 layers 2/3A and 5/6. Moreover, many V2 cells send both FB projections to V1 as well as horizontal axons to the V2 injected site. These findings demonstrate the existence of direct FB-to-FF connections that allow FB to rapidly modulate incoming FF signals.

Disclosures: C. Siu: None. **S. Merlin:** None. **F. Federer:** None. **A. Angelucci:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.01/CC14

Topic: D.07. Vision

Support: Deutsche Forschungsgemeinschaft: CRC/TRR-135
IRTG-1901
RU-1847

Title: Preattentive processing of visually simulated self-motion in humans and monkeys

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Abstract: Interaction with the environment requires fast and reliable sensory processing. The visual system is confronted with a continuous flow of high-dimensional input (e.g. orientation, color, motion). From a theoretical point of view, it would be advantageous if critical information was processed independent of attentional load, i.e. preattentively. Here, we hypothesized that (visually simulated) self-motion is such a critical signal and aimed for a neural signature of its preattentive encoding in both, humans and macaque monkeys. We studied event-related potentials (ERPs) in a visual oddball paradigm. In humans, we used a 64-channels standard scalp EEG (actiChamp). In the NHPs, we used the same system but only up to seven electrodes due to the smaller head-size. ERPs as observed in response to standard (80% occurrence) and deviant (20% occurrence) stimuli were compared in order to test for the occurrence of a visual mismatch negativity (MMN). The MMN is a component of an event-related brain potential that reflects a pre-attentive mechanism for change detection. Humans and NHPs had to actively fixate a central target during stimulus presentation, i.e. a simulated self-motion across a ground plane. Each trial consisted of a stationary phase, followed by a visually-simulated self-motion phase. Standard and deviant trials differed only in their simulated heading direction (forward-left vs. forward-right). EEG-data were aligned to the onset of the simulated self-motion. In order to test for a preattentive processing, we determined the difference of the ERP time courses for identical visual stimuli. In the one case, the stimulus had served as standard, in the other as deviant. As hypothesized, we found a visual MMN-negativity (stronger negativity for deviant as compared to standard stimuli) between 100 ms and 200 ms after stimulus motion onset in both, humans and monkeys. The occurrence of MMNs as observed in our study provides evidence for a pre-attentive processing of visually simulated self-motion direction. Importantly, the finding of a MMN in humans and NHPs provides further and strong evidence for the rhesus monkey as suitable animal model for visual cortical processing in humans.

Disclosures: A. Schütz: None. **J. Schwenk:** None. **C. Schmitt:** None. **A. Kaminiarz:** None. **B.O. Werner:** None. **J. Churan:** None. **F. Bremmer:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.02/CC15

Topic: D.07. Vision

Title: Dynamic perspective disambiguates depth from motion parallax: Human behavior and macaque v1 activity

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Abstract: Comprehending the 3-D structure of our environment is essential to many daily activities. Many brain regions and visual cortical circuits participate in computing depth from different cues. Some depth cues require binocular vision (two eyes), while others provide ample depth information from the images reaching only one eye (monocular cues).
One principal monocular depth cue is motion parallax (MP), which arises from the relative image velocities of objects located at different distances while an observer translates through the physical world. Previous psychophysical studies have demonstrated that signals related to eye rotation can disambiguate depth sign (near vs. far) from otherwise ambiguous MP cues. In addition, it has been suggested that global patterns of visual motion that simulate eye rotation during observer translation (dynamic perspective, DP) can also enable perception of depth-sign from motion parallax when the stimuli consist only. Recent neurophysiological findings from monkeys have demonstrated that neurons in macaque area MT show selectivity for depth sign based on DP cues. However, it is unclear whether this selectivity originates in MT, and the role of the primary visual cortex in signaling depth sign from MP and DP cues is unknown.
We first investigated the ability of humans to perceive depth-sign based on DP cues. Stimuli consisted of a small patch of dots containing depth-sign ambiguous MP cues, surrounded by a large 3D cloud of dots whose movement simulated eye rotation via DP cues. We found that DP cues enabled observers to unambiguously perceive depth-sign, and that observers showed orderly psychometric functions of stimulus depth. Reducing the proportion of background dots that carried the DP cue gradually impaired performance, and performance was abolished in the absence of background motion. Similarly, shortening the stimulus presentation time reduced depth-sign discrimination.
Finally, we performed voltage sensitive dye imaging (VSDI) of neuronal population activity in V1 of fixating monkeys. A small stimulus containing ambiguous MP cues was placed over the receptive field of V1 neurons, while the background either contained large-field motion with DP cues or was blank. By comparing responses to these two stimulus conditions, we were able to investigate whether V1 activity reflects the perceived depth-sign induced by DP cues.

Disclosures: G.C. DeAngelis: None. **H. Slovin:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.03/CC16

Topic: D.07. Vision

Title: Optic flow selectivity in the macaque motion area V6: A direct parallel with human V6

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Abstract: Neural representation of optic flow has been extensively studied in macaques and humans. In humans, several neuroimaging studies have demonstrated that passive viewing of optic flow stimuli activates higher-level motion areas in the temporal, parietal, insular and cingulate cortices. Some of these areas, like V6 and the cingulate sulcus visual area (CSv), are now consolidated egomotion regions. Surprisingly, we still know very little about the sensitivity of macaque V6 and CSv to optic flow stimulation. The only fMRI study on this issue have failed to reveal selectivity of macaque V6 (and Pc and p2v as well) to egomotion compatible optic flow (Cotterau et al, 2017, but see Fan et al. 2015). Yet, it is unknown whether monkey MT/V5 and V6 display any distinctive fMRI functional profile relative to the optic flow stimulation, as it is the case for the homologous human areas (Pitzalis et al., 2010). Here, cortical-surface-based functional MRI mapping techniques and motion stimulation were applied in two awake behaving macaques to describe the sensitivity of the monkey brain to two motion stimuli (radial rings and optic flow) originally used in humans to functionally map the motion middle temporal area MT/V5 (Tootell et al. 1995) and the motion medial parietal area V6 (Pitzalis et al. 2010), respectively. Whole-brain and regional analyses revealed regions commonly activated by the two visual stimuli while other regions were exclusively responsive to only one of the two motion stimuli. Specifically, in both animals, activity in areas V6+, MSTd, MT+, STPa, VPs, and in a region of the caudal part of intraparietal sulcus exhibited a clear preference for optic flow stimulation while activity in areas located in the inferior occipital and lunate sulci exhibited a clear preference for radial rings stimulation. Area V6+ was the most highly selective area for coherently moving fields of dots, further demonstrating the power of this type of stimulation to localize V6 in both humans and monkeys. We did not find any evidence that putative macaque CSv responds to optic flow. Overall, a direct comparison of our results with equivalent human studies reveals several commonalities but also some differences in the neural representation of optic flow across both species.

Disclosures: C. Galletti: None. **F. Hadj-Bouziane:** None. **G. Dal Bo:** None. **C. Guedj:** None. **M.L. Meunier:** None. **A. Farne:** None. **P. Fattori:** None. **S. Pitzalis:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.04/DD1

Topic: D.07. Vision

Support: NIH Grant F32 EY025121
NIH Grant R01 MH106520
NIH Grant T32 EY00703
NIH Grant R01 EB016089
NIH Grant P41 EB015909

Title: Glutamatergic facilitation of neural responses in area MT enhances visual motion perception in humans

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Abstract: There is large individual variability in human neural responses and perceptual abilities. The factors that give rise to these individual differences, however, remain largely unknown. To examine these factors, we separately measured fMRI responses to moving gratings in the motion-selective region MT, and perceptual duration thresholds for motion direction discrimination within the same group of male and female subjects. Further, we acquired MR spectroscopy data that allowed us to quantify an index of neurotransmitter levels in the region surrounding MT. We show that stronger Glx (glutamate + glutamine) signals in the MT region are associated with both higher fMRI responses and improved psychophysical task performance. Our results suggest that greater baseline levels of glutamate within MT facilitate motion perception by increasing neural responses in this region.

Disclosures: M. Schallmo: None. **R. Millin:** None. **A.M. Kale:** None. **T. Kolodny:** None. **R.A.E. Edden:** None. **R.A. Bernier:** None. **S.O. Murray:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.05/DD2

Topic: D.07. Vision

Support: NEI Intramural Program

Title: Short-latency ocular-following responses: Weighted average mechanism predicts the outcome of a competition between two sine wave gratings moving in opposite directions

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Abstract: We recorded, in three human subjects, horizontal ocular-following responses (OFR) to pairs of superimposed vertical sine wave gratings moving in opposite directions. This configuration elicits a winner-take-all interaction - when the relative contrast of the gratings is changed, the response transitions abruptly between the responses elicited by either grating alone. This has been described as a weighted sum of the responses to each grating presented alone, in which the weights are a nonlinear function of stimulus contrast (*C*, see equation below). Here we explore this interaction in many pairs of gratings that differ in both spatial and temporal frequency (SF and TF). For any pair, we define the dominant component as that which determines the direction of eye movement when the grating contrast is equal. Surprisingly, we found that in many cases the dominant component was not the component that produced the strongest response when presented alone. Our quantitative description captures this effect by adding a weighting coefficient to the response of one component. In most cases, this coefficient gave more weight to the higher SF in a pair - that is responses tend to be dominated by the higher SF. Above ~0.4 cpd this pattern reversed, and the lower SF tended to dominate. When the stimulus area was reduced fourfold, the relative weight of lower SFs was reduced. This could be explained if surround suppression helps to determine which SF is dominant: a smaller stimulus produced weaker surround suppression for lower SFs. Across all pairs we measured (11-13 in all) we found that the OFR recorded for a grating pair ($OFR_{1,2}$) was well be described as a weighted average of the OFRs to each grating when presented in isolation (OFR_1 and OFR_2) with the following equation: $OFR_{1,2}=(K_{TF}*K_{SF}*C_1^n*OFR_1+C_2^n*OFR_2)/(K_{TF}*K_{SF}*C_1^n+C_2^n)$. K_{SF} depends on both SF_1 and SF_2, but we found it was well described by the difference $f(SF_1)-f(SF_2)$ where $f(SF)$ is a skewed Gaussian function. The peak of this function is at a significantly higher SF than the peak in the response as a function of SF in single gratings. K_{TF} depended only on the ratio $g(TF_1)/g(TF_2)$, where g is the Gaussian function that describes TF tuning in single components. That this relatively simple function of SF, TF, and C successfully captures the

responses over a wide range of these parameters in pairs of gratings suggests that these interactions reflect a simple mechanism.

Disclosures: B.M. Sheliga: None. **C. Quaia:** None. **E.J. FitzGibbon:** None. **B.G. Cumming:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.06/DD3

Topic: D.07. Vision

Support: German Excellence Initiative of the German Research Foundation (DFG) grant number EXC307
Max Planck Society, Germany

Title: Decoding the direction of implied motion in human early visual cortex

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Abstract: Implied motion perception is a striking case of our capacity to infer motion features from static pictures that imply movement. At a higher, cognitive level, the mere configuration of an object (such as a snapshot of a walking human) can imply motion in a directional way. Previous studies have shown that implied motion processing recruits direction selective neurons and activates cortical motion processing regions. However, it is unknown whether object-processing regions or early visual regions are involved in implied motion processing. In the present study we used fMRI and multivariate pattern classification to examine which human brain regions differentiate implicit direction information in static images of implied motion. We hence examined BOLD activity patterns within independently defined early visual (V1-V3), motion (V5+/MT+) and object-processing (LO1, LO2) regions when participants viewed still images with directional implied motion (rightward vs. leftward). The stimuli contained both animate (birds) and inanimate (airplanes, cars) objects as sources of implied motion. The objects were presented at the center of the visual field on a horizontally blurred background in the periphery. We found that response patterns in visual areas V2, V3, human motion complex V5+/MT+, and object responsive region LO2 coded for the direction of the implied motion stimuli significantly better than chance. Decoding in visual areas V1 and LO1 was at chance level. We then examined decoding in retinotopically defined foveal and peripheral

representations of V1-V3. Only the foveal representation was stimulated by the foreground objects, the periphery by blurred background. We found that peripheral V1-V3 allowed decoding of implied motion directions, while foveal representations did not. Hence, high-level information of implied motion directionality is represented in peripheral V1-V3, i.e. regions that were never given the information through bottom-up stimulation. This suggests that higher-level cognitive processes (potentially based in LO2, V5+/MT+) detect implied motion direction based on object configuration and feed it back to cover the peripheral context in early visual cortex, potentially encoding expected background-motion. The results provide direct evidence for information in early visual cortex originating from feedback, compatible with predictive coding theory.

Disclosures: G. Altan: None. **A. Bartels:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.07/DD4

Topic: D.07. Vision

Support: Stanford Center for Neurobiological Imaging

Title: Flexible readout of stable cortical representations support human motion visibility perception

Authors: *D. BIRMAN, J. L. GARDNER
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Abstract: Cortical representation of two key components of motion visibility, contrast and coherence, are intertwined: both show monotonic increase in population response in overlapping portions of human visual cortex. How are such similar representational codes separated during perceptual discrimination of a single visibility feature?
We built a linking model connecting perception of motion visibility to cortical representation of motion using a framework based on previously measured BOLD responses. We quantified perception using a task where observers (n=21) judged the visibility of two patches of moving dots (11.5 x 14 deg, 7.75 deg left/right of fixation) in a two-alternative forced choice paradigm. Observers were cued before runs to base their judgements on either contrast or coherence. Patches contained an equal proportion of black and white dots (21 dots / deg, linearized gamma) moving toward or away from fixation. On each trial the dots increased in contrast (luminance relative to gray) and/or coherence (percent dots moving together), with the difference in increment between patches controlled by a staircase procedure. Psychometric functions from this task were fit by modeling a decision as a comparison of each dot patches' cortical response in retinotopically defined visual areas. Model comparison showed that a linking model with

additive rather than multiplicative noise and different weighting of cortical areas during discrimination of contrast and coherence accounted for the behavioral data.
Our linking model suggests that flexible weighting of cortical areas, rather than changes in sensory sensitivity, could account for task flexibility. We tested this prediction in two ways. First, we measured BOLD responses while a subset (n=11) of observers performed the task and compared these measurements between discrimination conditions. A single set of readout weights was insufficient to fit the psychometric functions, suggesting that sensory enhancement or suppression alone could not account for task performance. Second, we asked whether sensory responses were maintained even when one feature was irrelevant. On a subset of trials (1/7) after stimulus presentation we asked participants to report about the feature they were not currently discriminating. We found that observers were able to do this remapping with only a small penalty in performance, suggesting that participants flexibly re-weighted stable cortical representations. Each of these predictions confirmed what the linking model suggested: cortical representations appear to remain stable while readout shifts flexibly to accommodate task demands.

Disclosures: D. Birman: None. **J.L. Gardner:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.08/DD5

Topic: D.07. Vision

Support: Center for Integrative Neuroscience Tübingen
German Excellence Initiative of the German Research Foundation (DFG) grant number EXC307
DFG grant BA 4914/3-1
DFG SFB 1233 Robust Vision: Inference Principles and Neural Mechanisms: TP9
University Clinics Tübingen Fortüne grant nr. 2251-0-0
Max Planck Society, Germany

Title: Human V6 integrates visual and extra-retinal cues during head induced gaze shifts

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Abstract: A key question in vision research concerns visual stability: how is visual information in retinal coordinates integrated with non-visual cues of self-induced motion to form the

spatiotopic representations of the world that we perceive?
Eye movements have been found to modulate retinotopic representations at multiple stages along the visual stream, yet a special role has been attributed to human areas V3A and V6, as both cancel self-induced retinal planar motion during eye movements to a near complete extent (Fischer, Bülthoff, Logothetis, Bartels, 2012).
Beyond that, only little is known about which human visual processing stages integrate head motion signals with retinotopic representations as human fMRI is typically incompatible with execution of voluntary head movements.
We recently circumvented these limitations and introduced a novel paradigm that allows participants to move their heads during fMRI scanning (Schindler and Bartels, 2018). The functional characteristics of the BOLD signal allowed us to temporally decouple stimulus presentation from the acquisition of stimulus evoked responses. Our custom-built air pressure based head-stabilization system permitted head-rotation during trials, but stabilized head position during data acquisition. Video-based head-tracking and head-mounted goggles allowed for real-time generation of visual stimuli taking head-motion into account.
Observers viewed approaching visual flow through head-mounted MR-compatible goggles. A congruent condition simulated constant forward motion while the observer rotated the head relative to the body, as when looking around while being driven along a straight road. In the incongruent condition, observers performed identical head rotations, but the visual consequences were inversed such that visual and extra-retinal cues did not combine in any meaningful way. Crucially, both conditions were matched regarding head and retinal motion. Based on this paradigm, we previously examined the integration of head motion and visual signals in regions with established vestibular processing.
Here we asked whether early visual cortex as well as areas V3A and V6 may integrate retinotopic visual representations with voluntary head motion. Contrasting congruent versus incongruent conditions revealed differential responses in human V6 but not in early visual regions or V3A, consistent with multi-modal integration of visual cues with head motion in human area V6.
Our results extend previous evidence for multimodal integration in V6 to head-motion cues and are in line with the hypothesis of V6 as a crucial hub for compensation of self-induced motion.

Disclosures: A. Schindler: None. **A. Bartels:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.09/DD6

Topic: D.07. Vision

Support: NIH Grant EY05729

Title: Visual motion statistics during real-world locomotion

Authors: *K. MULLER, J. S. MATTHIS, K. BONNEN, L. K. CORMACK, M. M. HAYHOE
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Abstract: Many aspects of neural processing reflect the statistics of natural images (Geisler 2008). For example, disparity tuning distributions in V1 reflect disparities encountered during a range of naturalistic tasks (Liu et al., 2008). We asked whether tuning for visual motion reflects the statistics of the retinal motion signal experienced by observers during natural locomotion. These statistics are complex and shaped by the direction of gaze, the motion of the body, and the geometry of the environment. We measured these motion patterns using a Pupil Labs mobile eye tracker to record both binocular eye position and high-resolution scene video. We approximated the retinal motion input by aligning each frame to the point of gaze and then using the Farneback optic flow estimation algorithm to extract motion at each pixel of the video. The distribution of motion speeds is skewed towards slower speeds with half of the vector magnitudes being lower than 6 degrees per second, similar to the distribution of speed preference in MT (Nover and DeAngelis 2005). The distribution of motion directions is anisotropic, with a strong downward bias. We also calculated the motion speed and direction distributions at different locations across the visual field within regions matching the spatial characteristics of MT receptive fields. This analysis showed that distributions of motion in different visual field locations are biased as a function of both eccentricity and direction (relative to the fovea). Specifically, the distributions of motion speeds for more eccentric locations are biased towards faster speeds, and the vector average of motion directions tend to point away from the fovea (i.e. expansive flow field). This biasing of motion direction away from the fovea is present even in less eccentric locations, and increases monotonically as a function of distance from the fovea. This is partially consistent with the previously reported directional bias in MT (Albright 1989). While modal components of the flow fields we measured resemble expansive flow, there is a strong downward bias resulting from distortions caused by ground plane fixations. A remaining question is whether future neurophysiological data from MT will match the statistical patterns we observed.

Disclosures: K. Muller: None. **J.S. Matthis:** None. **K. Bonnen:** None. **L.K. Cormack:** None. **M.M. Hayhoe:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.10/DD7

Topic: D.07. Vision

Support: JSPS KAKENHI JP16H06566

Title: Increase in density of optic-flow deteriorates self-motion velocity perception and decreases implicit adjustments of walking speed

Authors: *S. TAKAMUKU, H. GOMI
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Abstract: Earlier studies have shown that we adjust our walking speed based on optic flow [Prokop et al., EBR, 1997] and that the adjustment involves estimation of translational self-motion velocity based on multiple depth cues [Takamuku et al., SfN, 2017]. Here, we examined whether and how the adjustment depends on the spatial pattern of the environment. Participants walked inside a virtual corridor shown with a binocular head-mount display. The walls on the sides occasionally moved either toward or against the heading direction to induce implicit adjustments of walking speed. We examined how the adjustment depends on the image pattern on the walls. In our first experiment, we varied the density of the checkerboard pattern on the walls (1.0, 3.2, 10.0 cycle/m). While there were small difference between low and intermediate density conditions, increasing the density from 3.2 to 10.0 cycle/m significantly decreased the adjustment despite the major increase in information on self-motion. Velocity perception performed by the same participants suggested that the increase in density deteriorated the precision of self-motion velocity estimation based on the optic flow. Similar trend was observed for the motor and perception tasks when grating patterns with matched spatial frequencies were used instead of the checkerboard patterns. Velocity discrimination precision decreased when the spatial frequency increased from 3.2 to 10 cycle/m, corresponding approximately to temporal frequencies of 2.56 and 8.0 Hz respectively. Our result suggests that precision of self-motion velocity estimation as well as the size of walking speed adjustments depend on the spatial frequencies of the optic flow, as previously reported for the precision of heading direction estimation [Kim and Turano, 1999] as well as sizes of postural responses [Masson et al., EBR, 1995]. Furthermore, the visual contributions to the walking speed adjustment may be scaled according to the reliability of the visual estimate in a manner consistent with the Bayesian theory of multimodal self-motion estimation [Fetsch et al., Nat. Rev. Neurosci, 2013], yet it is also possible that the decrease in the adjustment reflected distortions in the velocity estimation process per se.

Disclosures: S. Takamuku: None. **H. Gomi:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.11/DD8

Topic: D.07. Vision

Support: NEI EY013644

Title: An improved method for dissociating stimulus and choice contributions to neural responses: Application to area MT's role in coarse and fine depth discrimination

Authors: *M. POPOVIC[1], G. C. DEANGELIS[2]
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Abstract: In sensory areas, trial-to-trial variability in a neuron's response is often correlated with the animal's perceptual report, a correlation known as choice probability (CP). In a feed-forward framework, CP is related to a neuron's causal contribution to task performance. However, previous studies suggest a substantial top-down (feedback) contribution to CP (Nienborg and Cumming, 2009, Bondy et al. 2018). Interpretation of CP can be further complicated when neural responses are dominated by choice-related signals, such that CPs become artificially inflated (Zaidel, DeAngelis, and Angelaki 2018). Thus, Zaidel et al. (2018) developed an approach to separate the effects of stimulus and choice on a neuron's response. They found that choice and stimulus contributions to responses of ventral intraparietal (VIP) neurons were often opposite in sign, inconsistent with a simple feedforward framework. We present an improved method for separating the unique contributions of stimulus and choice to neural responses, which does not require assuming a parametric form of stimulus tuning. We applied this method to neural responses recorded from the middle temporal (MT) area while monkeys performed two different depth perception tasks. In the coarse discrimination task (Uka and DeAngelis, 2003), the monkey reports whether a cloud of dots is near or far relative to the fixation point, and task difficulty is manipulated by varying the fraction of binocularly correlated dots. In the fine discrimination task, the monkey is presented with a center/surround stereogram (100% binocular correlation) and reports whether the center portion is in front of or behind the surround. In this case, task difficulty is manipulated by finely varying the relative disparity between center and surround (Uka and DeAngelis, 2006). Previous studies found CPs consistently greater than chance (0.5) in the coarse task, but distributed broadly around 0.5 in the fine task; reasons for this difference are not clear. For the coarse task, application of our improved method reveals that stimulus and choice contributions to MT responses generally match in sign, such that a neuron's CP is predictable from its tuning. However, for the fine task, we find no systematic relationship between stimulus and choice contributions to MT responses. Thus, the relationship between stimulus and choice effects on MT responses is task dependent, and MT neurons may receive feedback signals during the fine task that are unrelated to stimulus tuning. These results highlight the importance of accurately dissociating the contributions of stimulus and choice to neural responses.

Disclosures: G.C. DeAngelis: None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.12/DD9

Topic: D.07. Vision

Support: NEI EY016178

Title: Active steering in macaques: Integration of visual and predictive estimates of self-motion

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Abstract: Our understanding of the neural basis of self-motion perception is largely based on how neurons with visual and vestibular selectivity represent movement through the environment. Previous studies have revealed basic mechanisms of multi-sensory integration underlying self-motion perception by passively moving animals through real or virtual environments. During natural navigation, however, we actively control our self-motion and therefore can predict our future trajectory prior to experiencing the sensory consequences of self-motion. When sensory cues become unreliable, predictions should play a greater role in perception and control of self-motion. To explore this idea, we developed an active steering paradigm in which trained monkeys use a joystick to navigate through a three dimensional virtual environment. In addition to visual feedback from optic flow, active steering implies an expected trajectory and allows for prediction of the sensory consequences of self-motion.
The animal is given 800ms to view a curved path that subsequently disappears, leaving only ground and ceiling planes of random dots. Optic flow simulates forward self-motion and the animal navigates the virtual environment by controlling their angular velocity with a joystick to stay within the invisible path boundaries while maintaining central visual fixation throughout the trial for a liquid reward. To manipulate reliability of optic flow, motion coherence is varied across trials. We perturbed the animal's motion trajectory on some trials, resulting in an unintended angular velocity component that altered the expected optic flow. If visual cues are reliable, the animal should rely heavily on visual feedback to compensate for the perturbation and stay on course. If visual cues are unreliable due to noise, the amount of compensation should decrease and the animal should rely more on their internal representation of the planned trajectory to steer.
Preliminary results show that animals can internalize the path and steer successfully within the invisible path boundaries. Compensatory steering is also evident for a variety of perturbations, indicating that the animals use optic flow along with the remembered path to navigate. On high coherence trials, compensation for perturbations is strongly evident. When coherence is

decreased, compensation for perturbations is reduced, as the animal presumably relies more on their internal representation of the path. These results shed light on how predictive estimates of self-motion that arise from active control contribute to perception of self-motion.

Disclosures: A.D. Danz: None. **A. Anzai:** None. **D.E. Angelaki:** None. **G.C. DeAngelis:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.13/DD10

Topic: D.07. Vision

Support: ANR-16-CE37-0002-01

Title: Stereomotion processing in the non-human primate brain

Authors: *Y. HÉJJA-BRICHARD[1,2], S. RIMA[1,2], E. RAPHA[2], J.-B. DURAND[1,2], B. COTTEREAU[1,2]
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Abstract: Motion perception is a fundamental property of the visual system in most animal species. Although numerous studies have examined how the primate brain processes 2D motion, much less is known about how it encodes 3D motion. A few neuroimaging investigations in humans found that stereomotion is mostly processed within the hMT+ complex and its neighbourhood. Here, we extend this work to non-human primates. Functional MRI recordings were performed at 3 Tesla in 2 awake behaving macaques using a custom 8-channel coil positioned above the animal's head. Our main condition (changing disparity over time, CDOT) consisted of a central disk filled with dynamic random dots (diameter = 19°, refresh rate = 30Hz). The dots' binocular disparity changed over time along opposite directions in the upper and lower parts of the disc (triangular functions between +/- 23 arcmin at 1 Hz). In two control conditions, we scrambled the temporal (TS) or spatial (SS) structure of the CDOT condition. All conditions were monocularly identical, shared the same disparity distributions but only the CDOT condition had uniform and continuous stereomotion. We interleaved those conditions with a baseline (fixation point) in a block-design paradigm. Eye movements were monitored while the monkey was performing a fixation task. We only analysed runs where fixation was above 80%. From a general linear model implemented in SPM 12 with saccadic eye movements and motion-related noise signals as repressors of non interest, we found that the CDOT condition led to stronger responses than both TS and SS control conditions in the superior temporal sulcus as well as in the occipito-parietal cortex. A region-of-interest analysis within retinotopic areas defined from standard procedures further established that CDOT specific responses existed

within the macaque MT/V5 cluster (most notably in areas MST and FST) and also in area CIP/PIP in the posterior part of the intra-parietal sulcus. Our results suggest that multiple regions process stereomotion in macaque and encourage further investigations in human.

Disclosures: Y. Héjja-Brichard: None. **S. Rima:** None. **E. Rapha:** None. **J. Durand:** None. **B. Cottereau:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.14/DD11

Topic: D.07. Vision

Support: NRSA Grant GM007507
NSF NRT DESE:1545481
Alfred P. Sloan Foundation
Whitehall Foundation Research Grant 2016-08-18

Title: Contributions of perspective and stereoscopic cues to motion-in-depth perception in macaque monkeys

Authors: *L. THOMPSON[1,2], B. KIM[1], B. ROKERS[2], A. ROSENBERG[1]
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Abstract: Perception of motion-in-depth (MID) is essential to intercept and avoid moving objects. Both stereoscopic and perspective cues contribute to MID perception. Stereoscopic cues are computed via comparisons of the two retinal images (e.g., changing disparity and interocular velocity differences). Perspective cues can be computed from information available to a single eye, based on optic flow and retinal density/size changes. An often overlooked fact, however, is that the perspective cues available to each eye tend to differ because they depend on stimulus location and trajectory relative to the eye. Here we investigated how the visual system integrates stereoscopic with left-eye and right-eye perspective cues.We used a towards/away discrimination task with variable motion coherence to evaluate sensitivity to MID cues in the macaque. Each stimulus consisted of a volume of dots that moved in depth, and contained: (1) only stereoscopic cues, (2) only perspective cues (presented to each eye separately), or (3) all cues combined. Sensitivity to these cues was assessed across the visual field (3-degree diameter apertures, &gt50 locations). Noise dots were replotted in a random location within the stimulus volume on each frame. Sensitivity decreased in an eccentricity-dependent manner for all cue conditions. Across the visual field, stereoscopic cue sensitivity was typically superior to both left-eye and right-eye perspective cue sensitivities, and combined cue sensitivity was superior to any of the isolated cue sensitivities. Using a maximum likelihood (ML) framework, we compared several integration

models for the three MID cues -stereoscopic, as well as left-eye and right-eye perspective cues. Combined cue performance was best predicted by an ML model that integrated all three cues according to their reliabilities. While previous work has examined 3D motion sensitivity in macaque monkeys, we provided the first systematic characterization of their behavioral sensitivity to isolated MID cues across the visual field, and explicitly examined cue integration. Our results suggest that non-human primates integrate MID cues near-optimally, and further demonstrate that motion perception in three dimensions relies on independent representations of stereoscopic, as well as both left-eye and right-eye perspective information.

Disclosures: L. Thompson: None. **B. Kim:** None. **B. Rokers:** None. **A. Rosenberg:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.15/DD12

Topic: D.07. Vision

Support: EY026274
ORIP
P51 OD010425
Unrestricted Ophthalmology departmental grant from Research to Prevent Blindness

Title: Motion integration during volitional smooth pursuit

Authors: *J. FLEURIET, M. MUSTARI
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Abstract: Under natural conditions, different visual motion signals can solicit two different neural pathways in human and nonhuman primates. One reflexive pathway modulates eye velocity with a very short delay (around 60ms) and another pathway, called voluntary, modulates eye velocity with a longer delay (around 100ms) and ensures that the fovea stays on target. The visual motion input first travels through common retinal-geniculo-striate pathway to dorsal stream areas (MT-MST) and then to the FEF for voluntary smooth pursuit (SP). Cortical signals reach the DLPN for the ocular following reflex (OFR) and NRTP for SP. These different pathways are usually studied separately in the laboratory by using different visual stimuli (large field visual stimuli to elicit the OFR or a single spot to be tracked for SP). Eye movements were recorded from two macaques during a step-ramp task (speed of 15°/s). A motion cloud in a display aperture surrounding the pursuit target appeared at different times during smooth pursuit (113 or 313ms after the target step). The motion inside the aperture disk was either iso- or contra-directional to the pursuit and target direction. Motion clouds velocity was always relative to the target spot and was either of 4, 8 or 16°/s. Different aperture sizes were used (2.5, 5, 10

and 15°). In another experiments, annular motion clouds were presented with different internal diameters (2.5, 5, 10 and 12.5°). For iso-directional motion clouds, a short latency (60ms) increase in eye velocity was observed after motion cloud appearance. Eye velocity reached a peak 100ms after motion cloud appearance and then dropped to control values 50ms later. Increase in motion cloud velocity and size increased the peak eye movement values. Similar observations were made with contra-directional motion clouds. The eye velocity first dropped before reaching a minimum 100ms after the motion cloud appearance. This drop was compensated toward control values 50ms later. The effects of the direction of the motion clouds varied depending on the timing of the appearance. When the motion cloud appeared during the acceleration phase, the increase (iso) and decrease (contra) in eye velocity were similar in amplitude. However, when the motion cloud appeared during the steady-state phase, the decrease in eye velocity (contra) was of a smaller amplitude than the increase (iso). The goal of our study was to understand how the voluntary pursuit pathway might modulate the additional drive coming from the reflexive pathway. Our study shows that the visual motion signals are not integrated uniformly during the course of the pursuit response but depend on the direction, size, and timing of the motion clouds.

Disclosures: J. Fleuriet: None. **M. Mustari:** None.

Poster

220. Visual Motion II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 220.16/DD13

Topic: D.07. Vision

Support: Max Planck Society

Title: Modulation of neural discharges and local field potentials in the macaque prefrontal cortex during binocular rivalry

Authors: *F. PANAGIOTAROPOULOS[1], V. KAPOOR[2], A. DWARAKANATH[2], S. SAFAVI[2], J. WERNER[2], N. G. HATSOPOULOS[3], N. LOGOTHETIS[4]
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Abstract: In binocular rivalry, our perception alternates spontaneously between mutually exclusive or mixed interpretations, although the physical stimulus remains constant. This enables us to study visual consciousness, as it allows a dissociation of sensory processing and conscious perception. Previous BOLD fMRI imaging studies in humans have implicated the role of the fronto-parietal network in mediating perceptual alternations. However, the extent of and the

nature of these modulations has been argued to reflect consequences of conscious perception, like introspection, monitoring and decision making. To resolve this issue we used a no-report binocular rivalry paradigm of vertically moving gratings, based on an Optokinetic Nystagmus (OKN) read-out of the content of consciousness. We show that slow cortical states in the delta-theta (1-9 Hz), and beta (20-40 Hz) regimes coupled via their up and down states, in the prefrontal cortex, are predictive of an upcoming change only when the percept switches spontaneously, but not physically. Physical transitions in the animal's percept manifest themselves strongly post-switch in the same oscillatory range. Moreover, we also show a clear dissociation between the change in the polarity of the OKN and this slow-state activity preceding a spontaneous transition. Furthermore, we found robust modulation in visually selective spiking activity recorded from the prefrontal cortex contingent on the animal's perception. The magnitude of these modulations was comparable to the activity elicited in response to presentation of monocular visual input. Taken together, these results strongly suggest that oscillatory activity in the prefrontal cortex plays a central role in refreshing the content of visual consciousness and spiking activity is modulated in accordance with conscious perception in a no report binocular rivalry paradigm.

Disclosures: F. Panagiotaropoulos: None. **V. Kapoor:** None. **A. Dwarakanath:** None. **S. Safavi:** None. **J. Werner:** None. **N.G. Hatsopoulos:** None. **N. Logothetis:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.01/DD14

Topic: D.07. Vision

Support: Partly funded by NIH Grant MH096482

Title: Measuring the similarity of BOLD resting-state activity patterns to stimulus-evoked patterns of common visual categories

Authors: *D. KIM[1], T. LIVNE[2], N. V. METCALF[3], M. CORBETTA[4,5], G. L. SHULMAN[6]
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Abstract: The relationship between evoked and spontaneous activity patterns is an important topic in neuroscience research. One hypothesis is that spontaneous activity patterns represent statistical regularities in the patterns of neural activity that are evoked in the course of an organism's experience. Here we conducted multivariate pattern analyses (MVPA) for an fMRI

experiment comparing resting-state BOLD activity to evoked activity for visual stimuli from common categories (e.g. faces, tools, words) and from non-ecological categories (e.g. phase-scrambled stimuli).
Categorical visual stimuli were chosen based on the large-scale hierarchical distinction of animate vs. inanimate objects (Kriegeskorte et al., 2008). Activation contrasts and searchlight analyses of localizer scans were used to select ROIs in the ventral occipital-temporal cortex, including classic category specific regions such as the fusiform face area. Multi-vertex pattern representations of categorical visual stimuli and corresponding representations of non-ecological stimuli were obtained for each ROI.
Representation similarity analysis (RSA) yielded a similarity structure for each ROI that reflected the ROI's selectivity. Leave-one-out-cross validation SVM classifiers yielded above chance level classification across ROIs, demonstrating that the ROIs distinguished categorical representations based on their activity patterns.
Intrinsic activity patterns for each ROI were obtained from independent resting-state scans (1500 TRs). Both representational similarity analyses and SVM classifier analyses indicated that intrinsic activity patterns were more similar to common categorical representations than to non-ecological representations (two sample t-test, p-val < 0.01 uncorrected). These results support the hypothesis that intrinsic cortical activity patterns reflect internal representations that are commonly evoked in everyday experience.

Disclosures: D. Kim: None. **T. Livne:** None. **N.V. Metcalf:** None. **M. Corbetta:** None. **G.L. Shulman:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.02/DD15

Topic: D.07. Vision

Support: CMU RKM Presidential Fellowship

Title: Biasing koniocellular and parvocellular input reveals independent dorsal and ventral pathway contributions to temporal dynamics of shape processing

Authors: *E. COLLINS[1], E. FREUD[2], Y. SIEH[3], J. CAO[3], J. M. KAINERSTORFER[3], M. BEHRMANN[2]
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Abstract: Shape perception is generally considered a function of the ventral visual pathway, but a recent fMRI study uncovers large-scale spatial and functional properties of shape processing

along both the dorsal and the ventral pathways (Freud et al., 2017). What remains to be determined, however, is how these shape representations unfold over time. Here, we conducted three EEG studies designed to examine the temporal dynamics of shape processing. The first experiment used greyscale object stimuli, scrambled at 5 different levels to decrement differentially the amount of shape information. We then measured shape sensitivity by correlating the amplitude of evoked responses with the level of object scrambling. These stimuli bias the processing in magnocellular inputs that project to both ventral and dorsal pathways and evoke broad and sustained patterns of shape sensitivity. Next, we modified the same stimuli to bias the processing in koniocellular inputs which project to the dorsal pathway directly from the LGN. To our knowledge this is the first EEG study ever to document koniocellular contributions to the dynamics of shape processing. Finally, we conducted a third experiment using the same objects, but calibrated to bias processing in parvocellular inputs. In both of the latter experiments, unique temporal patterns of shape sensitivity were found, including a rapid shape sensitive response as early as 50ms post stimulus in the koniocellular experiment. Importantly, we reveal that biasing input to the dorsal cortex alone is sufficient to evoke a temporal pattern of shape sensitivity similar to that evoked by propagating input to both dorsal and ventral visual cortices. Biasing activity in the parvocellular system evoked a more restricted period of shape sensitivity relative to that evoked using greyscale stimuli. To conclude, these findings suggest, that the dorsal and ventral cortex make unique contributions to shape perception. Namely, the dorsal pathway may be responsible for a more rapid shape sensitive response, while the ventral pathway may be responsible for periods of shape sensitivity traditionally associated with general object selectivity.

Disclosures: E. Collins: None. **E. Freud:** None. **Y. Sieh:** None. **J. Cao:** None. **J.M. Kainerstorfer:** None. **M. Behrmann:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.03/DD16

Topic: D.07. Vision

Support: NSF Grant 1532846

Title: Cortical representation of objects and their components

Authors: *T. S. ALTAVINI[1], G. ASTORGA[1], D. HARARI[2], S. ULLMAN[2], G. N. REEKE[1], W. FREIWALD[1], C. D. GILBERT[1]
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Abstract: Visual perception is subject to top-down influences. Even in early visual areas neuronal selectivity changes according to the task performed. Object recognition involves a combination of a bottom-up assembly of an object's components and top-down influences of expectation and perceptual task. To understand how objects are represented along the visual pathway, and the role of object expectation in influencing the stimulus selectivity of neurons at different stages along the visual pathway, we trained a monkey on an object recognition task. This enabled us to create a set of stimuli that are behaviorally relevant for object recognition and to use these stimuli to determine the functional properties of visual cortical neurons. We trained a macaque to perform a delayed match-to-sample task on a touch screen monitor, where it responded whether or not a cued image matched a subsequently presented target image. To determine which image components were informative for object recognition we measured the animal's ability to recognize objects from cropped images of object components. By changing the size and position of crops and analyzing the animal's performance in associating them with the parent object we have generated a library of images containing full objects, recognizable object components and unrecognizable components. To find which brain areas were responsive to the objects and shapes we performed a series of fMRI scans while the animal performed a passive fixation task. Pictures of objects belonging to different categories were presented while the animal fixated a spot on the center of the monitor. We identified the classical face patches in the temporal lobe as well as areas that were responsive to various object categories such as animals, fruits and vegetables, and inanimate objects. All object categories activated areas clearly distinct from face patches. Together with electrophysiological recordings in identified areas while animals perform the object recognition task, we are developing a computational model of the cortical visual pathway that takes into account top-down influences on the response properties of neurons along the visual pathway, which shows how feedback facilitates identifying the contours in an image.

Disclosures: T.S. Altavini: None. **G. Astorga:** None. **D. Harari:** None. **S. Ullman:** None. **G.N. Reeke:** None. **W. Freiwald:** None. **C.D. Gilbert:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.04/DD17

Topic: D.07. Vision

Support: NIH (NIDCD) 5R01DC013906-02
NIH (NIDCD) 1R01DC016363-01

Title: Fluctuating activity (time-division multiplexing) varies across sensory brain regions

Authors: *N. JUN[1], J. T. MOHL[1], M. R. COHEN[4], S. T. TOKDAR[2], J. M. GROH[3]
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Abstract: Much of our understanding of sensory perception comes from experiments which present only a single stimulus at a time. However, perceptual systems likely evolved to encode multiple simultaneous stimuli. It is not obvious how information about multiple stimuli is preserved in the neural code. We have recently proposed that the brain could accomplish this via time division multiplexing, or fluctuating signals that sequentially "represent" each stimulus that is present. We have developed a statistical method for identifying such fluctuations at various time scales, and found evidence in support of time division multiplexing in two brain regions that have large receptive fields, one sub-cortical (the auditory-responsive inferior colliculus) and one cortical (the visually-responsive AF and ML face patches of IT cortex) (Caruso et al., biorxiv, Soc. Neurosci. Abstr. 2017).
In this study, we tested the generality of this phenomenon by comparing firing rates of single- and multiunits recorded from several additional visual cortical areas (V1, V4, and MT) while monkeys viewed either single stimuli (gratings) or combined stimuli (superimposed gratings or plaids). V1 and MT both have comparatively small receptive fields, and thus constitute a useful "control" condition, whereas V4 is more similar to the IC and IT in the relative coarseness of its spatial coding. In short, the need for multiplexing is lower in V1 and MT than in V4. Indeed, we found little evidence of fluctuating activity patterns in V1 and MT, whereas V4 did exhibit fluctuating activity patterns, although at a lower incidence than what we have previously observed in the face patches or the IC.
It remains to be determined whether the relevant factor determining the presence/scope of fluctuating activity patterns is the brain region/coarseness of coding or the nature of the stimuli being represented. Notably, the present study concerned stimuli that, when presented together, "bind" to form a single perceptual object, whereas our previous work has concerned easily segregable stimuli. Either or both factors may be relevant to the deployment of time division multiplexing as a strategy for encoding multiple objects in the brain's coarsely-tuned sensory codes.

Disclosures: N. Jun: None. **J.T. Mohl:** None. **M.R. Cohen:** None. **S.T. Tokdar:** None. **J.M. Groh:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.05/DD18

Topic: D.07. Vision

Support: NEI grant R01EY018839
Vision Core grant P30EY01730
P51 grant OD010425

Title: Encoding of partially occluded objects in macaque inferior temporal cortex

Authors: *T. NAMIMA, A. PASUPATHY
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Abstract: Occlusions make object recognition a challenging problem. Primate inferior temporal (IT) cortex, the final stage of form processing along the ventral visual pathway, is likely important (Lerner et al., 2002; Hegde et al., 2008; Kovacs et al., 1995) but the specific role of IT responses in recognizing occluded objects is largely unknown. In the present study, we asked how IT neurons encode information about occluding and occluded objects and how those signals might subserve shape discrimination under occlusion. We studied the responses of 113 single IT neurons as animals performed a sequential shape discrimination task. The first stimulus in the sequence was unoccluded, while the second stimulus was partially occluded with a set of randomly positioned dots. Level of occlusion was systematically titrated with increasing area of occluding dots. Monkeys reported whether the two stimuli presented in sequence were the same or different with rightward or leftward saccade, respectively. Here we analyze the neuronal responses to the 2nd stimulus in the sequence, which was subjected to different levels of occlusion. Many neurons in our dataset (69/112, 61.6%) responded stronger to occluded stimuli, while others (43/112, 38.4%) responded best to the unoccluded stimulus. Consistent with Kovacs et al., 1995, we also found that IT neurons maintained their shape preference under occlusion. In neurons that responded stronger under occlusion, shape selectivity varied little as a function of occlusion but this was unlike other neurons that responded better to unoccluded stimuli. In this latter group, shape selectivity decreased with increasing occlusion. Besides, our control experiments showed that the color of the occluded or occluding stimuli and the shape of the occluders played a minimal role in dictating the responses of our IT neurons. These results suggest that the responses of IT neurons were predominantly modulated by the shape of the occluded object and the total area of the occluding dots. Our simulations indicate that the responses and shape selectivity can be recapitulated by a simple function of two variables: one that reflects the shape of the occluded stimulus and a second that reflects the occluder area. Present study suggests that, under the partial occlusion, some IT neurons maintain their shape selectivity by taking advantage of signal about occluders and those IT neurons might be involved in stable object recognition under the partial occlusion.

Disclosures: T. Namima: None. **A. Pasupathy:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.06/EE1

Topic: D.07. Vision

Support: JSPS KAKENHI 17K07046

Title: Surface materials are recognized by the visual and haptic clues in non-human primate subjects

Authors: *M. ITO, C. HATTA, S. YOSHIDA, K. KATSUBE, Y. MORISUE, T. IWATA
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Abstract: For object perception, materials on the surface of objects provides a powerful clue to recognize them quickly. Such material perception is given by an interaction between visual texture information and secondary haptic information such as rough/smooth, hard/soft, hot/cold or dry/wet. Although it might be dependent on animal's sensation and experiences, property of the haptic perception is not well understood in model animals used for physiological studies. Thus, it is important to examine the properties in non-human primates, in order to consider the physiological studies exploring underlying neuronal mechanisms. As we have reported in the last meeting, performance of the haptic discrimination task reporting 4 haptic scores was well consistent with that of the material discrimination task reporting resemblance with 5 reference materials in human subjects. Present study was aimed at examining the material categorization in non-human primate subjects, by the same discrimination task which might be easy for human subjects but very hard for non-human subjects. Two Japanese monkeys (macaca fuscata, female, 6.8 & 5.9kg) has been trained with the material discrimination paradigm over 23 & 17 months. After animals touched target material by holding a starting lever, they had to choose one corresponding lever from 5 response levers with 5 reference materials (metal, wood, carpet, soft-gel-sheet, and Fur) to get water reward. During the training period, animals were intensively trained to discriminate only these 5 reference materials. After the performance has improved above 95%, new object was presented once in a daily session. Then, animals have to choose one among 5 reference materials as a response of the task. Here, we found that 1) two monkeys have been trained to conduct the same task; their performance has been improved above 95% after long training procedures, 2) the way of error responses and improvement in their performances depended on target objects, indicating that they learned not only the rule of the discrimination task, but also properties of these material objects, 3) they were able to generalize their material categorization for new material objects. Their categorization were largely consistent with human subjects but showed peculiar differences for some objects. In conclusion, these results indicated

that our material discrimination task was sufficient for examining the relationships between haptic properties and material perception in both human and non-human primate subjects.

Disclosures: M. Ito: None. **C. Hatta:** None. **S. Yoshida:** None. **K. Katsube:** None. **Y. Morisue:** None. **T. Iwata:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.07/EE2

Topic: D.07. Vision

Support: Wellcome Trust 204788/Z/16/Z

Title: Clustering of functional subtypes in the zebrafish optic tectum

Authors: *T. SHALLCROSS[1], G. DIANA[2], M. MEYER[2]
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Abstract: Information in the brain is represented by the pattern of activation of neural populations, forming a neural code. Techniques for monitoring large populations of neurons allow estimates of the number of neurons required to encode information- a sensory feature for example, but because the identity of the active neurons is often unknown the precise nature of neural codes is largely unknown. It is for this reason that providing a systematic functional characterisation of cell types in the brain is a fundamental goal of neuroscience. Here we present a method to functionally categorise cells within the optic tectum of larval zebrafish. Functions attributed to the tectum include directing attention, object categorisation, decision making and generating approach and avoidance behaviours. Using a diverse set of visual stimuli, lightsheet functional imaging of the entire tectum with single neuron resolution and density based clustering of tectal cell responses we are able to functionally categorise tectal cell types and determine the 3D distribution of these neurons in the tectum. Our approach enables a cellular resolution description of tectal organisation and because it can identify functional cell types in live animals it paves the way for providing an unbiased description of the population codes underlying visually driven, tectally mediated behaviours.

Disclosures: T. Shallcross: None. **G. Diana:** None. **M. Meyer:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.08/EE3

Topic: D.07. Vision

Support: German Research Foundation Emmy-Noether Grant

Title: The time course of object location information in the human brain depends on clutter

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Abstract: The prevailing view of the ventral visual system is that object representations tolerant to particular viewing conditions such as location in the visual field emerge in high-level visual area IT, whereas object properties particular to the viewing situation are represented in low-level visual areas.
Contrary to this theory, a recent study using single-cell electrophysiology and modelling in monkeys (Hong et al., 2016) observed that IT represents both object identity and location information, and that low-level visual areas might fail to represent object properties specific to the viewing situation when objects appear under real-world cluttered viewing conditions.
Here, we investigated the processing of object location and category and its dependence on the nature of the background of the visual scene in the human brain using EEG and multivariate pattern classification. The rationale was that the latency with which object category and location representations emerge in the human brain indicate the processing stage in the ventral visual stream at which they emerge.
In the experiment, participants (N=25) viewed object images from four different categories, in four different locations displayed in three background conditions (high-, low-, and no-clutter). We found that object location information emerged later in time when objects were presented on cluttered backgrounds (70 ms later for low clutter and 100 ms for high clutter Fig. 1A). A time-generalization analysis revealed that location processing under clutter had similar, but delayed processing than when no clutter was present (Fig. 1B).
Together, our findings suggest that under real-world viewing conditions object location information might emerge in later processing stages than often assumed.

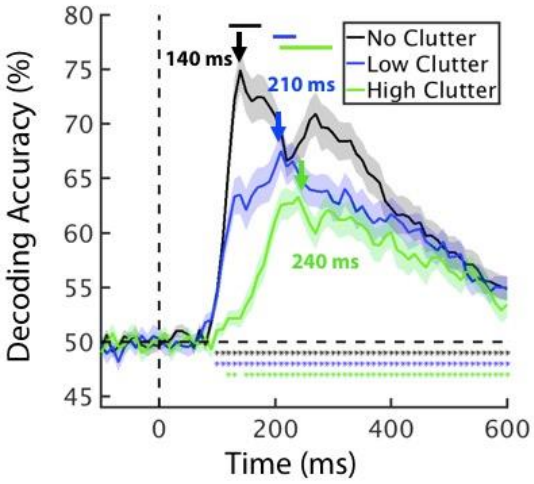

Fig. 1A EEG Timecourse of location processing tolerant to category. Low clutter (blue) peaked 70 ms later, and high clutter (green) peaked 100 ms later than no clutter and the difference between these curves is significant (FDR corrected, $p < .05/3$, difference curves not shown). Black, blue and green bars above the peaks indicate 95 % confidence intervals around the respective peaks, generated using bootstrapping. Black, blue and green stars below the the decoding curves indicate timepoints of significance. The horizontal dashed line indicates chance level decoding and the vertical dashed line marks stimulus onset.

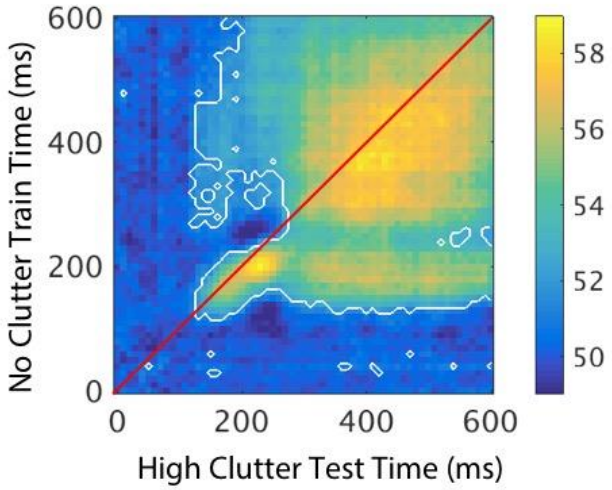

Fig. 1B Time-time decoding of category tolerant location across no and high clutter. A classifier was trained on one timepoint of the no clutter condition and tested on timepoints of the high clutter condition. Above chance decoding accuracies along the diagonal indicate that the no and high clutter conditions share the same information at the same timepoint. Above chance decoding accuracies below the diagonal indicate that information at a given timepoint in the no clutter condition is present in the high clutter condition at later timepoints. This result shows that location information in the no clutter condition is equivalent to information at later timepoints in the high clutter conditions (FDR corrected, $p < .017$ Bonferroni corrected for number of comparisons).

Disclosures: M. Graumann: None. **C. Ciuffi:** None. **R.M. Cichy:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.09/EE4

Topic: D.07. Vision

Support: EY014681

Title: Visual-haptic interactions influence shape recognition

Authors: *R. L. MILLER, D. L. SHEINBERG
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Abstract: Though typically thought of as primarily a visual capability, object recognition is also routinely accomplished through our other senses, including touch. The visual and somatosensory systems not only need to provide information about object properties using very different end organs, but they must also produce an internal representation of the object which facilitates comparison -- a supramodal representation. We designed a task paradigm allowing us to assess whether the manner in which this cross-modal comparison is made influences the learning of object recognition. Human participants (n=34) were simultaneously presented with visual (on a video display) and haptic (on a visually hidden physical shape 'carousel') shape stimuli and asked to determine whether they were the same shape or different. For one group of subjects, the visual and haptic presentations were always in the same relative orientation ("aligned" condition), while another group had visual and haptic stimuli which were typically not in the same orientation ("rotated" condition), thus forcing the subjects to mentally rotate one or both (visual and haptic) shapes for mutual comparison. These two groups were then tested on a task where they must first feel a shape and subsequently see a shape and judge whether the two shapes were the same or not. We found that, compared to the aligned group, the rotated group required slightly (though not significantly) less time to feel the shape and significantly less time to decide if the visual stimulus matched the haptic. Crucially, this difference exists despite both groups having virtually identical visual-only and haptic-only experience; the only difference was that one group was forced to perform mental rotation, suggesting that learning to recognize objects may be facilitated simply by mentally rotating them.

Disclosures: R.L. Miller: None. **D.L. Sheinberg:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.10/EE5

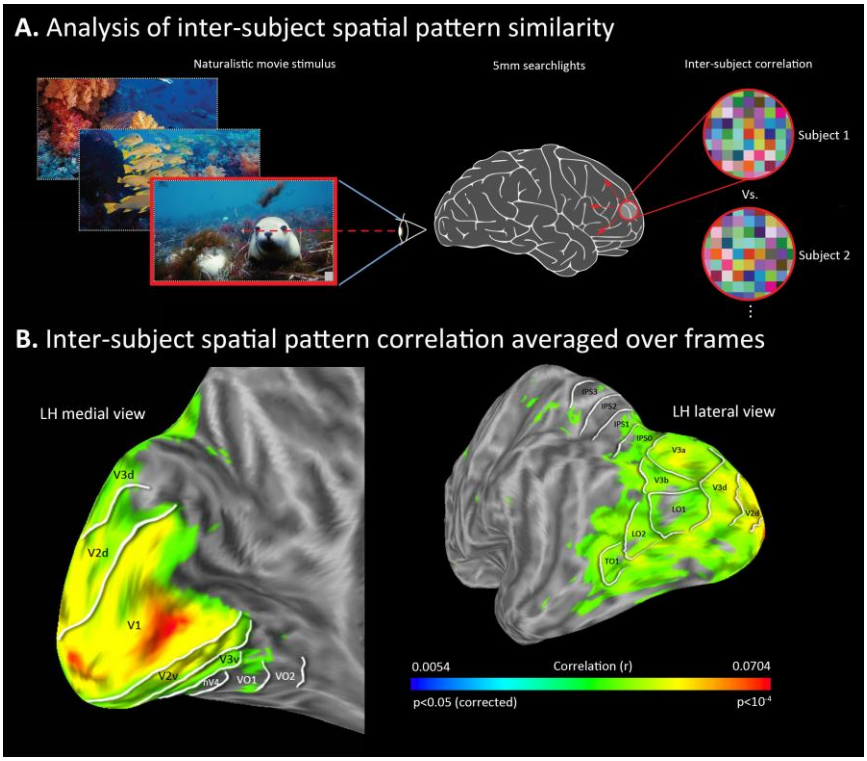
Topic: D.07. Vision

Support: FRQS Vision Health Research Network Common Infrastructure Program

Title: Common spatial patterns of activation revealed during movie viewing

Authors: *A. ZHANG, S. PROULX, Y. CHEN, R. FARIVAR-MOHSENI
McGill Univ., Montreal, QC, Canada

Abstract: All our experiences are coded as patterns of neural activity, therefore if there is a fundamental organization of the cortex, then a shared experience must result in a shared pattern of activity. This is true at a coarse scale, such as the relative size and location of visual areas, but it is unclear at a fine scale, such as the distribution of ocular dominance columns in primary visual cortex. We answered this question by creating a map of fine-scale spatial pattern correlations across a large cohort of subjects. We hypothesize that early retinotopic areas like V1 will activate in spatial patterns that are similar across subjects because the structure of these areas is believed to be innately determined during normal development. In contrast, areas driven by environmental cues (e.g. ventral object recognition areas) may have poor spatial pattern similarity across subjects, reflecting the individual's experiential history.We recruited 55 subjects to watch 2 movie clips during a functional Magnetic Resonance Imaging (fMRI) scan. Each 5-minute clip is presented in 2-D and 3-D, in random order. We calculated the inter-subject correlation of the spatial pattern inside predefined regions across the cortex in a searchlight manner (see A). To determine statistical significance, we conducted a single threshold permutation test with 10,000 permutations of the functional structure inside each searchlight. The results support our hypothesis that early visual areas exhibit higher spatial pattern correlations than ventral and dorsal areas such as the lateral occipital complex and intraparietal sulcus (see B). The results are summarized in a map indicating areas of the brain with a common spatial structure across subjects (see B), suggesting which regions are shaped by experience and which are likely defined innately. Understanding how the visual system organizes itself is fundamental to models of cortical visual hierarchy and visual information representation in the brain. This study sheds light on how experiences may govern this organization.



Disclosures: A. Zhang: None. **S. Proulx:** None. **Y. Chen:** None. **R. Farivar-Mohseni:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.11/EE6

Topic: D.07. Vision

Support: NSFC 31230029
MOST 2015CB351800
NSFC 31421003
NSFC 61621136008
NSFC 61527804
NSFC 31671168

Title: The causal roles of alpha activity in feature binding

Authors: *Y. ZHANG[1,2,3,4,5], Y. ZHANG[1,2,3,4,5], P. CAI[1,2,3,4,5], F. FANG[1,2,3,4,5]
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Abstract: Integrating different visual features into a coherent object is a central challenge for the visual system, which is referred as the binding problem. Recent studies suggest that brain oscillations are possibly involved in assembling features belonging to the same object. However, the function of brain oscillations, particularly their causal contributions, in visual feature binding is still largely unknown. Here, we explored the functional roles of brain oscillations in feature binding using an illusory color-motion misbinding stimulus (Wu et al., 20004). The stimulus consisted of two sheets of moving dots. One sheet moved upward and the other moved downward. For each sheet, the dots in the central and peripheral areas were rendered in different colors. For example, on the upward moving sheet, the color of the dots in the central area was red and that in the peripheral area was green. When subjects fixate at the center of the display, the color and motion of the dots in the peripheral area were perceived to be bound in the same (i.e., active binding state) or opposite (i.e., physical binding state) fashions as those in the central area. We first probed brain oscillations with EEG (electroencephalogram) when subjects were viewing the stimulus for continuous 180s. Subjects were asked to report their perceptual state - the active binding state or the physical binding state. We found that the alpha power in the left posterior area increased when subjects perceived the physical binding and the alpha power was negatively correlated with the duration of the active binding state. To further explore the causality between alpha oscillations and feature binding, we applied tACS (transcranial alternating current stimulation) over the left posterior area to modulate individual alpha activity. Our result showed that tACS at individual alpha frequency peak (IAF) could effectively increase the time proportion of the physical binding state. Furthermore, we delivered tACS stimulation at IAF+2Hz and IAF-2Hz respectively to investigate potential behavioral changes. We found that tACS at IAF+2Hz and IAF-2Hz could increase/decrease the switching rate between the two binding states. Taken together, these findings demonstrated that alpha oscillations can causally shape feature binding providing new insights into not only the neural mechanisms of feature binding, but also the functions of alpha oscillations.

Disclosures: Y. Zhang: None. **Y. Zhang:** None. **P. Cai:** None. **F. Fang:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.12/EE7

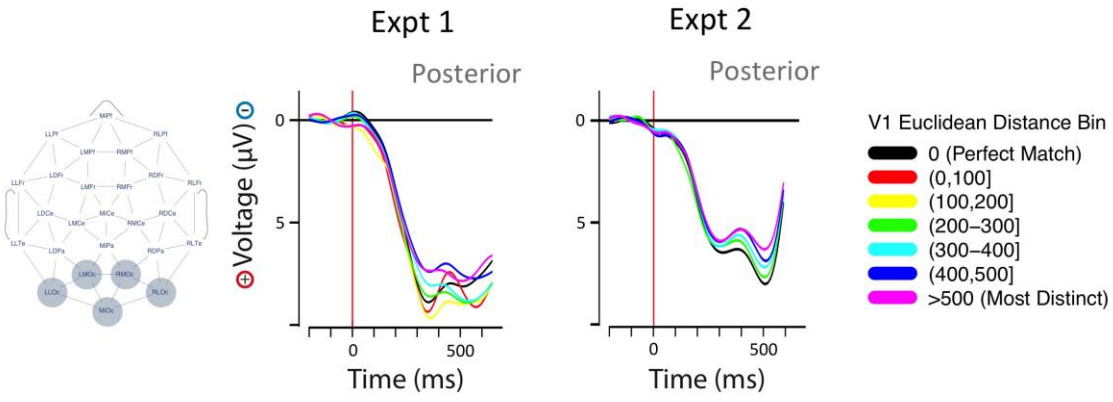
Topic: D.07. Vision

Support: NIA Grant AG2630 to K.D.F.
James S. McDonnell Foundation Award to K.D.F.
Neuroengineering IGERT Fellowship to C.M.S.
NSF Graduate Research Fellowship DGE-1144245 to C.M.S.

Title: Visual objects are rapidly compared to contextually associated object targets on the basis of a V1-like feature representation

Authors: *C. M. SMITH, K. D. FEDERMEIER
Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: How does the brain represent visual objects in memory, and how does it recruit this information in response to contextual cues to facilitate visual object processing? We recorded EEG while adult human participants (N=50; 34 females, sex differences unanalyzed) learned paired associations between scenes and novel objects from novel object categories. At test, scenes were presented and, after a delay, a matching or mismatching object appeared (match vs. mismatch judgment task). For each mismatching test object, similarity to the target (matching) object was computed. In recent work, we have demonstrated on several EEG datasets that "Alexnet" convolutional neural network layer-based metrics of visual distance to the target object correlate with ERP amplitude on mismatch trials. We now extend these analyses using features explicitly designed to capture known properties of primary visual cortex, computing visual distance on the basis of euclidean distance in a V1-like feature space (Pinto et al. 2008). In our first experiment (N = 24), a constant preview duration of 2500 ms for the context scene was used at test, and 'distorted' object images that differed only subtly from the target were included. In experiment 2 (current N = 26), scene preview time was either 200 or 2500 ms, alternately blocked or intermixed across trials, and only more visually distant (distance >200 in figure below) mismatch trials were included. Across both experiments, the ERP waveform to objects other than the target was more positive the more similar the presented object was to the target, in a broadly distributed sustained effect beginning at ~200 ms. Furthermore, longer scene preview times yielded larger ERP target distance effects. Results suggest that visual objects are rapidly compared to contextually congruent object targets on the basis of a V1-like feature representation. Moreover, this (implicit) comparison is facilitated by processing undertaken when viewing the predictive scene context alone, consistent with an account in which V1-like features of the target object are predictively preactivated.



Disclosures: C.M. Smith: None. **K.D. Federmeier:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.13/EE8

Topic: D.07. Vision

Title: Decoding identity and action properties of tools from pictures and pantomimes

Authors: *S. ROSSIT, D. TONIN, F. W. SMITH
Sch. of Psychology, Univ. of East Anglia, Norwich, United Kingdom

Abstract: In our everyday life we often encounter, manipulate and utilize many different tools. Several neuroimaging studies have identified a network of fronto-parietal and occipito-temporal regions that are consistently activated when viewing, imagining and pantomiming tool actions. However, it remains unclear what properties are represented within each region and how these representations overlap or change according to the task used. Here we used multivoxel pattern analysis to investigate the representation of identity and action properties for viewing tools and pantomiming tool-use tasks. Participants (N = 18) viewed pictures of tools (while performing a 1-back repetition detection task) and executed pantomimes of tools actions in response to tool names in different runs. We used familiar tool categories that varied according to two action properties: hand grip (power vs. precision) and hand movement (squeeze vs. rotation). In addition, for each participant separate localizer runs were used to define regions of interest in the left hemisphere. For both viewing pictures and pantomiming, we found reliable decoding for tool-identity, grip and movement types in lateral occipital temporal cortex (LOTC). Moreover, tool-identity and movement type could also be decoded from pictures and pantomimes in posterior middle temporal gyrus (pMTG), supramarginal gyrus (SMG) and intraparietal sulcus (IPS). Interestingly, we were even able to decode movement type from both pantomime and viewing 2D pictures in primary motor cortex. These results suggest that areas of both visual streams (LOTC, IPS) encode information about identity and action properties of tools. Moreover, our findings are in line with claims that even simply viewing pictures of tools automatically evokes sensorimotor representations associated with their use.

Disclosures: S. Rossit: None. **D. Tonin:** None. **F.W. Smith:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.14/EE9

Topic: D.07. Vision

Support: Fordham University Faculty Research Grant 2015
Fordham University Faculty Research Grant 2016

Title: Stimulus-dependent cortical representations of object semantics

Authors: D. SHUTOV[1], *D. D. LEEDS[2]
[1]Computer and Information Sci., Fordham Univ., New York, NY; [2]Computer and Information Sci., Fordham Univ., Bronx, NY

Abstract: Visual object perception recruits a network of cortical regions to extract diverse semantic properties from layers of visual information. Regions associated with a few selected object classes, such as faces, places, and hand-writing, have become popularly established. The question remains whether supposed "semantic class" areas for visual objects are formed based on coincidental visual properties, by abstract knowledge associated with the perceived object, or by a mixture of both. More broadly, cortical segmentation of visual and abstract properties remains unclear. In the present work, we use an fMRI voxel searchlight method to study cortical responses to sixty objects shown separately as pictures and written words (Leeds 2013). Cortical responses from three subjects are compared with 218 diverse candidate semantic groupings of the same objects (from Sudre 2012) using representational similarity analysis (Kriegeskorte 2008). Semantic groupings ranged from topics such as identity ("Is it an insect?", "Is it a tool?") to material/tactile properties ("Is it smooth?") to size/weight ("Can you hold it?") to emotions ("Do you love it?"). While familiar semantic-regional associations are apparent across subjects, we observe within-subject variability in cortical associations evoked by picture and word stimuli. Both picture and word stimuli evoke semantic matches (e.g., for animacy and size) with cortical activity in mid-level visual regions (including lateral occipital and fusiform cortices). However, within each subject the activated anatomical regions and exact locations within common regions differed between the two classes of stimuli. For several semantics groupings, either only word stimuli produced cortical matchings (e.g., subject S3 and "is it a vehicle") or only picture stimuli produced cortical matchings (e.g., subject S2 and "does it have paws"). Our results suggest differing cortical strategies for representation of picture and word objects - potentially drawing a line between coincidental visual properties and underlying abstract knowledge.

Disclosures: D. Shutov: None. **D.D. Leeds:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.15/EE10

Topic: D.07. Vision

Support: Alfred P. Sloan Foundation
Whitehall Foundation Research Grant 2016-08-18

Title: Responses of macaque V3A neurons to 3D object pose

Authors: *T.-Y. CHANG[1], B. KIM[1], A. SUNKARA[2], A. ROSENBERG[1]
[1]Dept. of Neuroscience, Sch. of Med. and Publ. Hlth., Univ. of Wisconsin-Madison, Madison, WI; [2]Dept. of Surgery, Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Three-dimensional (3D) visual perception is critical for interacting with objects. Because each eye detects two-dimensional (2D) projections, the visual system must reconstruct the 3D structure of the environment from ambiguous information. Here we examine hierarchical cortical processing underlying the 2D-to-3D visual transformation necessary to create unambiguous representations of 3D object pose (i.e., position and orientation). In an unambiguous neural representation of 3D pose, object orientation preferences will be invariant to position-in-depth. Previous work suggests that the caudal intraparietal (CIP) area of macaque monkeys represents objects in 3D. Whether 3D selectivity originates in CIP, is refined by CIP, or is simply inherited from an earlier area is unknown. Anatomical data and our ongoing neuroimaging work suggest that area V3A provides a primary source of visual input to CIP. Here we characterize the selectivity of V3A neurons for the 3D pose of planar surfaces. Surfaces were presented at all combinations of tilt (0° to 315° in 45° steps), slant (0° to 60° in 15° steps), and distance (37, 57, 97, and 137 cm). The stimuli subtended 20° of visual angle and were always presented directly in front of the animal with the center fixated. Surfaces were defined by random dot stereograms (N = 250 dots) with perspective and stereoscopic cues. In our current sample (N = 58 V3A neurons), 53% showed significant modulation in firing rate with both orientation and distance, 10% for distance only, and 37% showed no significant modulation although they were visually driven (2-way ANOVA). At each distance, response modulation with orientation was further assessed (1-way ANOVA), and a Bingham function fit to the significant responses to estimate preferred orientation. For cells which showed significant tuning that was well described by a Bingham function at two or more distances ($r > 0.7$; N = 27 neurons), we evaluated how orientation preference depended on distance. The maximum possible change in orientation is 90°. For most V3A neurons, the preferred orientation changed substantially with distance: average = 39.01° ± 4.24° SEM, indicative of an ambiguous 3D pose representation. However, the degree to which orientation preference changed with distance

ranged widely across cells: 9.42° to 86.37°, suggesting that the responses of some V3A neurons approach an unambiguous representation of 3D pose. The magnitude of orientation preference changes did not correlate with the size of the receptive field or the extent to which the stimulus overlapped the receptive field. These results suggest V3A is an intermediate stage in the 2D-to-3D visual transformation.

Disclosures: T. Chang: None. **B. Kim:** None. **A. Sunkara:** None. **A. Rosenberg:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.16/EE11

Topic: D.07. Vision

Support: HHMI

Title: Axis coding scheme of shape representation in object networks in IT cortex

Authors: *P. BAO[1], L. SHE[2], M. MCGILL[3], D. Y. TSAO[2]
[1]Biol., [3]Computation and Neural Systems, [2]Caltech, Pasadena, CA

Abstract: Inferior temporal (IT) cortex is crucial for visual object recognition. Chang & Tsao (2017) found that cells in IT face patches code axes in a high-dimensional face space. Whether axis coding is the canonical rule for other parts of IT is still not clear—it could be a special scheme used by for face cells due to the high topological similarity between different facial identities. To address this question, we performed extracellular recordings in six patches belonging to two object networks in IT cortex: the body network and a newly-discovered network lacking explicit semantic categorical preference (Bao & Tsao, 2016). During the recording sessions, monkeys passively viewed an image set consisting of 51 objects, with 24 views of each object. The same image set was also fed into a trained deep learning neural network, Alexnet. PCA was carried out on the responses of Alexnet units. By parametrizing object images as points in a 50-dimensional linear space by the first 50 principal components, we found that the firing rates of each neuron from both networks was proportional to the projection of an object onto a single axis in the object space. This suggests that cells in different IT networks encode different subspaces of object space using the same canonical coding scheme, axis coding.

Disclosures: P. Bao: None. **L. She:** None. **M. McGill:** None. **D.Y. Tsao:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.17/EE12

Topic: D.07. Vision

Support: CIHR

Title: The dynamics of depth cue invariance in 3-D object recognition

Authors: *Y. CHEN, R. FARIVAR
Ophthalmology Vision Res. Unit, McGill Univ., Montreal, QC, Canada

Abstract: Human can recognize objects in 3-D regardless of which abstracted form depth-cue is presented to the retina (Dehmoobadsharifabadi & Farivar, 2016). This invariance 3-D object recognition is driven by integration of information from brain areas that process different depth-cues in both ventral and dorsal visual pathways. Previous study in our lab provided evidence of information integration by showing cross depth-cue adaptation effects using MEG, indicating the object can be recognized by same neural population (Akhavein & Farivar, accepted in 2017). It is unclear whether single depth-cue is sufficient to form 3-D object information individually before integrated into a common mental representation. Understanding the hierarchical processes of depth-cue invariance is crucial for future construction of computer vision models that describe how human perceive 3-D world using 2-D retina images (Farivar, 2009). Here we investigated 3-D object recognition from three different depth-cues (shading, texture, and structure from motion), and three different objects (face, chair, and contour-of-a-face) by adopting MEG decoding analysis in sliding time windows. Using this method, we could identify decoding accuracy from object pairs at different time points. Cortical activity patterns from different depth-cues can reliably decode object label, but with different onset and peak time. Decoding brain activation pattern can be from generalization from one depth-cue to another, with short but significant onset lag compared to decoding from same depth-cue. Additionally, evidences from dynamics of cross validated Euclidean distances from brain patterns also suggested that invariance of depth-cue in brain activity happened after the objects can be decoded from individual depth cues. These results provide key evidence supporting the invariance 3-D object recognition from different depth-cues, as well as new evidences that perceptions of different depth-cues follow different mental 3-D object representations before integration.

Disclosures: Y. Chen: None. **R. Farivar:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.18/EE13

Topic: D.07. Vision

Title: What can be inferred about independence and invariance of brain representations from fMRI decoding studies?

Authors: *F. A. SOTO, S. NARASIWODEYAR
Dept. of Psychology, Florida Intl. Univ., Miami, FL

Abstract: Many research questions in visual neuroscience involve determining whether stimulus properties are represented and processed independently in the brain. Unfortunately, most previous research has only vaguely defined what is meant by "independence," which hinders its precise quantification and testing. Here we develop a new framework that links general recognition theory from psychophysics and encoding models from computational neuroscience. We focus on separability, a special form of independence that is equivalent to the concept of "invariance" often used by neuroscientists, but we show that other types of independence can be formally defined within the theory. We show how this new framework allows us, for the first time, to precisely define separability of neural representations and to theoretically link such definition to psychophysical and neuroimaging tests of independence and invariance. The framework formally specifies the relation between these different levels of perceptual and brain representation, providing the tools for a truly integrative research approach. In particular, the theory identifies exactly what valid inferences can be made about independent encoding of stimulus dimensions from the results of multivariate analyses of neuroimaging data. In addition, two commonly used operational tests of independence are re-interpreted within this new theoretical framework, providing insights on their correct use and interpretation. Finally, we validate this extended general recognition theory in an fMRI study involving gratings varying in orientation and spatial position. Participants completed 4 two-hour sessions in the MRI scanner, in which they were presented with oriented gratings varying in orientation in 45-degree steps (0, 45, 90, and 135 degrees) while they fixated to the center of the screen. Stimuli were presented in 3 different spatial positions in the visual field. The known features of receptive fields in primary visual cortex led us to expect that varying the position of stimuli should systematically change encoding separability of orientation, with lower separability for stimuli positioned farther apart. We show that a decoding test developed within the proposed framework can capture such variations.

Disclosures: F.A. Soto: None. **S. Narasiwodeyar:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.19/EE14

Topic: D.07. Vision

Support: Office of Naval Reserach, Multi University Research Initiative-60744752-3551877 (DiCarlo, subaward from Stanford)
Simons Foundation (SCGB [325500, 542965], [JJD])
NIH-NEI- R01-EY014970-11A1

Title: Chemogenetic down-regulation of macaque V4 responses produce reversible deficits in core object recognition behavior

Authors: *K. KAR[1], J. J. DICARLO[2]
[1]McGovern Inst. for Brain Res., [2]Brain & Cognitive Sci., MIT, Cambridge, MA

Abstract: The primate ventral stream houses a hierarchical neural network that comprises a series of cortical areas (V1, V2, V4, pIT, cIT, aIT) and underlies core object recognition behavior. Recent models of the ventral stream coarsely approximate the activity patterns at each of these cortical stages and core object recognition behavior. To constrain the development of more accurate models, we need to discover the nature of causal dependencies between these specific circuits and behavior. Therefore it is critical to investigate causal perturbation tools to reversibly interrogate these cortical circuits in behaving primates. Here we tested one such chemogenetic silencing strategy based on DREADDs (Designer Receptors Exclusively Activated by Designer Drugs). The potential to transfect larger (including sub-cortical) areas with a minimally invasive behavioral testing framework makes this a very promising approach compared to the pharmacological or optogenetic alternatives. We injected (~50 uL) of the viral construct, AAV8-hSyn-hM4Di-mCherry, that causes neuron specific inhibition, distributed over a 9 mm^2 patch of dorsal V4 in two macaques. To test for successful neural suppression, we chronically implanted a Utah array in the injected region. This allowed us to directly monitor the strength of neural silencing across time after DREADD activation via systemic CNO/clozapine injection. To estimate how perturbing a 9 mm^2 patch of macaque V4 cortex affects the downstream IT regions, we implanted 2 additional Utah arrays in pIT and cIT. We divided each experimental session into multiple blocks. In each block, monkeys performed two tasks: passive fixation while images were rapidly presented at the central 8^o, followed by an object discrimination task. At the end of the first block, we intramuscularly injected either CNO, clozapine or saline. Preliminary results show an overall reduction (max: ~18%) of the stimulus evoked V4 responses and a behavioral deficit (~8%) peaking around 100 mins post CNO/Clozapine injection.The behavioral deficit was significantly more pronounced when the

object position coincided with the receptive field of the transfected patch of V4, confirming the causal importance of cortical area V4 in the monkeys' core object recognition behavior. In sum, our results demonstrate the ability of DREADDs to reversibly down-regulate neural activity in a 9 mm^2 patch of macaque V4 and affect a behavior that it was assumed to support. This opens up the possibility of directly testing the causal link between multiple cortical areas and object recognition tasks, with the goal of guiding the discovery of the next generation of ventral stream neural network models.

Disclosures: K. Kar: None. **J.J. DiCarlo:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.20/FF1

Topic: D.07. Vision

Title: A search for the representational content in the putative number form area

Authors: *D. YEO[1,2], C. POLLACK[1], G. PRICE[1]
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Abstract: Recent studies suggest a putative number form area (NFA) in the inferior temporal gyrus (ITG) that responds preferentially to Arabic numerals versus other symbols. It is assumed to be recruited in any task that involves visual processing of Arabic numerals. Although meta-analytic convergence in the right ITG has been observed for numeral-selectivity, its recruitment is not as obligatory as previously assumed. It is thus unclear whether the NFA is specialized for processing visual shapes, semantic associations, or both, and whether prior findings depend on active processing of the numerals. Here we test the stronger claim of an NFA by investigating the content represented in an NFA during passive viewing of digits, letters, and scrambled digits/letters in 39 adolescents using multi-voxel representational similarity (RS) analysis. We tested RS in our data against 5 hypothetical models: (1) pixel- and (2) deformation-based physical shape similarity, (3) symbols versus novel characters, (4) digits versus non-digits, and (5) digits versus letters versus non-symbols. RS across exemplars of the 4 categories in the NFA did not match any of the hypothesized models. As within-category variability may mask potential between-category distinctions, we repeated the analysis using the averaged multi-voxel response pattern to each stimulus category. Results replicated our initial findings. In contrast, RS in the right inferior frontal gyrus (IFG) matched models 1, 2, and 3. These findings suggest that the NFA, at least during passive viewing, may lack categorical information. Minimally, existing work has shown that the shape identity needs to be actively processed for its recruitment, and could be part of an interactive loop with top-down processes from parietal regions. This suggests a nuanced role of the putative NFA in category specific digit processing that requires further

empirical investigation. The right IFG may be involved in the automatic retrieval of associations between shapes and concepts to distinguish familiar, identifiable shapes from novel, unidentifiable ones.

Disclosures: D. Yeo: A. Employment/Salary (full or part-time):; Nanyang Technological University. **C. Pollack:** A. Employment/Salary (full or part-time):; Vanderbilt University. **G. Price:** A. Employment/Salary (full or part-time):; Vanderbilt 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.; National Science Foundation.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.21/FF2

Topic: D.07. Vision

Support: NIH R01EY014681

Title: Movement improves shape discrimination under visual uncertainty

Authors: *D. BURK, D. L. SHEINBERG
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Abstract: As we move throughout the world, our brains continuously acquire sensory information to make predictions based on what we see. For example, an animal hopping in a foggy park could be perceived as a rabbit, even when the rabbit's form is too far away to be visible. Does the hopping movement allow for better discrimination between types of rabbits? More generally, objects often have stereotypical movements, but it remains unknown how movement is used in object recognition. Previous research has shown that the brain associates features (e.g. color, shape, size) to create a unified percept of an object. This percept can be retrieved when the appropriate group (or possibly a subset) of features is encountered again. We ask whether movement can be used as diagnostic information to improve perception of an object’s shape when shape is ambiguous. Specifically, we aim to address (1) under what circumstances a stereotyped, translational movement path associated with a class of shapes could aid shape recognition and (2) the neural mechanisms underlying this behavior. To investigate this, we developed a match-to-sample task for human and non-human primates that requires subjects to identify a moving shape in variable perceptual noise. Interestingly, behavioral data demonstrates that recognition of the movement pattern associated with a shape enhances perception of object shape in the presence of high noise. We also investigate the neural basis of this finding in an area that is sensitive to object features (inferior temporal cortex). Here we aim

to demonstrate that learning of associations between movements and shapes can lead to a perceptual benefit during object recognition.

Disclosures: D. Burk: None. **D.L. Sheinberg:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.22/FF3

Topic: D.07. Vision

Support: NSF grant IIS-1219252
NSF cooperative agreement SMA 1041755
A gift from Hewlett-Packard

Title: An anatomically-constrained model of the peripheral bias in scene recognition

Authors: *G. W. COTTRELL, P. WANG
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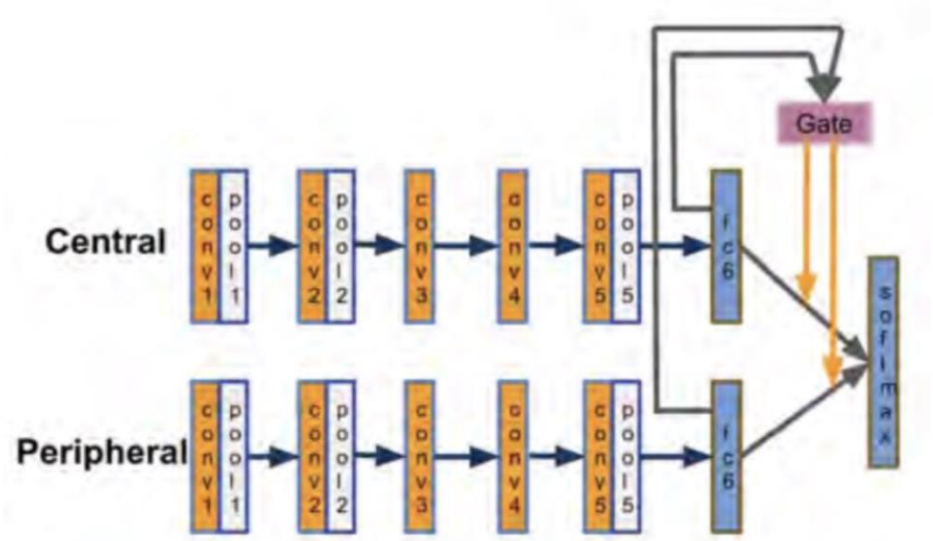
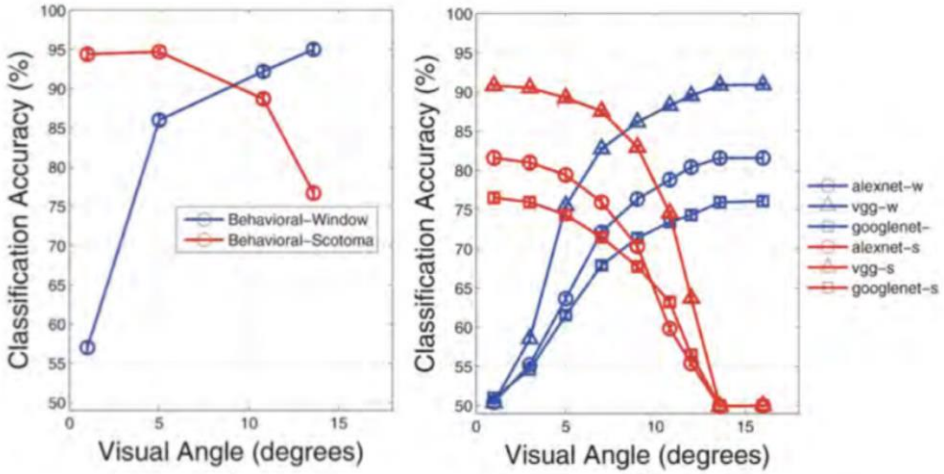
Abstract: What are the roles of central and peripheral vision in human scene recognition? Larson and Loschky (2009) showed that peripheral vision contributes more than central vision in obtaining maximum scene recognition accuracy. However, somewhat counterintuitively, central vision is more efficient for scene recognition than peripheral, based on the amount of visual area needed for accurate recognition. Here, we model these results using a deep network with a mixture-of-experts architecture. Our model is anatomically constrained in two ways: First, we use the log-polar transformation that provides cortical magnification by emphasizing foveal and parafoveal vision. We show that the log-polar transform gives results that are closer to the human data when compared to simply using a foveated representation of the image. Second, we use the fact that there is a bifurcation between the central and foveal vision pathways, where the peripheral pathway innervates the Parahippocampal Place Area (PPA), and the central pathway innervates the Lateral Occipital Complex (LOC). The peripheral advantage emerges naturally in the learning process: When trained to categorize scenes, the model weights the peripheral pathway more than the central pathway. Our model replicates the advantage of peripheral vision in scene recognition, as well as the efficiency advantage for central vision.



Deep mixture of Experts Model



Human Data Modeling Results

Disclosures: G.W. Cottrell: None. **P. Wang:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.23/FF4

Topic: D.07. Vision

Title: The timing of reading: Electrophysiological exploration of stimulus and task effects on routing visual information to the visual word form area and language cortex

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Abstract: The neural mechanisms underlying reading have been extensively studied using psychophysical and fMRI methods. However, mechanisms by which stimuli are routed from visual to language cortex remain opaque and are best explored by observing response timecourses at millisecond level in the human brain's reading network. We recorded intracranial EEG signals from 5 patients implanted with subdural electrodes while they viewed different types of word form stimuli. Stimuli comprised real words, pseudowords, consonant strings, and partially and fully noise-degraded words. We presented word stimuli in the central, ipsilateral, and contralateral visual fields. Using the same stimuli, patients were instructed two perform either a fixation color task or a lexical decision task. Power and onset time of high-frequency broadband (HFB, 70-170Hz) signal were used as measures for the level of cortical activation and its onset. Left visual word form area (VWFA) response amplitudes did not differ between real words, pseudowords, or consonant strings, but all of these responses were significantly larger than responses to fully noise-degraded stimuli. VWFA responses to suboptimal words (ipsilateral visual field or partially noise-degraded) were delayed in onset compared to optimal stimuli (central or contralateral visual field without noise), despite accounting for response amplitude. Response onset delays were similar, approximately 30ms. The decreased response amplitude, but not the response delay, can be mitigated by invoking top-down modulation through a lexical decision task. In a patient where we obtained simultaneous recordings from the VWFA and putative Broca's and Wernicke's areas, similar response onset latency differences were observed in these language areas. These delays may reflect synaptic delays due to ancillary processing of stimuli in supporting brain regions. The critical role of VWFA was also supported by the disruption of reading during electrical stimulation of the VWFA performed in two patients. These data provide information about the timing of electrophysiological responses to words in the VWFA and in other language areas, which will lead to deeper understanding of the neural mechanisms of reading.

Disclosures: A.M. Rauschecker: None. **R. Na:** None. **O. Raccah:** None. **J. Parvizi:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.24/FF5

Topic: D.07. Vision

Title: Retinal size rather than perceived size (post size constancy) determines reaction time for identifying puzzle pictures such as Mooney faces

Authors: *S. KANDALAFT[1], L. L. HAGOPIAN[2], M. VAJANAPHANICH[2], G. M. DANDREAPENNA[2], C. CHUNHARAS[2], V. S. RAMACHANDRAN[2]
[1]UC San Diego, San Diego, CA; [2]UCSD, La Jolla, CA

Abstract: When you see a person lying on the ground, with her head twice the distance from you as her feet, then on your retina her head subtends half the size as her feet. But your brain corrects for relative perceived size using relative depth cues so you don't see a microcephalic and see a normally proportioned person, i.e. "Size constancy". Does this correction for distance occur in the ventral stream where objects are recognized and associated with semantics, or the dorsal stream (parietal lobes) concerned with spatial vision, prehension, etc.?
We exploited Mooney faces to answer this. A person's face is strongly illuminated unidirectionally and binarized to empathize shadows producing splotches. The time taken to recognize this as a face depends on its size. The larger it is, the slower the recognition. If the face recognition is affected by size-constancy, one will expect that halving the size will facilitate the recognition more than doubling the viewing distance even though they both end up having the same retinal sizes.
Subjects were asked to decide if the stimulus was a face or non-face as fast and accurately as possible for each condition (Condition 1: Distance 1, Image Size 1; Condition 2: Distance 1, Image Size 1/2; Condition 3: Distance 1x2, Image Size 1). Reaction time and accuracy were recorded. We found doubling the distance was as effective as halving the size, suggesting retinal size, before constancy correction, was the relevant variable in visual pattern recognition. This makes sense given that color and shape are more diagnostic of objects than size which is primarily relevant for spatial vision including grasping and obstacle avoidance.
It is unclear whether what is addressed in this experiment is the recognition of the face *per se*, or the ability to extract 3D shape from shading. We are disentangling these variables by using puzzle block letters and Dalmatian dogs (figure 1) which do not require computation of depth of shading.
Therefore, puzzle pictures, like Mooney faces, can be used to reveal stages of perceptual processing involved in object recognition and the neural loci of these effects.

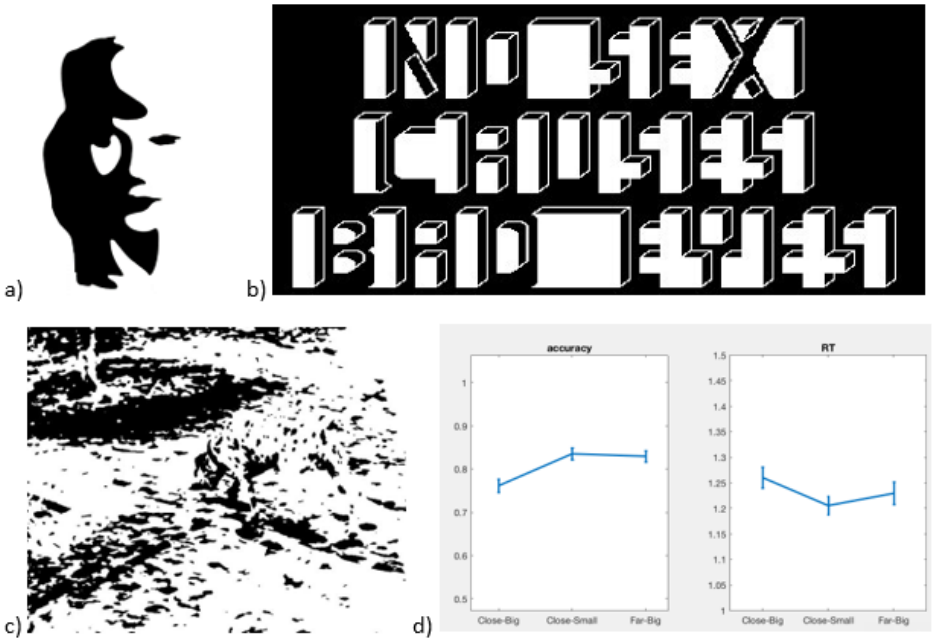

Figure 1: Puzzle Pictures: a) Mooney face; b) Puzzle block letters; c) Dalmatian dogs d) Retinal size vs perceived size in Mooney face pattern recognition: Depicts the accuracy for the Mooney face detection task. We found that subjects were more accurate and slightly faster when the display was either made 1/2 times smaller or when they were viewing the large display from twice as far.

Disclosures: S. Kandalaft: None. **L.L. Hagopian:** None. **M. Vajanaphanich:** None. **G.M. Dandreapenna:** None. **C. Chunharas:** None. **V.S. Ramachandran:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.25/FF6

Topic: D.07. Vision

Support: Intramural Research Program of the National Institutes of Health (ZIA-MH-002909)
Fellowship of the Humboldt Foundation (Feodor-Lynen program)

Title: Towards large-scale characterization of object representations in behavior and the human brain

Authors: *A. DICKTER[1], M. N. HEBART[3], A. KIDDER[4], W. Y. KWOK[4], C. Y. ZHENG[5], C. I. BAKER[2]
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Abstract: To gain an understanding of the cognitive and neural mechanisms of object recognition in humans, we need to broadly sample object categories using naturalistic object images and identify sensitive methods for relating them to human behavior. Here we report on our recent efforts to (1) systematically identify a broad set of basic-level object categories, (2) create an object image database useful for large-scale neuroimaging, and (3) develop and verify a behavioral task for measuring the behavioral similarity and relating it to representations in the human brain.
In a first step, we sought to identify a representative set of basic-level object categories. After extracting concrete English nouns from a list of concreteness ratings for 40,000 English lemma (Brysbaert et al., 2014), we excluded scenes and non-depictable objects, carried out word-sense disambiguation using Wordnet, and used object image naming on Amazon Mechanical Turk (AMT) to identify a set of consistently named object categories. This process led to a set of 1,854 basic-level object categories spanning a wide range of man-made and natural objects.
In a second step, we built a large-scale natural object image database for presentation of images in the MRI and MEG, with at least 12 images per object category, based on scraping of images from search engines and Imagenet, and manually selecting images with natural background and high image quality. This process led to more than 22,000 object images with natural background.
Finally, to relate object representations to behavior, we tested the use of an odd-one-out task based on object triplets and verified its utility using deep neural network models (Alexnet), high-dimensional word embeddings (GloVe), as well as human neuroimaging data (MRI / MEG). The odd-one-out triplet task outperformed standard behavioral similarity tasks in correlating with representations in both models and neuroimaging data, demonstrating the general sensitivity and utility of the task for measuring behavioral representations.
Together, this work lays an important foundation for a systematic and large-scale assessment of object representations both in the human and animal brain as well as in behavior.

Disclosures: A. Dickter: None. **M.N. Hebart:** None. **A. Kidder:** None. **W.Y. Kwok:** None. **C.Y. Zheng:** None. **C.I. Baker:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.26/FF7

Topic: D.07. Vision

Support: Intramural Research Program of the National Institutes of Health (ZIA-MH-002909)
Fellowship of the Humboldt Foundation (Feodor-Lynen program)

Title: Uncovering the large-scale representation of behaviorally-relevant object dimensions

Authors: *M. N. HEBART[1], C. Y. ZHENG[2], F. PEREIRA[2], C. I. BAKER[1]
[1]Lab. of Brain & Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD; [2]SFM, NIMH, Bethesda, MD

Abstract: We can categorize the objects around us according to a nearly infinite number of criteria, yet some object dimensions (e.g. category, color) are more relevant than others in our everyday interactions with the objects around us. These behaviorally-relevant object dimensions structure the large-scale space of our mental representation, yet most research on understanding object representations has focused on small numbers of object categories or exclusively on semantic representations.
To overcome these limitations, we built a large-scale behavioral similarity matrix spanning a wide range of 1,854 object categories, allowing us to use data-driven methods to extract behaviorally-relevant object dimensions. We acquired millions of similarity ratings in a large-scale online experiment using an odd-one-out task on object triplets (three objects). Although the reconstruction of this behavioral similarity matrix was based on less than < 0.1 % of all possible trials, we found a strong correspondence to a fully-sampled behavioral similarity matrix of 48 objects, demonstrating excellent reconstruction of the large-scale similarity structure.
The similarity matrix allowed us to extract a set of sparse dimensions that characterize the mental representation of the objects. These dimensions were highly reproducible and interpretable, corresponding to both high-level object categories (e.g. animals, food) as well as perceptual features (e.g. color, shape), revealing among others that human-related categories (e.g. woman) are not judged as being part of an animal-related dimension.
Finally, we aimed at predicting the similarity of objects and images not included in the original set. We used Elastic Net regularized regression to predict the sparse object dimensions from computational models of vision and semantics, using a convolutional neural network trained on object images and word vectors from a state-of-the-art semantic word embedding. This yielded a high predictive accuracy, allowing us to combine the predicted dimensions to estimate the behavioral similarity for images of categories not included in our original set. This analysis demonstrates the generality of our method and extends its utility to objects for which behavioral measures are not available.
Together, this data-driven approach presents a powerful method for identifying a small number of interpretable, behaviorally-relevant object dimensions that can be directly related to neural activity in humans and animal models.

Disclosures: M.N. Hebart: None. **C.Y. Zheng:** None. **F. Pereira:** None. **C.I. Baker:** None.

Poster

221. Vision: Representation of Objects and Scenes

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 221.27/FF8

Topic: H.01. Animal Cognition and Behavior

Support: ONR Grant N00014-16-1-2276

Title: Awake fMRI of dogs reveals mechanisms for processing 2D representations of 3D objects

Authors: *A. PRICHARD[1], R. CHHIBBER[1], K. ATHANASSIADES[2], V. CHIU[3], M. SPIVAK[4], G. S. BERNS[1]
[1]Psychology Dept., [2]Sch. of Nursing, [3]Biol. Dept., Emory Univ., Atlanta, GA; [4]Comprehensive Pet Theraphy, Atlanta, GA

Abstract: Though most dog studies use visual stimuli, few have examined whether pictures serve as visual representations for the concrete. There is one example of dogs abstracting pictures or miniatures to familiar objects, and some evidence suggests that dogs successfully translate pictures of faces to familiar humans. However the neural mechanisms for how dogs abstract stimuli remain relatively unknown. Using awake fMRI of domestic dogs, we measured neurobiological responses to two dimensional (2D) and three dimensional (3D) versions of objects. Half of the dogs were trained on 2D stimuli and half on 3D stimuli. Prior to scanning, one stimulus of the trained pair was associated with food (CS+) and the other with nothing (CS-). During scanning, both 2D and 3D stimuli were presented. Similar to human studies, activation in the canine brain to 2D and 3D stimuli occurred in the dorsal parietal cortex and in a region similar to the human lateral occipital cortex ($p<.05$). Here we demonstrate the application of fMRI to examine the neurological mechanisms for dogs' abstraction of perceptual stimuli to concrete objects. While behavioral evidence for abstraction is mixed, our approach illustrates the potential for more complex perceptual capacities in dogs.

Disclosures: A. Prichard: None. **R. Chhibber:** None. **K. Athanassiades:** None. **V. Chiu:** None. **M. Spivak:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dog Star Technologies. **G.S. Berns:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dog Star Technologies.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.01/FF9

Topic: D.08. Visual Sensory-motor Processing

Support: HHMI
MPG

Title: Neural basis for directed courtship in *Drosophila*

Authors: *I. M. RIBEIRO[1], M. DREWS[1], A. BAHL[2], A. BORST[1], B. J. DICKSON[3]
[1]Max Planck Inst. Neurobio., Planegg, Germany; [2]Harvard Univ., Cambridge, MA; [3]Janelia Res. Campus, HHMI, Ashburn, VA

Abstract: Pursuit of prey or of a potential mate are daily tasks in the lives of many animals that, in most species, rely on vision. How visual information is processed in the brain to guide this directed behavior remains poorly understood. *Drosophila melanogaster* males use vision to chase the ambulatory female and direct courtship at the female. We found that LC10 neurons, a class of visual projection neurons that relay visual information to the central brain, play an essential role in this context. LC10 neurons are preferentially sensitive to small bars in contrast to wide field motion stimuli. Moreover, LC10 neurons responded strongly to a dark or bright bar bestowed with dynamic angular sizes and speeds extracted from a behavioral episode that included bouts of chase and directed courtship. When visual stimuli were presented isolated from other forms of sensory input in fly-on-ball assays, LC10 neurons output proved to be necessary to track a small 3-D virtual bead. In contrast, blocking LC10 neurons left the optomotor response to wide-field moving gratings unaffected, as well as the fixation of a thin long bar. Moreover, unilateral subsets of LC10 neurons elicited ipsilateral turning and extension of the wing ipsilateral to the stimulated side. Interestingly, LC10 neurons are monomorphic neurons, presenting similar dendritic morphologies and sensitivity to visual stimuli in males and females. Yet, only males chase and court. How LC10-visual information is processed in the central brain might differ between males and females. To test this, we artificially activated the male-specific P1 neurons for a short time, a manipulation known to induce a state of courtship arousal that outlasts the acute stimulation by several minutes. The number of elicited single-wing extensions upon activation of LC10 neurons was much higher in males in an induced state of courtship arousal compared to uninduced males, suggesting that male-specific P1 neurons affect how LC10-visual information is used in the central brain. Together our findings indicate that LC10 neurons represent a major visual pathway mediating directed courtship and open the door to elucidating the neural processing underlying pursuit behavior in more detail.

Disclosures: I.M. Ribeiro: None. **M. Drews:** None. **A. Bahl:** None. **A. Borst:** None. **B.J. Dickson:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.02/FF10

Topic: D.08. Visual Sensory-motor Processing

Support: NIH R01 NS095251
DGE-1324585

Title: Muscle kinematics play a large role in primary somatosensory cortical neural activity

Authors: *R. H. CHOWDHURY[1], C. VERSTEEG[2], T. TOMLINSON[4], J. SOMBECK[2], L. E. MILLER[3]
[1]Biomed. Engin., Northwestern Univ., Evanston, IL; [2]Biomed. Engin., [3]Physiol., Northwestern Univ., Chicago, IL; [4]Physiol., Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL

Abstract: Sometimes called the "hidden, sixth sense", proprioception, the sense of body state, is crucial to our ability to move our limbs, yet it remains poorly understood. Common experience suggests that at a conscious level, our perception of arm position is focused on the location of the hand and its movement, rather than joint angles or muscle lengths. This has also been the classic assumption for how proprioceptive neurons in the somatosensory cortex (S1) represent reaching movements. That is, these studies typically neglect the possible relation of these signals to peripheral mechanics. Here, however, we show that muscle kinematics can explain features of neural activity in S1 that cannot be explained by the classic model, underscoring the importance of the periphery in determining S1 discharge.

In this project, we examined three aspects of proprioceptive neural activity in S1. In the first experiment, we examined whether the representation of movement in S1 was truly hand-related or whether it arose from a simple combination of muscle stretch sensors. We found that when measured in two different postures, the preferred hand movement directions of most neurons shifted, a phenomenon inconsistent with the hand-based model of neural activity. However, a muscle-based model accurately predicted this shift. In the second experiment, we extended this analysis to examine how muscle kinematics contribute to the representation of kinematically similar but dynamically different movements, specifically actively generated arm movements and passive perturbations of the arm. Previous results from our lab showed that while neurons generally have similar active and passive tuning curves, the two types of movements have significantly different representations at the population level. This difference cannot be explained by the classic hand-based model of S1, but a simple muscle kinematics model was enough to predict this difference in representation. In our final experiment, we examined whether apparent tuning related to the direction of a load on the hand, a feature of the classic model, might also arise from a model based purely on muscle kinematics. Indeed, we found that the apparent load tuning of 50% of neurons could be explained by a muscle-kinematics model.

Taken together, these results demonstrate that despite the hand-centered nature of conscious proprioception, neural activity in S1 remains closely related to muscle properties. Given the close relationship between S1 and primary motor cortex, this conclusion may reflect the inherent difference in requirements between the perception of movement and control of movement.

Disclosures: R.H. Chowdhury: None. **C. Versteeg:** None. **T. Tomlinson:** None. **J. Sombeck:** None. **L.E. Miller:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.03/FF11

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC Discovery Grant, RGPIN 311680

Title: Faster moving targets evoke larger and more prevalent stimulus locked responses on human upper limb muscles

Authors: *R. A. KOZAK, B. D. CORNEIL
Neurosci., Western Univ., London, ON, Canada

Abstract: To reach towards a visible target, such as a coffee mug, visual information about the mug has to be transformed into reaching motor commands. Visual information such as the colour, shape, and size of the mug is processed within numerous cortical areas, then relayed to the motor periphery. However, in order to catch a falling mug, we must rapidly transform only the necessary or available visual information into motor commands. These fast visuomotor transformations, and their underlying neurological substrates, are poorly understood in humans. Recently, we have identified an aspect of motor activity theorized to be a signature of the fast visuomotor system, which are termed stimulus-locked responses (SLRs). SLRs are bursts of muscle activity that occur time-locked within 100 ms of visual stimulus presentation, well before the onset of the intentional movement. SLRs have been observed both in neck and upper limb muscles in humans, and persist even if the movement is temporarily withheld or moves away from a visual stimulus. These observations have led us to hypothesize that SLRs arise from the tecto-reticulospinal tract. To better understand the nature of visual input received by the fast visuomotor system, we have examined SLR activity while systematically varying visual stimulus parameters. For example, we have recently shown that SLRs are preferentially evoked by stimuli composed of low spatial frequencies, which is consistent with magnocellular (M) visual input into the fast visuomotor system. To further examine M pathway involvement, here we tested whether SLRs are preferentially evoked by moving stimuli, as motion is a feature proposed to be carried by the M pathway. Human subjects placed in a robotic exoskeleton generated left and right planar arm movements towards targets as surface electrodes recorded electromyographic (EMG) activity from the clavicular head of the right pectoralis major muscle. Targets moved horizontally towards participants, following a bifurcating path where the fork was occluded. Visual stimuli moved at 5, 7.5 and 10 cm/s, or were presented statically. Currently, we have observed prominent SLRs in all subjects in at least one of the motion conditions, whereas SLRs were less likely to be evoked by a static stimulus. Although SLR latency does not appear to change when evoked by static or moving stimuli, the magnitude of the SLR was far greater when

evoked by moving stimuli. Overall, our results demonstrate that the SLR, which represents the earliest wave of limb muscle recruitment in response to visual target presentation, is preferentially evoked with moving stimuli, consistent with M pathway input into the fast visuomotor system.

Disclosures: R.A. Kozak: None. **B.D. Corneil:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.04/FF12

Topic: D.08. Visual Sensory-motor Processing

Title: Direct visual control of interception

Authors: *J. B. SMEETS, E. BRENNER
Human Movement Sci., Vrije Univ. Amsterdam, Amsterdam, Netherlands

Abstract: When making goal-directed hand movements, one can adjust one's movement to a change in target position with a latency of 100 ms. When intercepting a target that is moving perpendicular to one's own motion, one has to guide one's hand to a position at which the target will be at the time the hand reaches the target's trajectory. How are such movements controlled? Do participants accumulate information about the target's changing position to build a smoothed representation of the target's motion to predict where the target will be at the time of interception or do they use the noisy visual input directly?
To answer this question, we let participants intercept targets that moved across a large 120Hz display. Each target moved with an average speed of 0.6 m/s, but rather than having this speed on every frame, the targets' displacements corresponded with a speed of either 0.4 or 0.8 m/s on every frame. The speed was chosen at random for each frame. By selecting trials that had the same target speed at a certain instant and comparing the average lateral movement of the hand on these trials with the average lateral movement on the other trials, we were able to determine the response to a 1 frame speed difference of 0.4 m/s resulting in a step-difference in position of 6.67 mm. By doing this for various instants relative to the time of the tap, we examined how information about the target's motion was used to guide the hand.
We found a clear response in the lateral velocity of the hand 100ms after the frame with the selected target speed difference. The response lasted a bit more than 100ms. The exact shape of the response depended on the frame with the speed difference. For speed differences occurring late in the movement (less than 200 ms before interception), the amplitude of the peak was 0.1 m/s and it was 150 ms after the difference. For earlier speed differences, the peak response was later (180 ms after the difference) and lower in amplitude (0.04 m/s). This pattern of responses resembles that of a second order linear system with constant mass and damping and a stiffness

that increases during the interception movement, as has been found for the control of goal-directed movements to static targets (Liu & Todorov, J. Neurosci 2007). It is the opposite of what one would expect for a control mechanism that accumulates information to obtain a better estimate of the target's motion.
Thus, we show that human interceptive movements are guided directly by the instantaneous noisy input rather than being guided by a smoothed representation of such input that allows one to better predict the target's near trajectory.

Disclosures: J.B. Smeets: None. **E. Brenner:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.05/FF13

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC

Title: Pantomime resolution for 'very small' targets matches visually guided grasping

Authors: *N. AYALA, D. SHUKLA, M. HEATH
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Abstract: Previous work employing the psychophysical principles of Weber's law has shown that the just-noticeable-difference (JND) for pantomimes (a simulated motor act) increase linearly with increasing target size (i.e., adhere to Weber's law), whereas JNDs for grasping do not reliably vary with target size (i.e., violate Weber's law). These findings have been interpreted to reflect that pantomime and grasping are mediated via relative and absolute visual codes, respectively. Notably, however, work to date has not examined how accurate pantomime and visually guided grasp aperture scaling is for 'very small' targets. Thus, in the current confirmatory study, we examined whether peak grip aperture (PGA) for pantomime and grasping reliably differ for target sizes with widths that differed by 1% (i.e., 40 mm vs. 40.5 mm target, and 45 mm vs. 45.5 mm target). We hypothesized that the relative visual information mediating pantomimes would render PGAs that did not scale to target size, whereas the absolute visual information mediating grasping would result in PGA/target size scaling. Participants (N=15) pantomimed and grasped one target from a pair in which the difference in size was 0.5 mm. As expected, PGAs for pantomimes were less than grasping ($p<.001$) - a result attributed to the fact that pantomimes do not require a safety-margin task-set. Moreover, and in contrast to our prediction, PGAs for pantomimes and grasping scaled to target size ($p<0.02$), and the magnitude of the PGA/target size scaling did not vary between tasks. Accordingly, pantomimes and grasps across the two sets of target objects demonstrated comparable resolving power for the target

sizes used here. Therefore, we conclude that the resolution of the perceptual system for pantomimes is more accurate than the perceptually determined threshold (3%).
Funding provided by NSERC.

Disclosures: N. Ayala: None. **D. Shukla:** None. **M. Heath:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.06/FF14

Topic: D.08. Visual Sensory-motor Processing

Title: Multisensory integration for the planning vs. the control of upper-limb reaches

Authors: *R. GOODMAN, G. MANSON, L. TREMBLAY
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Abstract: Sensory information is required to plan voluntary movements. During upper-limb reaches, multiple sensory modalities are deemed to be combined and integrated to obtain the most accurate representation of target features (e.g. Ernst & Bulthoff, 2004). However, it has also been suggested that when planning upper-limb movements, target and effector information must be mapped in the same sensory coordinate system (e.g. Battaglia-Mayer et al., 2003). Other researchers have argued that the reference frame employed to prepare a movement is context specific (Sober and Sabes, 2005). Further, sensory information from a target location has been shown to also influence movement kinematics (Bernier et al., 2007). The current study employed visual, somatosensory, and visual-somatosensory (i.e. multisensory) targets to assess how voluntary reaching movements are prepared and executed. Participants were asked to reach quickly and accurately with their right limb towards one of three fingers of the occluded left hand that were used as targets. The targets were prompted with a light (i.e. visual), a tactor (i.e. somatosensory), or both (i.e. multisensory). Participants exhibited comparable endpoint amplitudes, however, movement onset and duration latencies were modulated as a function of target modality. The target position elicited shortest reaction time (RT) when prompted with the light and tactor (i.e. multisensory). In contrast, the visual condition yielded shorter movement execution time (MT) than with both somatosensory and multisensory target conditions. These results provide evidence that participants may initially leverage multisensory information to encode target positions, but rely more on visual feedback to control the ongoing movements.

Disclosures: R. Goodman: None. **G. Manson:** None. **L. Tremblay:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.07/FF15

Topic: D.08. Visual Sensory-motor Processing

Title: Eye-hand coordination deficits in individuals with diabetes during a cognitive-motor integration task

Authors: *M. DALECKI, J. C. ADKINS, C. STOKES
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Abstract: Diabetes is increasingly prevalent in our society, which necessitates the need for a detailed understanding of potential emerging eye-hand coordination and cognitive deficits. Brain imaging studies have shown white matter tract changes in participants with diabetes, even in young and middle-aged individuals. These changes were prominent in fronto-parietal networks, networks that are heavily involved in cognitive-motor integration (CMI) tasks. CMI tasks require rule-based visuomotor transformations, e.g., when we are moving to the left while looking away. The aforementioned diabetes studies focused on brain imaging and did not assess eye-hand coordination outcomes. It is, therefore, still unknown whether participants with diabetes show eye-hand coordination deficits during a brain challenging CMI task. Thus, the present study investigates CMI task performance in participants with diabetes and in healthy age-matched controls. We collected pilot data of 13 participants (age 18-53 yrs; M=31 yrs), including 5 participants with diabetes and 8 healthy age-matched controls. Participants slid their index finger along a laptop touchscreen to move a cursor from a central to a peripheral target in two conditions: 1) a direct task, with vision and finger movement direction in alignment; 2) a CMI task, with vision and movement direction decoupled, i.e., eyes and finger move to the opposite direction and in a different plane. We analyzed whether movement preparation, timing, and execution variables differed between participant groups (diabetes, controls) and age (young adults, M=21 yrs; middle-aged, M=43 yrs). We observed eye-hand coordination deficits in middle-aged participants with diabetes. Across both conditions, movement preparation (increased reaction time; $p<0.05$) and timing (increased movement time; $p<0.01$) were significantly slower compared to the age-matched control group, with a trend for a more pronounced effect in the CMI condition. Notably, in the young adult group, there was no performance difference between the participants with diabetes and the healthy controls (all $p>0.05$). Our preliminary results show CMI performance deficits in middle-aged individuals with diabetes. Based on previous studies, we propose that these deficits may be due to less efficient fronto-parietal white-matter tract networks. However, the results are preliminary, and more data collection is needed for valid conclusions. Currently, we are examining in more detail which disease types, duration, and age groups may present CMI deficits in individuals with diabetes.

Disclosures: M. Dalecki: None. **J.C. Adkins:** None. **C. Stokes:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.08/FF16

Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant 2R25GM069743

Title: Rule-based visuomotor transformations differ between the dominant and non-dominant hand

Authors: B. JONES, *A. W. VAN GEMMERT, M. DALECKI
Kinesiology, Louisiana State Univ., Baton Rouge, LA

Abstract: The human motor system is capable to move in a direction unaligned with veridical perception of information. These tasks, requiring rule-based visuomotor transformations and decoupling of vision and action, can be called cognitive-motor integration (CMI) tasks. Although CMI tasks are often used in daily life, many studies have focused on CMI, and research has shown that neural networks controlling the dominant and non-dominant hand differ, non-dominant hand use has not received much attention. Thus, the aim of this study was to determine performance of the dominant and non-dominant hand across different CMI complexity levels. We hypothesized that i) CMI non-dominant task performance efficiency is lower than CMI dominant task performance, and ii) that CMI performance differences become more pronounced between the hands when the level of decoupling between vision and action increases. Eighteen young adult right hand dominant participants (M=23 yrs; 7 males) were required to slide their finger along a vertical laptop touchscreen to move a cursor to 4 peripheral targets in 4 perceptual-action conditions: 1) finger and cursor move in the vertical plane and same direction; 2) finger and cursor move in the vertical plane, but cursor and finger movement direction are opposite; 3) finger movements are made in the horizontal plane while cursor movement directions are the same but displayed in the vertical plane; 4) finger movements are made in the horizontal plane while cursor movement directions are opposite and displayed in the vertical plane. Performance variables were reaction time (RT), movement time (MT), peak velocity (PV), initial direction error (IDE), path length (PL), and endpoint error (AE). CMI performance between the hands differed, showing a higher IDE and larger PL with the non-dominant hand (both $p<0.001$). In contrast, RT, MT, PV, and AE did not differ between the hands (all $p>0.05$). IDE and PL failed to show a significant effect for the interaction between hands and conditions (all $p>0.05$), suggesting that the decoupling of vision from action is independent from hand used. The present results provide support for the notion that CMI performance differs between the hands. Even though timing variables did not differ between the hands, spatial dominant hand

performance features (i.e., IDE & PL) were superior. Unexpectedly, the level of decoupling did not affect these hand differences. Current research is focused on determining whether the pattern of findings differ between the sexes. Previous studies have shown that females are more efficient than males performing challenging bilateral eye-hand coordination tasks.

Disclosures: B. Jones: None. **A.W. Van Gemmert:** None. **M. Dalecki:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.09/FF17

Topic: D.08. Visual Sensory-motor Processing

Support: Hermann and Lilly Schilling Foundation
DFG FOR 1847GA1475-B4, KA 3726/2-1

Title: Bihemispheric effects on dorsal pulvinar inactivation on saccade and reach representations in parietal cortex

Authors: M. PACHOUD[1], D. ARABALI[1], L. SCHNEIDER[1], M. WILKE[2,1,3], *I. KAGAN[1,3]
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Abstract: Evolutionary history of the thalamic dorsal pulvinar in primates and reciprocal connectivity with frontoparietal cortex suggest its involvement in sensorimotor processing and coordination of eye and hand movements. The neuronal signature and functional significance of pulvinar contribution to sensorimotor regions in the parietal cortex are poorly understood. We performed unilateral reversible pharmacological inactivation of the dorsal pulvinar (medial pulvinar and dorsomedial portion of lateral pulvinar) by injecting the GABA-A agonist THIP, while a monkey performed delayed visually-guided reach (with left or right hand) and saccade tasks. Concurrently, we recorded spiking and local field potential (LFP) activity bihemispherically from the medial or the lateral bank of the intraparietal sulcus (areas MIP and LIP), before and after inactivation. In line with previous results, pulvinar inactivation led to predominantly contralesional hand and spatial impairments such as increased error rates, reaction and movement times, and spatial choice bias. Inactivation effects on individual unit spiking activity in both MIP and LIP showed either enhancement or suppression of firing, in both hemispheres. In many units these effects persisted across several task epochs, and were not strongly affected by hand and space contingencies. On the population level, however, MIP but not LIP in the intact hemisphere contained significantly more units showing post-injection enhancement than suppression. In the two hemispheres, there was an opposite effect on low vs.

high frequency LFP power modulation: delta-theta-alpha strongly increased in the inactivated hemisphere, while high beta [18-30 Hz] and gamma increased in the intact hemisphere. In MIP in the inactivated hemisphere, cue/delay period hand-specific modulations included decrease of beta power for the ipsilesional hand and increase for the contralesional hand, which might be linked to the contralesional hand deficits. Conversely, in the intact hemisphere there was decrease of low beta [13-18 Hz] and alpha mainly for the contralesional hand. In addition, LFP-LFP synchronization (pairwise phase consistency) in theta and alpha bands was up- or down-regulated in hemifield-dependent manner in the inactivated hemisphere, while beta band showed decrease both within the inactivated hemisphere and across the two hemispheres. These results are consistent with the notion that the pulvinar is important for maintaining "alert cortical state". But we also show that the removal of pulvinar drive leads to activity up-regulation in the opposite hemisphere, which might reflect maladaptive or compensatory processes.

Disclosures: M. Pachoud: None. **D. Arabali:** None. **L. Schneider:** None. **M. Wilke:** None. **I. Kagan:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.10/GG1

Topic: E.04. Voluntary Movements

Support: EY-012135

Title: Beta frequency range local field potentials in the parietal reach region reveal mechanisms of bimanual coordination

Authors: *E. F. MOOSHAGIAN[1], C. D. HOLMES[2], L. H. SNYDER[3]
[1]Neurosci., [2]Biomed. Engin., Washington Univ. Sch. of Med., Saint Louis, MO; [3]Dept of Neurosci., Washington Univ. Sch. Med., Saint Louis, MO

Abstract: Primates use their arms in complex ways that frequently require coordination between the two arms. The planning of bimanual movements has not been studied. We recorded from the parietal reach region (PRR) in both hemispheres simultaneously while monkeys planned and then executed unimanual and bimanual reaches. We measured the task information contained in the local field potential (LFP), a population measure that reflects summed synaptic inputs. We show that information about the two limbs is shared across the hemispheres in a frequency and task-specific manner. Compared to baseline coherence, beta band LFP coherence between left and right PRR increases when planning a bimanual reach to a single target and decreases when planning a bimanual reach to two different targets. Coherence in other frequency bands is unchanged. In line with beta band specific coherence modulation, beta band LFP power contains

a rich representation of intended reach movements. In sharp contrast, gamma band LFP power, like the single unit response, encodes only contralateral arm movements. Modeling demonstrates that the observed pattern of beta band power is explained by combining the spike output from the two hemispheres. We conclude that bimanual reach planning involves interhemispheric communication between the left and right posterior parietal cortex. Information about the movements of each arm is shared across the hemispheres, and the shared information is manifest in the beta band of LFP power.

Disclosures: E.F. Mooshagian: None. **C.D. Holmes:** None. **L.H. Snyder:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.11/GG2

Topic: E.04. Voluntary Movements

Title: Effects of symbolic and direct cuing on interference in a bimanual reaching task

Authors: *A. T. BRUNFELDT, P. C. DESROCHERS, A. HAUGHN, F. A. KAGERER
Michigan State Univ., East Lansing, MI

Abstract: Several studies have shown that in bimanual reaching tasks, symbolically cuing targets interferes with coordination more so than direct cuing. In symbolic cuing, movement is initiated after symbols (often letters) appear, indicating the targets toward which the participant must reach. In direct cuing, it is the appearance of the targets themselves that cues movement. While previous studies focus mainly on reaction time or movement amplitude coupling, we assessed the effect of cuing on spatial interference. In our task, we had participants move both hands simultaneously, while one hand experienced a visuomotor perturbation and the contralateral hand moved under kinesthetic control (without visual feedback). We hypothesized that there would be more interference in symbolic cueing compared to direct cueing because there exists a goal-selection conflict that requires movements to be programmed simultaneously for both hands.
Right-handed participants (n=10) performed a bimanual center-out reaching task using a KINARM endpoint robot to two peripheral targets either 90^o or 270^o (distance 10cm). Participants were provided visual feedback of hand position with two cursors, but vision of the hands was occluded. Following a visual baseline, the cursor display of the left hand was removed, and participants were instructed to move to where they thought they would hit the target. The exposure phase consisted of 140 trials with a 40^o rotation in visual feedback for the right hand, while left hand visual feedback remained off. Participants were randomly assigned to either a directly cued or symbolically cued group. In the direct group, movement initiation was cued by target presentation. In the symbolic group, the targets were always visible, but

movement initiation was cued with either the letter “U” or “D” for the 90º and 270º targets respectively. Spatial interference was assessed using initial directional error (IDE) and lateral endpoint error (EPX).
Preliminary results indicate reaction time was substantially longer and more variable in the symbolically cued group compared to the directly cued group. The directly cued group had EPX values greater than zero at the midpoint of exposure, but the symbolically cued group showed greater variance in interference throughout. Contrary to our hypothesis, we did not see increased interference in the symbolically cued group. These results support recent work that suggests coupling is confined to planning stages, and spatial coupling in particular is mitigated when corrections are permitted via online feedback.

Disclosures: A.T. Brunfeldt: None. **P.C. Desrochers:** None. **A. Haughn:** None. **F.A. Kagerer:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.12/GG3

Topic: E.04. Voluntary Movements

Title: Simultaneous visuomotor and kinetic perturbations of one hand and their effects in a bimanual interference task

Authors: *P. C. DESROCHERS, A. T. BRUNFELDT, F. A. KAGERER
Dept. of Kinesiology, Michigan State Univ., East Lansing, MI

Abstract: During complex bimanual movements, the action of one hand can influence the action of the other hand in a process called interference. Interference can be investigated by using a visuomotor perturbation in the right hand and observing directional error in the non-visible left hand. Interestingly, we discovered that when participants instead experience a kinetic perturbation in the right hand, they exhibit limited interference. However, unimanual studies have demonstrated that simultaneous visuomotor and kinetic perturbations show a synergistic motor response, in which the response to both perturbations is greater when the two are combined. Our objective was to investigate the synergy resulting from simultaneous exposure to both a visuomotor and kinetic perturbation and its effect on interference. Twenty participants were randomly assigned to one of four groups: no-perturbation, kinetic perturbation only, visuomotor perturbation only, or combined perturbation. Participants moved two robotic manipulanda simultaneously from two home positions to two targets located 10 cm from the home positions (90° or 270°). Hand position was represented by a cursor on a screen that occluded vision of the hands. Participants performed unperturbed reaches during two blocks of 30 trials. Hand feedback was first displayed for both hands and then removed for the left hand,

requiring participants to rely on kinesthetic control for that hand. In the exposure block of 250 trials, participants were exposed to the perturbation. During the visuomotor perturbation, the cursor representing the right hand was rotated 45° clockwise, such that participants needed to adapt their right hand movement trajectory to hit the target. During the kinetic perturbation, the participants encountered a 25 N per m/s force perpendicular to their movement direction. The combined perturbation group received both perturbations simultaneously, while the control group received no perturbation. Directional interference in the left hand was assessed at the moment of peak velocity, at the end of the initial ballistic movement, and at the end of the reach. Contrary to previous findings and our predictions, preliminary results show that all three perturbation groups demonstrate similar amounts of interference at the end of exposure in the left hand as opposed to controls ($p<.05$). The time course of interference was different between groups. The visuomotor group showed interference immediately after perturbation onset, whereas interference developed more slowly in the combined and kinetic perturbation groups ($p<.05$).

Disclosures: P.C. Desrochers: None. **A.T. Brunfeldt:** None. **F.A. Kagerer:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.13/GG4

Topic: E.05. Brain-Machine Interface

Support: MIUR
H2020MSCA734227-PLATYPUS
Regione Emilia Romagna FSE ob.10B
NHMRC APP1083898
NHMRC APP10821441

Title: Population decoding reveals a rapid transition from visuospatial to hand motor processing in macaque medial parietal area V6A

Authors: *M. FILIPPINI[1], A. MORRIS[2], K. HADJIDIMITRAKIS[2,1], R. BREVEGLIERI[1], P. FATTORI[1]
[1]Univ. of Bologna DIBINEM, Bologna, Italy; [2]Neurosci. Program, Biomedicine Discovery Institute, Dept. of Physiol., Monash Univ., Clayton, Australia

Abstract: Neural prostheses aim to restore motor function in patients with tetraplegia and other mobility impairments. Such patients typically have intact eye movement control and visual function, suggesting that cortical visuospatial signals could be used to guide a robotic arm. Neurons in area V6A mediate sensory-motor transformations and show sensitivity to visual

locations, hand position and movements, and other spatial variables. To study how spatial information is represented at the population level, and its suitability to support a prosthesis for arm movements, we recorded extracellular action potentials from 145 V6A neurons in two macaques while they performed two different tasks: (1) an instructed-delay reaching task, in which the animal maintained fixation on one of nine targets in 3D space and then reached toward the target after a delay, and; (2) a fixation-only task, which was similar except that the animal released a button rather than performing a goal-directed reach. A Maximum Likelihood Estimation decoding algorithm was used to predict the reach/fixation target location in each of the tasks. We first confirmed that target position could be extracted reliably in from the population activity within each task. We then compared these population-level representations across tasks using a generalization approach; that is, we trained a decoder on the spike data from one task and then tested its performance on the data from the other. During the initial fixation and delay epochs, this across-task decoder performance was comparable to its within-task performance (i.e. that observed when the decoder was applied to independent data from the task on which it was trained). This suggests that visuospatial and motor preparation codes were similar during the delay period. The two codes diverged, however, shortly after the cue to execute the required motor response (reach/release). These results show that while V6A signals encode the spatial location and thus are insensitive to the future motor plan during the delay period, they are updated just before the movement execution in an intention/motor-dependent way. Combined, these properties could support prostheses that extract the target of a movement and respond as the intention to move is formed.

Disclosures: M. Filippini: None. **A. Morris:** None. **K. Hadjidimitrakis:** None. **R. Breveglieri:** None. **P. Fattori:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.14/GG5

Topic: E.05. Brain-Machine Interface

Support: Firb 2013 N. RBFR132BKP (MIUR)
Platypus (EU H2020-MSCA-RISE-2016 734227)

Title: Hand movement representation in the monkey medial posterior parietal cortex: A reduction dimensionality approach

Authors: *P. FATTORI, A. BOSCO, R. BREVEGLIERI, M. FILIPPINI, C. GALLETTI
Dept. Biomed. and Neuromotor Sci., Univ. of Bologna, Bologna, Italy

Abstract: Area V6A is a high-order area of the medial posterior parietal cortex involved in reaching and grasping movements in both monkeys and humans and represents a prospective site for implementing brain-machine interfaces (BCI). In fact, the neural activity in V6A is deeply related to the spatial location, to the shape and orientation of the targets of action and to the visual feedback during the movement. The common approach of previous studies on V6A was to correlate these variables with the neural activity of single cells. In the present study, we investigated the encoding of these parameters at population level by a dimensionality reduction method, the demixed principal component analysis (dPCA). dPCA was applied to V6A neuronal activity recorded while the animals executed reaching and grasping movements in light and dark conditions in three different tasks: the *reach direction* task, in which we investigated the effect of visual information and target location; the *wrist orientation* task, in which we assessed the effect of visual information and wrist orientation; the *grip type* task, in which we evaluated the effect of visual information and grip type on neuronal activity. We studied the influence of these parameters on the population activity as percentage of variance captured and we performed a direct comparison of the time course of discrimination ability during the trial and among the three studied tasks. We found that the amount of variance related to *visual information* was similar in the three tasks (29%, reach direction task, 29% wrist orientation task, 22% grip type task). An increasing amount of variance was captured during *wrist orientation* (18%), *grip type* (21%), and *reaching direction* (28%) tasks. Furthermore, we found that V6A activity discriminated the visual condition and the other task parameters in a way that strongly depended on the task requirements, suggesting a flexible encoding of variables not visible applying only single-cell analyses. The dimensionality reduction performed in the present study allowed to extract important features of the population activity in few dimensions. This may be essential for improving computational efficiency in handling massive amounts of neural data for BCI applications.

Disclosures: P. Fattori: None. **A. Bosco:** None. **R. Breveglieri:** None. **M. Filippini:** None. **C. Galletti:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.16/GG7

Topic: I.04. Physiological Methods

Title: Age-dependent performance on pro-point and anti-point tasks

Authors: *E. LI[1], A. B. SERENO[2]
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Abstract: Adolescence is a sensitive period of life where many developmental changes take place. The prefrontal cortex (PFC) is responsible for many of the characteristic behaviors observed during this time. Dysfunction of the PFC is a sign for potential neurophysiological disorders. Using a novel tablet-based pointing task modeled after saccadic technology, this study aims to establish an age-based standard for performance on cognitive tasks in order to track the development of the PFC. Prior studies on development have shown that cognitive functions follow a U-shaped trend with peaks in performance occuring during adolescence. 82 participants were recruited to participate in this study. Results show that cognitive and sensorimotor functions are age dependent with fastest response times found during adolescence. Likely explanations for this finding are natural development of the PFC during adolescence and deterioation during adulthood. Implications of this study are important for understanding age appropriate performance on cognitive and sensorimotor tasks. Results similar to studies measuring development using saccadic technology highlight the efficacy of the practical tablet-based tasks.

Disclosures: E. Li: None. **A.B. Sereno:** None.

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.17/GG8

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC Engage 513272-17
NSERC Discovery RGPIN-2016-04669
Technical support from BKIN Technologies, Ltd.

Title: Age-related developments in motor function and coordination

Authors: *S. C. DOBRI[1], S. H. SCOTT[2], T. DAVIES[1]
[1]Mechanical and Materials Engin., [2]Biomed. and Mol. Sci., Queen's Univ., Kingston, ON, Canada

Abstract: *Background:* Motor control processes coupled with child development are affected by neurological milestones. Quantifying age-specific progress of motor function and coordination in typically developing children can facilitate quantification of differences in pathological populations. The KINARM Exoskeleton has been used to evaluate motor impairments in adults using gamification to engage participants in tasks that test upper-limb motor function and coordination. The objective of this research was to model age-related task performance measures using KINARM tasks to assess the development of motor function and coordination in children and youth. The performance models accounted for participant age, sex, and hand dominance.

Using these models as a basis for comparison with other neurological abilities will enable detailed understanding of neuro-motor control and enhance rehabilitation methods.
Design: Cross-sectional design
Participants: The study was approved by the Health Sciences and Affiliated Hospitals Research Ethics Board (HSREB) (application number 6004951). A total of 207 typically developed youths (age range: 5 – 18 years [mean = 13, SD = 3], 143 males, 64 females) were recruited from Kingston, Ontario. Parental consent was obtained, and assent was provided by the participants.
Methods: Each participant was seated in the KINARM with visual feedback of arm position occluded. Participants were asked to reach towards visual targets as quickly and accurately as possible when the targets appeared. There were 24 reaching trials per arm, and each arm was assessed separately. The reaching task has been designed and validated to assess motor function and coordination.
Results: The reaching task was assessed with 14 different performance measures, some of which included reaction time, maximum hand speed, and initial direction angle of the movement. The median value across all 24 trials was reported for each assessment for each participant. Performance variability tended to be greater for younger participants and decreased with age, while performance improved with age. Ranges of performance at each age (stratified yearly) were developed from which deviations can be used to identify and monitor neurological impairment (including developmental coordination disorder and cerebral palsy).
Conclusions: Age-specific models of healthy performance based on participant age, sex and hand dominance were developed using KINARM data. This database allows clinicians to monitor motor control performance of children, first assisting in the identification of any neurological issues, and secondly providing quantification of rehabilitation outcomes.

Disclosures: S.C. Dobri: 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.; NSERC Engage Grant with BKIN Technologies, Ltd.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BKIN Technologies, Ltd. (technical support). **S.H. Scott:** 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.; Receives grant funding to work with BKIN Technologies.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder and Chief Scientific Officer of BKIN Technologies, Ltd. **T. Davies:** 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.; NSERC Engage Grant with BKIN Technologies, Ltd..

Poster

222. Visual Sensory-Motor Processing: Visually-Guided Reaching and Related Behaviors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 222.18/GG9

Topic: D.08. Visual Sensory-motor Processing

Title: Lower limb representation in the human dorsomedial precuneate cortex

Authors: *S. PITZALIS[1,2], C. SERRA[1,2], S. DI MARCO[1,2], P. FATTORI[3], G. GALATI[2,4], V. SULPIZIO[2,3], C. GALLETTI[3]
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Abstract: Evidence from literature showed that in the macaque monkey the cortex hidden into the parieto-occipital sulcus (POs) contains three functionally and cytoarchitectonically distinct areas: the visual motion area V6, and the visuo-motor reaching areas V6Av and V6Ad, both responsive to arm reaching movements. Anteriorly to the POs, in the medial superior parietal lobule (SPL), two areas showed responses to leg movements, area PEc (Brodmann's area 7) and area PE (Brodmann's area 5). Thanks to wide-field retinotopic mapping and functional tests, V6, V6Av, and V6Ad have been mapped also in the human brain, while little is known about the possible location and functional role of the putative homologue of PEc. Somatotopic representations of the lower limb have been found in the medial part of the primary sensorimotor cortex (S1) and in a region of area 5 likely corresponding to macaque area PE. To date, the functional profile of the several areas representing the leg has never been tested, and the few fMRI studies on this matter showed only partially segregated BOLD signals. In this study, we combined fMRI brain mapping methods and resting-state functional connectivity to functional characterize the human medial parietal and precuneate cortex respect to a visual (optic flow), a visuo-motor (eye/hand/foot pointing) and a motor task (arm and leg movements). We have found a wide pointing selective area in the precuneate cortex, that included one region anterior to the motion area V6+ that was unresponsive to leg movements (like the macaque area V6Ad), and another region in the anterior precuneus responsive to both arm and leg movements and, marginally, to optic flow (like the macaque area PEc). Finally, another region in the medial SPL, between the putative areas PEc and S1, was responsive to leg but not to arm movements (like the macaque area PE). Our findings demonstrate a gradient of functional specialization and cortical connections from the POs to the anterior precuneus, with more posterior regions primarily dedicated to the analysis of visual attributes for spatial orientation and more anterior regions devoted to integrate visual and somatomotor spatial information from both limbs relevant for arm and leg movements. Notably, the functional and connectivity pattern found for the putative human PEc nicely corresponds to the macaque counterpart. It is worthwhile to notice that both

macaque and present data revealed strong connections between PEc and motor and premotor areas that host a representation of the lower limbs, suggesting that along the sensorimotor pathway, PEc might have a specialized role in locomotion and in coordinated movements in the environment.

Disclosures: S. Pitzalis: None. **C. Serra:** None. **S. Di Marco:** None. **P. Fattori:** None. **G. Galati:** None. **V. Sulpizio:** None. **C. Galletti:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.01/GG10

Topic: D.09. Multisensory Integration

Support: Sir Henry Wellcome Postdoctoral Fellowship: 110120/Z/15/Z
Wellcome Trust: 205093
Wellcome Trust: 102264
ERC: 694401
Gatsby Charitable Foundation: GAT3531

Title: Cortical basis of audiovisual spatial localization in mouse

Authors: *P. COEN, M. J. WELLS, D. MYERS-JOSEPH, M. CARANDINI, K. D. HARRIS
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Abstract: The ability to combine visual and auditory cues to localize objects in space is critical to many organisms, whether prey, predator, or pedestrian crossing the street. Neural mechanisms supporting this form of multimodal integration have been found in the Superior Colliculus, but multisensory signals in cortex also appear important. Cortical inactivations in cat perturb performance on audiovisual tasks, but the temporal precision and reversibility of such inactivations were limited by previous techniques.
By using mice to assess the role of cortex in audiovisual integration, we can pair rigorous psychophysics with comprehensive and reversible inactivation across the dorsal surface of cortex. However, recent work suggests that mice do not perform optimal audiovisual integration, displaying unimodal dominance when two cues are presented in conflict, rather than independently combining information from auditory and visual cues (Song et al, 2017). Do mice combine audiovisual cues independently in a spatial context, and do they use cortex to do so?
To answer this question, we modified a two-alternative forced choice task (Burgess et al, 2017), where head-fixed mice turn a wheel to indicate whether a stimulus appeared on the left or right. In our version of the task, the stimuli could be auditory, visual, or a combination of the two, presented in coherent or conflicting locations. Mice typically learned this task in < 10 sessions,

and generalized between multisensory and unisensory conditions without further training. Mice integrated auditory and visual cues appropriately regardless of whether they were coherent or in conflict. In fact, a simple logistic regression model, with weights for each individual auditory and visual stimulus, accurately predicted the performance of mice on all cue combinations. This indicates that mouse audiovisual spatial integration follows the same computational framework as other mammals.
To test the role of cortex in audiovisual integration, we optogenetically inactivated different spots across dorsal cortex on individual trials while mice performed this task. We identified distinct roles for different cortical regions. For example, inactivating V1 specifically perturbed visual, but not auditory, performance. Conversely, unilateral inactivation of secondary motor cortex created behavioral biases which were independent of sensory modality.
Our results demonstrate that mice appropriately combine audiovisual cues to solve a spatial integration task, and that different regions of cortex have distinct roles in this process.

Disclosures: P. Coen: None. **M.J. Wells:** None. **D. Myers-Joseph:** None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.02/GG11

Topic: D.09. Multisensory Integration

Support: NSF Grant 1753915

Title: The impact of visuo-proprioceptive realignment on motor control

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Abstract: Multisensory integration of visual and proprioceptive estimates of hand position gives us flexibility to cope with both environmental and internal changes. For example, a spatial mismatch between visual and proprioceptive representations causes spatial realignment in both modalities, suggesting a change in perceived hand location. However, it is unknown whether such a change affects motor planning with that hand, or if these systems are functionally independent. If multisensory perception and motor control share a common sensorimotor map, then in the absence of performance feedback we would expect visuo-proprioceptive misalignment to cause a systematic change in movements made by that hand. 11 healthy right-handed adults performed a center-out reaching task of 80 trials with a robotic manipulandum (KINARM) in a null field before and after a perceptual learning task. Reaching targets were positioned 10cm from the center “home” position. Importantly, subjects were instructed to move

briskly through the target in a straight path and had no visual cues of the moving (right) hand. Because subjects had no online or endpoint error information, the manipulandum was programmed to stop the subject's hand when they had moved more than 10cm away from the center position. The distance between hand endpoint and target in the Y dimension (forward/backward) was computed. For the perceptual learning task, participants used their unseen left (indicator) hand to indicate a series of perceived targets related to the stationary right (target) hand. The task included 84 trials with visual (V), proprioceptive (P), and visuo-proprioceptive (VP) targets. Participants experienced gradually misaligned VP targets, with the visual component shifting 70mm forward of the proprioceptive component. This perturbation results in the perception that the proprioceptive estimate is further forward than it is, and that the visual estimate is closer to the subject than it is. In other words, the hand is perceived as further away. If this is taken into account in motor planning, then center-out reaches should end closer to the subject relative to before the perceptual task. Indeed, in the dimension of visuo-proprioceptive misalignment, subjects' reach endpoints shifted toward their body by 2.8 ±1.7 mm after perceptual learning. The direction of this change is consistent with our prediction. However, the magnitude is substantially smaller than subjects' mean total perceptual realignment of 47 ± 4.5 mm, suggesting that any impact of visuo-proprioceptive realignment on a common sensorimotor map is not straightforward.

Disclosures: Y. Liu: None. **J. Waran:** None. **H. Block:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.03/GG12

Topic: D.09. Multisensory Integration

Support: NIH Grant R01NS065395
DFG Grant RE 3693/1-1

Title: Face viewing behavior predicts multisensory gain during speech perception

Authors: *J. RENNIG, K. WEGNER-CLEMENS, M. S. BEAUCHAMP
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Abstract: Speech perception is multisensory: visual speech information from the talker's face improves the ability to understand noisy auditory speech. Recent studies have shown substantial interindividual variability in face viewing behavior, with some individuals preferentially fixating the mouth and others the eyes. We speculated that participants with a preference for mouth fixation might form stronger associations between visual and auditory speech, resulting in improved comprehension of noisy speech. To test this idea, eye movements of 33 participants

were recorded with an infrared eye tracker (EyeLink 1000 Plus, SR Research Inc.). In the first task, subjects identified the syllables presented during clear audiovisual speech, an easy task (98% accuracy). Replicating previous studies using this task, there was substantial interindividual variability in the amount of time participants fixated the mouth of the face, ranging from 11% to 99% of total fixation time. Next, we measured eye movements and comprehension during identification of single words presented with high levels of auditory noise, either with or without visual speech. When visual speech was present, all participants primarily fixated the mouth (72% to 100% of total time) and derived substantial benefit, recognizing on average 31% more words than for noisy auditory speech alone. However, there was high interindividual variability, with multisensory gain ranging from 6% to 56%. The benefit of visual speech for each participant was predicted by the eye movements made during the initial task (r = 0.44, p = 0.01) but not by eye movements during the noisy speech task (r = 0.05, p = 0.77), an observation confirmed with Bayesian model comparison. Participants who fixated the mouth when it was not important (during the clear speech task) received more benefit from fixating the mouth when it was important (during the noisy speech task). These findings suggest an unexpected link between eye movement behavior during face viewing and audiovisual speech perception and suggests that individual histories of visual exposure shape human abilities across cognitive domains.

Disclosures: J. Rennig: None. **K. Wegner-Clemens:** None. **M.S. Beauchamp:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.04/GG13

Topic: D.09. Multisensory Integration

Support: NSFC31571084

Title: Neural substrates underlying self-awareness of arm location in macaque monkeys

Authors: *J. LI[1], W. FANG[2], G. QI[1], S. LI[1], P. GUI[1], L. WANG[1]
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Abstract: An accurate representation of the body is fundamental for the self-perception and the interaction with the environment. One powerful experimental tool to investigate it is to induce body illusions where we perceive artificial body parts as belonging to ourselves. However, the mechanisms underlying the self-perception and body illusion in space remain unknown and there is a lack of animal models. Here we used a virtual reality system to manipulate the spatial relationship between the seen (visual) and veridical (proprioceptive) location of arms in both

macaque monkeys and humans, together with a reaching task to measure the "proprioceptive drift", a behavioral correlate of body illusion. Similar to humans, monkeys preferentially integrated visual-proprioceptive information when the disparity between the vision and proprioception was small, but were more apt to segregate the two signals as the disparity became large. The estimation of arm location was also modulated by the prior internal body representation and occurred even at the planning stage of movement. Finally, the dynamics of sensory integration and updating were well represented by the hierarchical Bayesian Causal Inference model. The subjective ratings of the body illusion in humans were faithfully predicted by the posterior probability of common cause. With single-unit recordings, we further demonstrated that the encoding of arm position in macaque premotor neurons indeed follows the schema of vision-proprioception reweighting, in accordance with the degree of owning the virtual arm.

Disclosures: J. Li: None. **W. Fang:** None. **G. Qi:** None. **S. Li:** None. **P. Gui:** None. **L. Wang:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.05/GG14

Topic: D.09. Multisensory Integration

Support: R01 DC013906
R01 DC016363
NDSEG fellowship

Title: Distinct codes as a substrate for causal inference in primate superior colliculus neurons

Authors: *J. T. MOHL, S. TOKDAR, J. M. GROH
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Abstract: Perceptual experience depends on combining information across multiple senses. For instance, auditory and visual information can be combined to produce better estimates of the spatial location of an object or event. However, cues should only be combined when they originate from the same source, and otherwise kept separate. This requires that the brain perform a causal inference in order to correctly combine (or not) multisensory information. It is unknown how and where this inference occurs.
We created a multisensory localization paradigm for primates which requires them to report the location of visual, auditory, and paired cues in both single (integrated) and multiple (segregated) target locations. This behavior was performed while we recorded single unit activity from a multisensory brain region, the superior colliculus (SC). Behavioral modeling shows that

monkeys, like humans, are able to shift between integrating and segregating audio-visual information depending on target separation in a manner consistent with an approximation of optimal causal inference.
Contrary to previous studies that focus primarily on the "integrated" sensory condition, recorded SC neurons rarely illustrated responses in the additive range on combined modality trials. Rather, most responses were best described as winner-take-all of one modality over the other or as switching between visual and auditory responses across individual trials. These results suggest functionally distinct subpopulations, with some neurons representing stimuli as discrete (and separable) while others combine them into a single representation. Interactions between these subpopulations could provide a neural substrate for causal inference seen at the behavioral level.

Disclosures: J.T. Mohl: None. **S. Tokdar:** None. **J.M. Groh:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.06/GG15

Topic: D.09. Multisensory Integration

Support: Knut and Alice Wallenberg Foundation, project grant KAW2014.0051
Swedish Research Council, project grant 542-2014-2350
Kempe Foundation project: JCK-1727

Title: Multisensory integration in a identified parieto-frontal connection in the mouse brain

Authors: *S. SULIS SATO, S. PAPAIOANNOU, A. TRIPATHI, K. ANTOS, P. MEDINI
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Abstract: The information coming from the external world is acquired via the sensory organs and processed in the primary sensory cortices. From there, depending on the modality and psychophysical nature of the stimulus, the information flows through different parieto-frontal (PF) pathways to reach, after several steps of computation, the final output of the brain located in the frontal lobe: the motor cortex. In our study, we focused on a recently characterized in mice PF connection, linking a secondary visual area (area A) to the motor cortex. This visual area has been described as a part of the "dorsal stream". This visual area is still not well characterized, although the highlighted monosynaptic connection with the motor cortex and its role is still under debate because of its lack of a clear retinotopic organization. An important feature of many secondary sensory areas is that they are the place where different sensory modalities are merged and integrated. In particular, some of the posterior parietal areas like RL, are proved to integrate visuo-tactile stimuli. We first wanted to test if the area A similarly to the adjacent RL, responds to tactile and visual stimulation and at which degree the two sensory modalities are integrated.

To do that, we first elucidate the inter-areal anatomical connectivity within this PF stream. We then studied the multisensory features of this brain area by means of wide field calcium imaging in a transgenic mouse model expressing the GCaMP6s calcium sensor in the cortex. After that by using a molecular method to mark selectively the projecting cells, and with an Acousto-Optic Deflector (AOD) based, two-photon microscope, we studied the visuo-tactile response of the projecting cells. Finally, to further investigate the multisensory integration on a dendritic level, we improved a sparse labeling method in order to have only few labeled cells needed to have enough contrast for the dendritic imaging. From the anatomical data we found that this area projects mostly in the secondary motor cortex and that it is wider than the visual area A. The calcium imaging data showed that the projecting neurons have nonlinear multisensory properties, integrating the visual and tactile information. In addition to that we observed that these neurons have low activity compare to the primary sensory cortices, indicating that only a more specific stimulus can activate this stream and/or that the activation of other pathways, as a feedback connection, need to be active at the same time. These data suggest that the tactile and visual information that is sent to the motor cortex via this pathway, is already partially integrated in the posterior parietal cortex.

Disclosures: S. Sulis Sato: None. **S. Papaioannou:** None. **A. Tripathi:** None. **K. Antos:** None. **P. Medini:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.07/GG16

Topic: D.09. Multisensory Integration

Support: Research Grants Council of Hong Kong N_HKUST606/12, 605813 and 16322616
National Basic Research Program of China 2014CB846101
Natural Science Foundation of China 31261160495

Title: Antagonistic cross-links and reciprocal couplings emerge in optimal multisensory integration

Authors: *H. H. WANG[1], W.-H. ZHANG[1,2], M. K. Y. WONG[1], S. WU[3]
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Abstract: Information from multiple modalities is integrated in the brain in a near-optimal way. In self-motion perception, various cortical areas have been identified as multisensory regions tuned to both vestibular and visual signals, potentially forming parallel and partially redundant pathways. However, the neural mechanism and the optimal network architecture underlying

multisensory integration are largely unknown. Based on a decentralized architecture suggested by physiological and theoretical studies, we investigate how multisensory information is encoded in different components of a Bayes-optimal modular network architecture. In this architecture, each module is able to function independently. To achieve inter-modular communication, each module receives direct inputs from other modalities through the cross-links, and indirect inputs from other multisensory modules through reciprocal couplings. The inputs from the lower-order areas are assumed to represent the unisensory likelihoods, and the steady state activity of the multisensory modules are assumed to represent the marginal posterior distributions in the corresponding modalities. We found that the unisensory likelihoods are encoded in the same-channel connections and the multisensory prior information is encoded in the cross-talks in a distributed manner. The most striking discovery is that the feedforward cross-links and the reciprocal couplings form an antagonistic pair. The feedforward cross-links are inhibitory in the short range but excitatory in the long range, serving to cancel out noises and improve integration for cues with moderate disparity, whereas the reciprocal links are excitatory in the short range but inhibitory in the long range, stabilizing a more reliable population activity. Although this antagonistic pattern is primarily found when the two modalities are weakly correlated, it persists for a range of correlation strengths and a variety of correlation structures. The complementary roles played by different types of cross-talks between multisensory areas can be verified in future experiments on the brain.

Disclosures: H.H. Wang: None. **W. Zhang:** None. **M.K.Y. Wong:** None. **S. Wu:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.08/GG17

Topic: D.09. Multisensory Integration

Support: Natural Sciences and Engineering Research Council of Canada
Canada Foundation for Innovation
Ontario Research Fund
JSP KAKENHI (JP17H00753)
Japan Science and Technology Agency CREST (JPMJCR14E4)

Title: Modulation of unimodal vs. multisensory processes at target vs. non-target locations

Authors: *T. LORIA[1], K. TANAKA[3], K. WATANABE[4,2], L. TREMBLAY[2]
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Abstract: Evidence both for and against the hypothesis that attention is required for multisensory integration have been reported in the literature (see Koelewijn et al., 2010 for a review). However, attention is also strongly linked to goal-directed action mechanisms (i.e., Tipper et al., 1992). The current study employed a reaching movement towards a central target to investigate how auditory cues influence the perception of visual cues at a target vs. a non-target location. Preparing an action could facilitate the processing of visual relative to auditory information (e.g., visual dominance), such that auditory cues would be more likely to influence the perception of visual cues at non-target locations. In contrast, preparing a goal-directed action could constrain multisensory processing to the target area, such that auditory cues would be more likely to influence the perception of visual cues at a target location. During a baseline test, three squares were displayed, and no movements were executed. In all trials, two visual flashes (F) were presented in the central square with zero, one, or two auditory beeps (B), which yielded unimodal (2F0B), bimodal congruent (2F2B), and bimodal incongruent (2F1B) conditions. After each trial, the participants reported the number of perceived flashes, which revealed the expected fusion illusion in the 2F1B condition (i.e., Andersen et al., 2004). In the experimental trials, the participant's primary task was to point/ reach towards the central square. At movement onset, the above-mentioned unimodal, bimodal congruent, and bimodal incongruent audio-visual stimuli were presented in one of the three squares. The results showed that accuracy in the perceived number of flashes in the unimodal (2F0B) condition was greater at the central baseline and target vs. the non-target locations, indicating that participants were likely focusing on the central location. In contrast, accuracy in the bimodal congruent (2F2B) condition did not differ between the central baseline, target and non-target locations. Critically, the accuracy in the bimodal incongruent conditions (2F1B) was better (i.e., less fusion illusion) in the non-target relative to the target and baseline central locations. The better unimodal processing at the baseline central and target locations than at the non-target location likely indicate more attention paid to the central square. However, the bimodal incongruent condition results may indicate that multisensory integration mechanisms are influenced by attention. Altogether, attention can facilitate unimodal processing while potentially restricting multisensory integration to a target or attended location.

Disclosures: T. Loria: None. **K. Tanaka:** None. **K. Watanabe:** None. **L. Tremblay:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.09/HH1

Topic: D.09. Multisensory Integration

Support: MSTP Sackler Institute of Graduate Biomedical Sciences Fellowship
NYU Whitehead Fellowship

Whitehall Foundation Award
Sloan Research Fellows Award
Leon Levy Foundation Award
Simons Klingenstein Foundation Award

Title: Function of LEC in shaping task-selective spatial representations in dorsal CA1

Authors: *R. ZEMLA, S. SUNDAR, M. A. DUFOUR, J. BASU
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Abstract: Functional interaction between the entorhinal cortex and hippocampus is necessary for spatial navigation and episodic memory formation and retrieval. Canonically, medial entorhinal cortex (MEC) processes spatial information while lateral entorhinal cortex (LEC) processes non-spatial contextual information. These 'where' and 'what' information streams project to the hippocampus where they are believed to support the formation of long-term representations associating sensory and spatial features of the environment.
Representation of space has been well characterized in the hippocampus through the study of hippocampal place cells and the contribution of MEC - which exhibits spatial tuning in the form of grid and head-direction cells - to place cell formation and stability. However, little is known about how hippocampal spatial representations are influenced by sensory context to support goal-directed navigation. The convergence of spatial and sensory information onto the same population of pyramidal neurons in CA1 suggests that distinct behaviorally-relevant sensory inputs may modulate spatially-dependent activity in CA1. To determine how salient sensory inputs associated with a spatial learning task shape place cell activity, we developed an odor-cued head-fixed spatial navigation behavioral paradigm that we termed odor-cued goal-oriented learning (OCGOL). In this task, an animal is required to discriminate between two odors and navigate to a distinct reward location associated with each odor on a linear track. Using two-photon (2P) imaging of GCaMP6f-expressing CA1 pyramidal neurons during the task, we find the emergence of task selective spatially-tuned neurons (place cells), consistent with previous studies. These task-selective place cells (TSPCs) show spatially-dependent calcium activity at distinct locations on the track depending on which odor-cued reward location the animal is navigating to. We hypothesize that the LEC imparts task selectivity onto otherwise behaviorally unbiased place cell ensembles to support goal-directed navigation. Ongoing studies aim to understand the contribution of LEC during distinct phases of goal-oriented behavior to task performance and place cell assemblies in CA1.

Disclosures: R. Zemla: None. **S. Sundar:** None. **M.A. Dufour:** None. **J. Basu:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.10/HH2

Topic: D.09. Multisensory Integration

Support: NIH Grant R01MH111439

Title: Comparison of functional localizer- with resting state fMRI-based parcellations in the macaque

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Abstract: Understanding the systems level organization of the primate brain involves discovering how function maps onto anatomical structures. Recent advances in the use of resting state functional magnetic resonance imaging (rsfMRI) to divide the brain into meaningful functional regions, or parcels, has provided a powerful method for functional mapping of the whole brain in humans. The current study used these methods to define cortical parcellations for a set of rhesus macaques. For each animal in our population (six rhesus macaques: 3 male / 3 female), we collected 120 mins of resting state data under light anesthesia. The resting state data were used to compute functional connectivity similarity maps, from which we derived individual subject cortical parcellations. To better understand how resting state parcellations compare with task activation, we have collected functional localizers for multiple functional subdomains of the somatosensory cortex including both hands, the right foot, and right lip regions, in each subject in a separate set of anesthetized MRI sessions. The resultant task activation from the somatosensory localizers will allow us to compare the boundaries of the individual subjects resting state parcellations to the estimated boundaries of functional activity. Finally, in a subset of the animals (1 male / 1 female), the subjects were trained for awake neuroimaging sessions, during which they participated in a naturalistic viewing paradigm. Naturalistic viewing sessions require the subjects to watch dynamic visual stimuli, or movies, that contained heterospecific macaques and humans engaged in social interactions. The naturalistic movies have been characterized for a number of low and high level visual features, which allowed us to functionally map regions driven by these visual properties, such as motion and faces. The functional maps from the naturalistic viewing will then be compared with the resting state parcellation, to expand the results of the somatosensory to visual cortex.

Disclosures: B.E. Russ: None. **T. Xu:** None. **A.Y. Falchier:** None. **G.S. Linn:** None. **D.A. Ross:** None. **K. Shannon:** None. **S. Colcombe:** None. **C.E. Schroeder:** None. **M.P. Milham:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.11/HH3

Topic: D.09. Multisensory Integration

Support: NSERC Discovery Grant (to SLP)

Title: Competition of attentional cues varying in strength and modality in the line motion illusion

Authors: *S. L. PRIME, A. J. WICKENHAUSER, A. J. SINCLAIR
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Abstract: The line motion illusion (LMI) refers to the illusory percept of a line presented all at once appearing to shoot away from a preceding visual flash presented at one end of the line. Shimojo et al (1997) showed that the LMI can also be elicited by non-visual stimuli, such as an auditory tone presented from a speaker near one of end of the line. The LMI has been attributed to attention being drawn to the initial cued location (i.e., the flash or tone) thereby producing faster visual processing for the end of the line close to the cue and progressively slower processing for the rest of line extending away from the cue (Hikosaka et al, 1993). Given this, the LMI offers a novel paradigm to examine how stimuli both within and across modalities compete for attention. We were especially interested in testing how auditory and visual stimuli either combine or compete for attention when the cues were spatially congruent or incongruent, respectively. In Experiment 1, we examined unimodal competition in the LMI by presenting either a pair of visual cues or pair of auditory cues simultaneously on opposite ends of the line. Cues differed in signal strength by varying their relative sizes or contrast levels for visual cues and volumes for auditory cues. We found in all unimodal conditions subjects reported the illusory motion as shooting away from the location of the strongest cue (i.e., largest size, greatest contrast, and loudest volume). In Experiment 2, we assessed our subjects' perception of the LMI in the crossmodal condition by presenting auditory and visual cues simultaneously either in the same or opposite ends of the line. Our results showed that in the incongruent condition (auditory and visual cues at opposite locations) subjects reported the illusory motion as shooting away from visual cue significantly more than the auditory cue. The congruent condition (auditory and visual at the same location) yielded a statistically similar LMI effect as that produced by the visual cue in the incongruent condition and by a solitary visual cue in an additional control condition, but a stronger LMI compared to a solitary auditory cue. These results suggest that

spatially congruent audiovisual cues are not combined to facilitate attention, rather attention is driven primarily by the visual cue to produce the LMI. Taken together, our findings clarify the extent to which cue strength and modality compete for the putative capture of the attention in the LMI.

Disclosures: S.L. Prime: None. **A.J. Wickenhauser:** None. **A.J. Sinclair:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.12/HH4

Topic: D.09. Multisensory Integration

Title: Effect of tactile sensory substitution on upper limb proprioceptive error

Authors: G. C. ORTHLIEB, 85287-9709[1], D. SHUMATE, 85287-9709[2], J. C. TANNER[3], *S. I. HELMS TILLERY[4]
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Abstract: A previous study reports that spatial estimation of the hand in two dimensional space is improved with the addition of tactile information delivered to the fingertip. In this study, the effect of fingertip electrotactile and vibrotactile feedback on proprioceptive estimation error are investigated. It is unclear whether vibrotactile and electrotactile sensory substitution will effectively support necessary multisensory integration. Subjects estimated their forefinger positions after a blinded passive movement to a location on a horizontal flat grid. At the target location, subjects received one of four stimuli to the fingertip: null (hover), applied tactile feedback, electrotactile stimulation, or vibrotactile stimulation. In an ANOVA comparison of these conditions, hovering over the grid produced significantly higher error than every other condition. Vibrotactile stimulation reduced error over hover, but not as much as normal touch. Errors under electrotactile stimulation were not significantly worse than contact with the surface, which produced the lowest magnitude of error. A Kolmogorov-Smirnov (KS) test of angle distribution between the conditions yielded statistically similar error vector angle distributions, pointing toward a stable and idiosyncratic proprioceptive error map across all conditions. These results persist across measures of handedness and gender. Statistically, it appears electrotactile stimulation is compariably effective to normal tactile feedback, while vibrotactile stimulation is not. Potentially, the latter activates primarily rapidly adapting mechanoreceptors, while the former would indiscriminately activate local afferents - providing more diverse peripheral “information.” The difference in error magnitude between the two indicates a shift in sensory integration.

Disclosures: G.C. Orthlieb: None. **D. Shumate:** None. **J.C. Tanner:** None. **S.I. Helms Tillery:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.13/HH5

Topic: D.09. Multisensory Integration

Support: SFB/TRR31
Auditory Cognitive Neuroscience

Title: Integration of cross-modal information over time improves auditory gap detection performance

Authors: *A.-K. BAUER[1,2], M. G. BLEICHNER[2], S. BAILLET[3], S. DEBENER[2]
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Abstract: Our sensory systems are continuously receiving many inputs that are often interrelated, so that visible events often precede and cause subsequent sounds. Here, we ask whether visual rhythmic stimulation modulates subsequent auditory cortex activity by reorganising the phase of auditory cortex oscillation. In two independent experiments, using either electroencephalography (EEG; N = 28) or magnetoencephalography (MEG; N = 12) respectively, we investigated the temporal dynamics of cross-modal phase reorganisation by contrasting auditory-only and visual-auditory stimulation conditions in an auditory gap detection task. Listeners were presented with auditory-only (~4.33 s) and visual-auditory stimuli (~7 s) and had to detect short silent gaps that were systematically distributed with respect to the phase of a 3 Hz frequency-modulated tone. In the visual-auditory condition, the visual stimulation consisted of a Gaussian pulsating circle, which preceded the auditory stimulation by ~2 s and was presented either in phase with the auditory tone or anti-phasic. We found that gap detection performance increased for the visual-auditory conditions relative to the auditory-only condition and gap detection accuracies were modulated by stimulus phase. Analysis of the power spectral density revealed spectral peaks at 3 Hz and the 6 Hz harmonic at the sensor level (EEG) and source level (MEG). The subsequent analysis of the inter-trial phase coherence revealed a single peak in the 3 Hz frequency band for both visual and auditory stimulation (EEG & MEG). ERP analysis on the sensor level and source level ERF analysis in the auditory ROI revealed higher amplitudes for detected gaps. Cross-modal spectral analysis revealed enhanced power in the auditory cortex during visual stimulation (MEG), suggesting that the auditory cortex prepares for the upcoming auditory stimulation. The cross-modal temporal dynamics are characterized by a

sharp increase of the stimulus-brain coupling for both the visual and auditory stimulation in the respective visual and auditory regions of interest (MEG). In both studies, we showed that cross-modal phase entrainment leads to enhanced gap detection performance and neural entrainment effects, suggesting that visual rhythmic stimulation has beneficial effects on auditory perception both on a behavioural and neural level.

Disclosures: A. Bauer: None. **M.G. Bleichner:** None. **S. Baillet:** None. **S. Debener:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.14/HH6

Topic: D.09. Multisensory Integration

Support: T32DC005361
R01DC013260
R01EY012925
R00DC014288

Title: Temporal coherence of audio-visual objects in human primary auditory cortex

Authors: *K. H. CHANG[1], R. K. MADDOX[4], A. K. LEE[2], G. M. BOYNTON[3]
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Abstract: We studied the effect of selective attention on audio-visual temporal coherence using functional magnetic resonance imaging (fMRI) in human primary auditory cortex (PAC).
We first characterized subjects' tonotopic and retinotopic organization by measuring population receptive fields (pRFs) within each subjects' auditory cortex. Tonotopic organization was characterized by presenting subjects with randomized pure tone stimuli and modeling the frequency tuning of each fMRI voxel as a 1-dimensional Gaussian in log frequency space (Thomas et al., 2015).
For the attentional scans, we presented subjects with simultaneous binaural auditory streams (325 or 1400 Hz) with orthogonally modulating amplitudes as either a target stream or masker stream. Subjects were instructed to detect fluctuation events (± 1.5 semitone frequency modulation) within the target stream and ignore similar events in the masker stream. A visual disk was presented at fixation that modulated in radius that was temporally coherent with either the target or the masker stream.
We created a linear forward model that predicted the time-course of each voxel's response to a stimulus based on each subjects' pRF maps. We assumed that fMRI responses in the forward model were scaled by two gain parameters that served as "attentional weights" for each auditory

stream. Linear regression was then used to estimate these weights to best predict the fMRI time-courses in the attentional scans.
We found an increase in attentional weighting for the auditory stream that was temporally coherent with the visual disk. We also looked for an interaction effect of attention and temporal coherence such that the effect of attention varied for whether the attended stimulus was temporally coherent with the visual disk.

Disclosures: K.H. Chang: None. **R.K. Maddox:** None. **A.K. Lee:** None. **G.M. Boynton:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.15/HH7

Topic: D.09. Multisensory Integration

Support: This research was supported by the Scientific and Technological Research Council of Turkey (TUBITAK Grant 113K547).

Title: Neural mechanisms underlying auditory time interval effects on perceived visual speed

Authors: *H. KAFALIGONUL[1,2], U. KAYA[1,3]
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Abstract: Concurrent presentation of auditory stimulus alters visual motion perception in many aspects. For example, the time interval demarcated by brief static sounds has been found to modulate the perceived speed of apparent motion (Kafaligonul & Stoner, 2010; Ogulmus et al., 2018). Although these effects of auditory (i.e., static sound) timing have been well studied at the perceptual level, the underlying cortical mechanisms remain largely unknown. In the current study, we focused on understanding when and where auditory timing and time intervals take place for perceived visual speed and attempted at revealing cortical processes underlying such multisensory nature of speed estimation. We acquired both behavioral and EEG (Electroencephalography) data in tandem while participants (n=19) compared the speed of apparent motions presented with different auditory time intervals in succession and random order. Each apparent motion was two flashed bars (50 ms duration) with 1.3 deg spatial displacement and 100 ms inter-stimulus interval. Auditory stimuli were a pair of clicks (20 ms duration) temporally centered with each presentation of apparent motion. In terms of visual stimulation, each consecutive presentation of apparent motion was exactly the same, but the time interval between the static clicks differed. In agreement with the previous studies, we found that the apparent motion with short auditory time interval was perceived to move faster than the one with a long time interval. Also, this perceived speed difference (short vs. long) was increased

when the temporal disparity level between auditory time intervals became higher. Spatiotemporal investigation of the neural activity revealed significant effects of auditory timing and time intervals over medial parieto-occipital and parietal, right centro-parietal, and right frontal scalp sites. Moreover, these significant effects were observed over early (e.g., 150-200 ms) and late (> 300 ms) ERP components. Thus, these results indicate that auditory timing and time intervals can take place at both early and late stages of motion processing. Overall, our findings here suggest the involvement of distinct cortical mechanisms operating at different stages of visual motion processing, and more generally they highlight the multistage and diversified nature of audiovisual temporal processing (Cecere et al., 2017).

Disclosures: H. Kafaligonul: None. **U. Kaya:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.16/HH8

Topic: D.09. Multisensory Integration

Support: NIH Grant T32HL007909
NIH Grant R01NS086859
NIH Grant F31NS093873

Title: Cellular and molecular mechanisms encoding temperature information across temporal scales

Authors: *M. H. ALPERT, D. D. FRANK, M. FLOURAKIS, E. KASPI, A. PARA, M. GALLIO
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Abstract: The ability to detect and respond to rapid temperature changes provides motile organisms with a critical selective advantage and, therefore, may represent one of the most ancient sensory modalities. Temperature readings are relevant on a broad range of time scales, ranging from millisecond to minutes to daily and seasonal rhythms. How are sensory signals on such diverse timescales encoded in the activity of thermosensory circuits, and relayed to different brain region to support appropriate behavioral responses? We study these questions in the relatively simple brain of the fruit fly, *Drosophila melanogaster*. *Drosophila* detect rapid temperature changes using dedicated sensory neurons located in the antenna. Temperature receptor neurons (TRNs) project from the periphery into the brain and target the posterior antennal lobe (PAL), where their activity represents external temperature as a simple sensory map for hot and cold. We recently identified an ensemble of 2nd order thermosensory projection neurons (TPNs) that receive direct synaptic input from TRNs and broadcast temperature

information to higher brain centers. Interestingly, different TPN cell types are characterized by different tuning and adaptation properties, indicating that distinct features of the external stimulus are extracted already at the first central synapse. To better understand the molecular, cellular and circuit mechanisms that make this differential feature extraction possible, we have now systematically characterized the properties of second-order TPNs using 2-photon guided patch clamp electrophysiology followed by RNAseq. Our results show that temperature signals occurring on different timescales are segregated to dedicated relay circuits in the *Drosophila* brain, and demonstrate that unique molecular and cellular mechanisms support a diversity of responses to temperature, impacting behavior on different time scales.

Disclosures: M.H. Alpert: None. **D.D. Frank:** None. **M. Flourakis:** None. **E. Kaspi:** None. **A. Para:** None. **M. Gallio:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.17/HH9

Topic: D.09. Multisensory Integration

Title: A comparison of binocular and binaural summation in unisensory and multisensory perception

Authors: *C. OPOKU-BAAH[1], M. T. WALLACE[2]
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Abstract: Although the auditory and visual systems differ in terms of their structural and functional organization, one shared characteristic is the combination of signals received from two external sense organs (ears and eyes respectively) into a unified, coherent percept. While over two millennia of research have been devoted to investigating the benefits and mechanisms of binocular summation, the study of binaural summation started a few centuries ago and has received relatively little attention. Moreover, only a handful of studies has investigated the similarities between the two mechanisms. To this end, this study aimed at investigating the relationship between binaural and binocular summation using two perceptual tasks: a unisensory (auditory and visual amplitude modulation tasks) and a multisensory (audiovisual temporal order judgment task) task. In order to establish a common ground for comparison across tasks and modalities, binaural (binaural/better ear) and binocular (binocular/better eye) summation ratios for both unisensory (modulation sensitivity) and multisensory (just noticeable difference) tasks were converted into Z-scores. Also, the Z-scores for Interaural (better ear/worse ear) and Interocular (better eye/worse eye) dominance ratios for both unisensory and multisensory tasks were computed. Comparing unisensory and multisensory tasks, we found that subjects who showed binocular and binaural enhancement on the unisensory task showed more improvement

(compared to the mean of the population) on their respective multisensory tasks than those who did not improve. Secondly, across tasks and modalities, dominance ratio Z-scores correlated with Z-scores for summation ratios such that the larger the difference between the performance levels of the two sense organs, the smaller the summation effect. Lastly, there was a significant correlation between binaural and binocular summation Z scores for both unisensory and multisensory tasks. Our results suggest that binaural and binocular summation are related and may share a similar mechanism for combining sensory information.

Disclosures: C. Opoku-Baah: None. **M.T. Wallace:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.18/HH10

Topic: D.09. Multisensory Integration

Title: A large-scale investigation of the temporal binding window in children and adolescents

Authors: *J. CHAN[1], A. TESSARI[2], G. OTTOBONI[2], A. SETTI[1]
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Abstract: The temporal binding window (TBW) is an interval of time whereby input from different stimuli are integrated to form a single percept. It is believed that the TBW exists to take into account the physical transmission times to our sensory organs. It has been demonstrated that the temporal binding window changes with age, with young children having a TBW compared to older children and adults (Hillock-Dunn et al., 2012; Noel et al. 2016). There are a number of empirical methodologies to measure the TBW. These previous studies have used simultaneity judgements or temporal order judgements. In this study, 239 individuals between the ages of 6 to 26 years of age performed a sound-induced flash illusion (SiFI). This is a multisensory illusion where two beeps are presented at a relatively short SOA, accompanied by a single flash. If the SOA between beeps is short than participants will perceived two flashes. The SOAs presented were 70ms, 110ms, 150ms, 190ms, and 230ms. The participant's task was to indicate how many flashes were presented. Using a classification analyses (Support Vector Machine) with a cross-validation, we were able to classify distinct age bands whereby age can be dissociated by SOAs, in particular the longer SOAs. These age bands were: <12 years, 12-16 years, and 17-26 years of age. These results provide additional evidence that TBW is modulated by age. It has been demonstrated that children with developmental disorders exhibit wider temporal binding windows compared to healthy controls. However, in order to use TBW as a diagnostic tool normative values must be established. These results add to our understanding of the developmental trajectory of multisensory integration, with the hope of a future diagnostic tool.

Disclosures: J. Chan: None. **A. Tessari:** None. **G. Ottoboni:** None. **A. Setti:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.19/HH11

Topic: D.09. Multisensory Integration

Support: ERC-STG multsens

Title: What is the role of alpha frequency in visual temporal discrimination?

Authors: *S. BÜRGERS, U. NOPPENEY
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Abstract: Alpha oscillations (~10 Hz) measured over posterior brain regions have been proposed to instantiate perceptual cycles. In line with this notion, a larger temporal integration window and a lower temporal resolution in perception has been observed for a longer alpha wavelength. However, the role of alpha frequency in shaping temporal binding and discrimination remains controversial. Reports across studies vary substantially in i. the frequency range considered, ii. the electroencephalography (EEG) channels or sources where a significant effect is found, and iii. the presence of a significant correlation between temporal discrimination performance and alpha wavelength within subjects, between subjects or both. Moreover, prior research used experimental designs that did not always afford a dissociation of temporal discriminability from perceptual and response biases, limiting their conclusiveness. The present study combined EEG and psychophysics to characterize the relationships between temporal discrimination performance and trial-specific pre-stimulus, or trait individual alpha frequency in the visual system. To account for perceptual and response biases we investigated the role of alpha frequency in visual temporal discrimination using 2 (visual flash: one vs. two) x 3 (auditory beep: zero vs. one vs. two) designs across three experiments. Experiments 1 and 2 factorially manipulated stimulus onset asynchrony (SOA) of the second stimulus in yes-no or two interval forced choice tasks. Experiment 3 adjusted the SOA for each participant in adaptive staircases. Temporal discriminability was quantified as the SOA that corresponded to 50% discrimination performance based on psychometric functions (1, 2) or adaptive staircases (3). Participants' trait alpha peak frequency was estimated from EEG activity during eyes-closed and task performance. Evidence for and against the null hypothesis was quantified in terms of Bayes factors. In contrast to previous reports, Bayes factors provided robust evidence that temporal discriminability was not related to individual alpha peak frequency as obtained from eyes-closed or task related EEG at the sensor or source level. Further, there was no evidence for faster pre-stimulus alpha oscillations to be associated with higher temporal resolution within participants.

Our results challenge current notions of a role of posterior alpha frequency in shaping visual temporal integration or segregation. Further experimental and theoretical research is required to develop a mechanistic understanding of the putative role of alpha oscillations in visual temporal binding.

Disclosures: S. Bürgers: None. **U. Noppeney:** None.

Poster

223. Multisensory Integration: Cross-Modal Processing: Spatial and Temporal Factors

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 223.20/HH12

Topic: D.09. Multisensory Integration

Support: ERC-STG multsens

Title: Resolving audiovisual recalibration in time and space

Authors: *M. ALLER, A. MIHALIK, U. NOPPENEY
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Abstract: Adapting dynamically to changes in the world around us and the sensorium of the body is a fundamental challenge facing the brain throughout lifespan. Changes in our sensorium may result from physical growth during neurodevelopment, presbyacusis or sensory aids. Critically, these changes dramatically alter the sensory cues that guide the brain's construction of spatial representations. In order to maintain auditory and visual spatial maps in co-registration the brain thus needs to recalibrate them dynamically. In experimental settings the spatial ventriloquist aftereffect serves as a prime example for rapid audiovisual (AV) recalibration. It emerges when the brain is exposed to synchronous, yet spatially discrepant auditory and visual signals. Despite much behavioural research into AV recalibration the neural substrates are unclear. We combined psychophysics, functional magnetic resonance imaging (fMRI), electroencephalography (EEG) with multivariate decoding, representational similarity analysis (RSA) and computational modelling to study the ventriloquist aftereffect and characterize how disparate visual signals recalibrate auditory spatial representations. Human participants were presented with unisensory auditory signals before and after adapting to audiovisual spatially conflicting signals. First, we defined the key regions representing auditory space by decoding auditory locations from blood oxygenation-level-dependent (BOLD) response patterns of regions of interest in a fronto-temporo-parietal system. Second, we assessed which of those neural representations were recalibrated by disparate visual signals. Third, we defined the neural dynamics of these spatial representations pre and post-adaptation by decoding spatial locations from EEG topographies. We used RSA to compare the representational spaces obtained from

EEG and fMRI and from the predictions provided by a spatial hemifield model with population rate code. Our results show that auditory space is encoded and recalibrated in a widespread system of regions including Heschl's gyrus (HG), Planum Temporale (PT), parietal and frontal cortices. Critically, after recalibration EEG was able to resolve the evolution of spatial representations in time: while early activity at about 100 ms was associated with spatial representations in HG, later activity at about 250-300 ms was linked with spatial encoding in PT and parietal cortices. Collectively our results demonstrate that audiovisual recalibration induces rapid plastic changes in auditory spatial representations that are formed dynamically in a hierarchy of cortical regions in the human neocortex.

Disclosures: M. Aller: None. **A. Mihalik:** None. **U. Noppeney:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.01/HH13

Topic: E.04. Voluntary Movements

Support: NIH 5T32NS064929
Grossman Center for the Statistics of Mind
Simons Foundation

Title: Neural activity in primate motor cortex during bimanual versus unimanual rhythmic movements

Authors: *K. C. AMES, L. F. ABBOTT, M. M. CHURCHLAND
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Abstract: Motor cortical dynamics have primarily been examined during contralateral movements. However, motor cortex is also active during bimanual and ipsilateral movements. It is therefore imperative to understand the dynamical rules governing neural activity during bimanual movements, and how these responses relate to movements of either arm individually. We trained two monkeys (E, F), to perform bouts of bimanual and unimanual cycling. In blocks, monkeys cycled using the right hand, left hand, both hands with a 0-degree offset, or both hands with a 180-degree offset. There were only small kinematic differences between unimanual and bimanual cycling (e.g., angular velocity was 5% (E) and 17% (F) slower for bimanual cycling). EMG patterns (recorded in one monkey) were also similar regardless of whether the arm moved on its own or with the other arm ($r = 0.91$).
We recorded bilaterally in primary motor cortex (E: 636 units; F: 342 units). Most neurons were active during movements of either arm. However, a neuron's activity during movements of one arm alone was very weakly correlated with its activity during movements of the other arm alone

(E: median r = 0.17; F: r = 0.027). Further, pairs of neurons that were correlated during movement of one arm alone had little tendency to be correlated during movement of the other arm alone. Thus, the population response occupied essentially orthogonal dimensions when cycling with one arm versus the other.
Bimanual neural activity showed both simple and complex relationships with unimanual activity. A substantial portion (but not the entirety) of neurons' bimanual activity could be predicted as a linear combination of their own unimanual activity (E: generalization R^2 = 0.68; F: R^2 = 0.51). Consistent with this, during bimanual movements, activity continued to occupy the two subspaces occupied during unimanual movements. However, the magnitude of activity in those subspaces was reduced, by 31% (E) and 30% (F). For each hemisphere, this effect was larger for the space associated with the ipsilateral arm. That is, a given hemisphere was responsive during movements of both arms, but with a contralateral bias that became stronger when the arms moved together.
In summary, to some degree motor cortex seems to treat bimanual movements as a combination of unimanual movements. However, this was only approximately true. In particular, signals related to the movement of each arm, and especially the ipsilateral arm, became compressed during bimanual cycling. This might potentially reflect basic circuit properties - e.g., divisive normalization - or a property of network dynamics - e.g., suppression of some network modes when others become active.

Disclosures: K.C. Ames: None. **L.F. Abbott:** None. **M.M. Churchland:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.02/HH14

Topic: E.04. Voluntary Movements

Support: National Institute of Dental and Craniofacial Research (NIDCR)-RO1 DE023816.

Title: Movement type dependent beta oscillation bands in primate primary motor cortex

Authors: N. HUH[1], N. G. HATSOPOULOS[2], *K. TAKAHASHI[3]
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Abstract: It is often the case that neural signals recorded from the primary motor cortex (M1) are related to the behavior of the contralateral arm while subjects are making discrete reaching movements. However, humans, and certainly non-human primates, make unimanual or bimanual rhythmic movements. It remains unclear whether such movement types are encoded in the neural activities of M1, particularly how types of movements and laterality of arm used are reflected in

local field potential (LFP), especially in the beta oscillation (15~35 Hz). In order to investigate that, two female monkeys (Macaca mulatta) were trained to reach and grasp one of 8 bars attached a metal wheel with one hand and to pull down to rotate the wheel, and as a new bar approached to the animals, they repeated the same sequence with either arm of their choice at their own pace without getting any specific visual cue. During the task we recorded simultaneously LFPs from MI on the left hemisphere with a Utah microelectrode array and behavior with a CCD camera and reflective markers placed on their arms with a motion capture system. Then we quantified the movements into 6 types: Ipsilateral bimanual (IB), Contralateral bimanual (CB), Ipsilateral unimanual (IU), Contralateral unimanual (CU) rhythmic movements and Ipsilateral discrete (ID) and Contralateral discrete (CD) movements. We aligned the beta signals to the time of hand contact to a bar. Both monkeys exhibited consistent rhythmic movements and unimanual movements were slower than the bimanual rhythmic movements. For ID, beta power decreased around the movement onset and rebounded during power grip while for CD, beta power increased prior to the bar touch onset momentarily (~150 ms) and further increased during the power grip. For IB, beta power was maintained except for a brief period after bar contact, while for CB significant power drops ~100 ms prior to the bar contact for ~100 ms. For IU, beta power was attenuated around250 ms around the touch onset except for a brief increase around 200 ms after the touch, while for CU two brief increases were observed round 50 and 250 ms after the touch onset. Our results suggest that beta power modulates to behavior drastically depending on the types of movements and the side of the effector.

Disclosures: N. Huh: None. **N.G. Hatsopoulos:** None. **K. Takahashi:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.03/HH15

Topic: E.04. Voluntary Movements

Title: Interlimb differences during bimanual aiming after stroke: Effect of target distance

Authors: *R. VARGHESE, J. E. GORDON, C. J. WINSTEIN
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Abstract: Previous studies suggest that when the two hands move towards independent target goals, there is a strong tendency to synchronize movement times (Kelso, 1979). Do the two hands achieve this high degree of temporal synchrony by adopting similar movement trajectories? In this study, we examined the effect of manipulating target distance on movement time and directional error during bimanual aiming movements in non-disabled adults (ND) and chronic stroke survivors. Six right-hand dominant non-disabled young adults and 2 chronic stroke survivors – 1 left- (LHD) and 1 right-hemisphere damaged (RHD) – performed bimanual

aiming movements to two visual targets in a frictionless 2D workspace, without vision of their hands. Visual feedback of hand position was not given during movements, but was available at the end of each trial. Additionally, performance feedback was given in the form of a numeric score. In 5 experimental conditions, target distance was manipulated symmetrically (6-6, 10-10, and 14-14 cm), and then asymmetrically (i.e., 6-10, 6-14 for the right hand, or, 10-6 and 14-6 for the left hand). We quantified movement time (T) and directional error at peak acceleration (DE-PA) and movement end (DE-ME) for the two hands and compared them across conditions in ND and stroke. Compared to ND, both LHD and RHD cases show a significant increase in T, DE-PA, and DE-ME (Wilcox $p < 0.0001$). We summarize and focus here on our findings for ND. First, ***as distance increases symmetrically*** (10-10, 14-14), ND showed a significant increase in T and DE-PA, especially for the farthest target (14-14 compared to 6-6), but only for the right hand ($p < 0.01$). DE-ME did not change across symmetric conditions. Second, for ***asymmetric-right conditions*** (6-10 and 6-14) T was longer for both hands ($p < 0.001$), and DE-PA were smaller but only for the right hand. Again, DE-ME did not change across asymmetric-right conditions. Third, for ***asymmetric-left conditions*** (10-6, 14-6), T was longer only for the left hand. As distance increased, DE-PA were smaller for the left hand, but larger for the right hand. DE-ME was significantly larger for the left hand ($p < 0.001$) but did not change for the right hand. Findings suggest that movement time synchrony is modified by target distance, particularly for the right hand. When present, such temporal synchrony is achieved through different movement trajectories by the two hands, as indicated by interlimb differences in directional error. Directional errors were also modified by target distance, and may provide insight into the locus of movement time asynchronies. Preliminary analyses of stroke cases suggest that bimanual movement deficits may differ between LHD and RHD.

Disclosures: J.E. Gordon: None. **C.J. Winstein:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.04/HH16

Topic: E.04. Voluntary Movements

Support: AHA Grant 16GRNT31010001
FAPESP Fellowship 2016/17126-5

Title: Interlimb facilitation of the speed and frequency of wrist diadochokinesis is scaled to opposite arm force generation

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Abstract: There has been general agreement regarding the role of interhemispheric inhibition (IHI) in facilitating the performance of asymmetrical bimanual patterns of movement (See Reid S.C. and Serrien D.J. 2102, for review). However, such a mechanism must be highly modulated, in order to allow for the broad pattern of bilateral actions required for functional activities. Indeed, Perez and co-workers (Long J. et al., 2016) have recently shown that IHI (sampled through TMS) is inhibited (Interhemispheric Facilitation-IHF), when healthy young participants performed an isometric contraction at greater than or equal to 70% of maximum voluntary isometric contraction (MVIC) of a homologous muscle. We now hypothesize that such interhemispheric facilitation might occur during more general patterns of coordination. We predicted that isometric resistance to finger flexion in one hand should facilitate (increase) the speed at which the other hand performs a repetitive wrist diadochokinesis task in a plane. To test this prediction, participants performed a targeted wrist radial-ulnar deviation task paced by a 1 Hz metronome, while the participants produced an isometric force at 40% and 70% of MVIC with the opposite hand index finger. Two groups of ten right handed participants (age 18-39, mean 24.77± 1.60 SE) performed this task with either the right hand (wrist repetitive motion) while the left hand performed the isometric task, or vice versa. In both cases, the moving hand showed a substantial increase in movement frequency, reflecting an increase in speed and a decrease in duration, with no significant change in movement distance. This speed increase scaled with opposite hand isometric force. It should be noted that the subjects were unaware of the increase in frequency, even though their movements became less-well paced with regard to the
metronome. We tested whether these effects could be attributed to an attentional distraction by having subjects perform the movements while counting backward from 500. However, this condition produced a slowing of the movement, suggesting that distraction did not account for the previous results. These results might be explained by disinhibition of IHI. We suggest that this might result from a dopamine mediated increase in movement "vigor" (Panigrahi B et al., 2015).

Disclosures: J.E. De Araujo: None. **R.L. Sainburg:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.05/DP10/HH17

Topic: E.04. Voluntary Movements

Support: DOC2AMU EU Horizon 2020 Cofund Programme
Marie Skłodowska-Curie Grant Agreement No713750
A*MIDEX No. 11-IDEX-0001-02
Regional Council of Provence- Alpes-Côte d'Azur

Investissements d'Avenir project, French Government

Title: Does the corpus callosum have a role in mediating interlimb transfer of motor learning: Insights from corpus callosal patients

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Abstract: Learning a motor skill can generalize to another scenario involving, for example, a different motor task or a different limb. The generalization of motor learning across limbs, known as interlimb transfer, has been well demonstrated by research on short-term sensorimotor adaptation, yet underlying neural mechanisms remain unclear (Criscimagna-Hemminger et al. 2003; Perez et al. 2007). Amongst the various theoretical models, many of them highlighted the corpus callosum (CC) as a key brain structure mediating interlimb transfer (Taylor and Heilman 1980; Parlow 1989). However, Criscimagna-Hemminger et al. (2003) reported interlimb transfer of force-field adaptation in a split-brain patient with complete commissurotomy. Here we aimed to expand on this research by studying a range of CC pathologies to clarify the role of the CC in interlimb transfer. According to the callosal access model, we hypothesized impaired interlimb transfer in CC patients as compared to healthy controls. After assessing baseline performance in a reaching task, we used a confirmed prismatic perturbation procedure to assess interlimb transfer: participants wore prisms (which deviated the visual field by 17°) while reaching for 100 trials with the dominant arm, before subsequent testing of the unexposed non-dominant arm looked to examine interlimb transfer. Preliminary data indicate normal prismatic adaptation and significant interlimb transfer for one patient with CC agenesis and one patient with CC lesions following a ruptured brain aneurysm. Whilst more controls and patients with CC lesions must be examined, our preliminary findings fall in line with research done by Criscimagna-Hemminger et al. (2003) suggesting adaptation with the dominant arm could generalize to the non-dominant arm through non-callosal connections, potentially ipsilateral corticospinal projections.

Disclosures: P.A. Tilsley: None. **P. Romaiguère:** None. **E. Tramoni:** None. **O. Felician:** None. **F.R. Sarlegna:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.06/II1

Topic: E.04. Voluntary Movements

Support: MRC MR/K023012/1
BBSRC BB/P019757/1

Title: Bilateral organisation in the primate cervical spinal cord

Authors: *D. S. SOTEROPOULOS[1], P. TREBILCOCK[2]
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Abstract: For most everyday movements both hands are used together in a co-operative fashion. In order to carry out such bimanual movements, afferent feedback from each hand needs to be integrated. This integration occurs at multiple levels of the neuraxis, including cortical and subcortical motor areas, but it is unclear if such integration also occurs at the level of the spinal cord for the upper limb. To start addressing this we tested whether spinal interneurones in the cervical cord receive afferent information from both upper limbs.
Extracellular recordings were made through multi-contact probes in the lower (C7-T1) cervical spinal cord (SC) in a terminally anaesthetised adult female macaque monkey. Nerve cuffs were implanted in median and radial nerves at the elbow bilaterally. Spontaneous activity was recorded from multiple interneurones while these different sources were stimulated (single shock biphasic stimulation, up to 3x motor threshold, ~300 stimulus repetitions). The activity of over 80 interneurones was recorded during stimulation and responses were analysed through peri-event time histograms. Significant responses (paired t-test, $p < 0.05$) were detected by comparing the rate during a 10ms post-stimulus epoch with a 10ms pre-stimulus epoch. Mixed afferent stimulation through the ipsilateral nerve cuffs produced a significant response for substantial fraction of SC cells. Over 50% of neurones responded to stimulation of either ipsilateral nerve (39% of cells responded to radial and 40% to median nerve stimulation). Responses were also seen to stimulation of the contralateral upper limb as well. Over one quarter of neurones (28%) responded to stimulation of at least one of the contralateral nerves tested (18% of cells responded to contralateral radial and 17% responded to contralateral median nerve stimulation). For the cells that responded to both ipsilateral and contralateral stimulation (14% of cells), responses to the crossed stimulation had an onset latency that was on average 2.1 ms larger, and this was significantly different (paired t-test, $p < 0.01$).
As this difference is too small to allow for a supraspinal crossover, this suggests that crossed responses are mediated through the spinal commissural system. This highlights the possibility that sensory integration across both upper limbs can also occur at the level of the SC and not just at higher levels of the motor system.

Disclosures: D.S. Soteropoulos: None. **P. Trebilcock:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.07/II2

Topic: E.04. Voluntary Movements

Title: Direct current stimulation-induced desynchronization of the right motor cortex boosts bimanual control in aging

Authors: *A. JAMIL[1], K. CUYPERS[3], M. K. RAND[4], M. A. NITSCHE[2], R. MEESEN[5]
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Abstract: Introduction: Accompanying the natural advancing of age is a decline in cognitive and motor functions, which can significantly impact the daily life activities in the elderly. Such declines may involve altered neuroplasticity, due to changes in synaptic function and neurotransmission. On the other hand, recent work has shown that transcranial direct current stimulation (tDCS), which has been shown to increase excitability and reduce interhemispheric coherence, may be a useful tool to restitute these altered age-related mechanisms, and improve performance of motor skills.
Objectives: Using EEG, the present study first addresses the key question on whether age-related reduction in inhibitory beta oscillations underlie impaired executions in interhemispheric coordinative processes, such as in bimanual control. Second, the study assesses whether performance of complex bimanual motor skills might be enhanced following tDCS.
Methods: Initially, 43 healthy subjects (22 young/21 elderly) were recruited for performing the bimanual tracking task (BTT), a complex task requiring the skilled use of in-phase and anti-phase movements at various frequencies. Three blocks of the task were performed (180 total trials) while EEG was recorded. In a second double-blinded, sham-controlled experiment, another 40 subjects (20 young/20 elderly) were recruited for evaluating whether right M1 anodal tDCS (1.0 mA, 20 min) could improve performance in the task, particularly in the non-dominant left hand.
Results: Overall, younger subjects performed the task more accurately, and also showed higher movement-related beta (13-30 Hz) desynchronization (MRBD) and reduced sensorimotor and visuo-motor connectivity. tDCS improved bimanual control over both groups of subjects, with older subjects having greater gains in performance, especially in control of the non-dominant hand. MRBD and visuo-motor functional connectivity in the elderly also declined after tDCS. Further exploratory analyses showed a stimulation-induced increase in movement speed for elderly subjects, signifying a shift in performance strategy.
Conclusion: Beta oscillations, functional connectivity and inter-limb kinematics underlying

bimanual motor coordination are different between the young and elderly. Further, a single session of tDCS applied to the motor cortex improved bimanual performance in both young and elderly. Although further studies are needed to optimize tDCS parameters for enhanced and prolonged effects, this non-invasive stimulation technique may be a viable tool in restituting and even further optimizing the learning of complex motor functions in the aging population.

Disclosures: A. Jamil: None. **K. Cuypers:** None. **M.K. Rand:** None. **M.A. Nitsche:** None. **R. Meesen:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.08/II3

Topic: E.04. Voluntary Movements

Support: Cluster of Excellence Cognitive Interaction Technology 'CITEC', German Research Foundation (DFG)

Title: Development of visual-proprioceptive integration for hand motor control

Authors: *M. MARTEL, T. HEED
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Abstract: Spatial integration across sensory modalities supports fine-tuned motor control. During movement, both vision and proprioception signal the location of our body parts. Yet, we lack knowledge on how interactions between multisensory integration and motor control develop in humans. In children, some multisensory functions develop over a protracted period, and adult-like weighted integration that yields to optimality principles is not evident until at least 8-10 years of age. At present, it is unclear whether a similar protracted development occurs for the use of multisensory information in motor control.
Here, we investigated the performance of 4-12-year-old children and a control adult group in unimanual and bimanual motor tasks with proprioceptive, visual, and proprioceptive-visual input. Participants operated an apparatus that had two handles that could move in circles. Handle positions could be displayed as cursors on a cover over the workspace. Participants had to symmetrically coordinate circular movements with the two unseen hands (proprioceptive only), or additionally received cursor feedback (proprioceptive-visual). In a third condition, they coordinated one hand with the circular movement of a cursor (visual only). In two further conditions, we tested whether participants could maintain an asymmetrical rhythm (2 circles with one, and 3 with the other hand) when visual feedback was veridical or modified to appear symmetrical.
For all ages, performance was adequate during symmetric coordination when proprioceptive

information was available and was not improved by adding visual information. Yet, accuracy, measured as absolute angle difference between the two hands, decreased with age, suggesting continuous fine-tuning during development. Performance with vision alone was impaired until about age 9, and improved until adult age hereafter. Consistent with previous reports, asymmetric coordination with veridical feedback was impossible for most participants even for adults. When asymmetric hand movements were converted to symmetrical visual feedback, performance improved gradually, starting at about 9. Children aged 11-12 years performed similarly well as adults in the symmetric conditions, but much worse in asymmetric condition. Our results reveal that despite an improvement in visual feedback integration with age, there is a lack of visual-proprioceptive integration in children that contrasts with the dedicated use of vision for motor control in adults. As adult performance was not reached for all conditions even by age 12, the development of multisensory integration for motor control is likely to continue well into adolescence.

Disclosures: M. Martel: None. **T. Heed:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.09/II4

Topic: E.04. Voluntary Movements

Support: a Grant-in-Aid for Young Scientists (18K17894)

Title: Detection of task-relevant and task-irrelevant motion sequence: Application to motor adaptation in goal-directed and whole-body movements

Authors: *K. TAKIYAMA, D. FURUKI
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Abstract: Motor variability is unavoidable in our body movements. The variability has at least two striking features. A feature is suppression of the variability in task-relevant dimension (Scholtz & Schoner, 1999, Todorov & Jordan, 2002, Muller & Sternad, 2003, Cusumano & Cesari, 2006). Another feature of motor variability is embedded in a few number of dimensions (Bizzi+, 1991, Lacquaniti+, 1994). Previous methods were proposed to quantify each feature separately (e.g., Uncontrolled manifold (UCM) can quantify the first feature and principal component analysis (PCA) can quantify the second feature. Few methods thus can simultaneously evaluate the two features. In addition, previous methods have pros and cons; therefore, each method can be applied to a limited range of motion data (e.g., in UCM, it is difficult to consider task function and, in GEM or TNC, it is difficult to consider motion sequence). Here, we propose a simple machine learning technique to quantify the variability in

task-relevant dimension, that in task-irrelevant dimension, and contribution of each principal component to task performance. Our method relies on two procedures; 1) ridge regression (Hoerl+, 1970), a linear regression technique related to PCA and useful in modeling the relation between motion and performance (Furuki & Takiyama, 2017), and 2) decomposition of input data into output-relevant and output-irrelevant dimension. Our method is flexible because it automatically detects linear task function in a data-driven manner, the relevance of each principal component to task performance, and the relevance of motion sequence to task performance. Further, our method does not rely on nonlinearity, which enables to consider different types of movements simultaneously. We applied our method to motion data in our experiments: motor adaptation in goal-directed and whole-body movements. Our experiment utilized two kinds of perturbation; gradually increased perturbation and constant perturbation. First, we clarified that our method can quantify the suppression of the motor variability in task-relevant dimension. Second, we clarified that motor adaptation induces the modulation of motor variability. Interestingly, the schedule of the applied perturbation affected the modulation; gradually increased perturbation increased the variability in task-irrelevant dimension and constant perturbation increased the variability in task-relevant dimension. In summary, we propose a simple machine learning technique that can flexibly quantify features of motor variability. Our method could clarify the modulation of motor variability in motor adaptation.

Disclosures: K. Takiyama: None. **D. Furuki:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.10/II5

Topic: E.04. Voluntary Movements

Support: NIH Grant 1R03NS103006-01

Title: Neuroplasticity and upper limb loss: Predicting and improving functional rehabilitation outcomes

Authors: *B. ALTERMAN[1], L. A. WHEATON[2]
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Abstract: After amputation surgery, there exists a time window during which the fitting of a prosthesis yields higher acceptance rates. As most patients are not able to be fitted within this window, often times, benefit is lost. This study examines interlimb transfer, seeking to evaluate whether a prosthesis training paradigm using the unaffected limb will increase functional outcomes of prosthesis use on the affected limb. Here, healthy, intact participants underwent

three days of prosthesis training on their non-dominant side between testing sessions on their dominant side. Testing sessions consisted of a prescribed number of repetitions of 4 reach, grasp, and manipulation tasks. Training sessions involved 4 different tasks and participants were asked to complete as many repetitions as they could within 8 minutes. Total training time using the non-dominant limb was 96 minutes. A control group performed only a pre-test and follow-up test on day 5 using their dominant side. Kinematic, electroencephalography (EEG), and behavioral measures were collected and analyzed for changes in both quantitative and qualitative movement performance. We hypothesized that participants undergoing interlimb training would show increases in peak movement velocity and reductions in movement variability, as well as increases in bihemispheric coherence measures. Kinematic results found differences in movement variability in the simplest testing task (grasping and transporting a metal disk onto a target plate) from pre- to post-test. Additionally, there was a significant inter-group difference in peak movement velocity and variability, possibly due to the reduced sample size. This work will form the foundation for research in patients with amputation to examine clinically-significant effects of interlimb training in motor rehabilitation.

Disclosures: L.A. Wheaton: None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.11/II6

Topic: E.04. Voluntary Movements

Support: Supported by the Grant GINOP 2.3.2-15-2016-00022.
Laboratory support from Pazmany Peter Cath. Univ and National Institute for Medical Rehabilitation, Hungary

Title: Graph based dimension reduction to discern kinematic synergies in cycling arm movements

Authors: *J. LACZKO[1,2,3], L. BOTZHEIM[1], S. MALIK[2], M. MRAVCSIK[2], S. SZABO[1]
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Abstract: We propose a graph based dimension reduction algorithm to locate 1-dimensional (1D) subspaces in high dimensional kinematic spaces. Finding such subspaces we identify variables which can be controlled by one common control variable. We validate this method by applying it to arm cycling. Able-bodied participants performed cycling arm movements on an ergometer. They grasped the handle and rotated the crank of the ergometer in the sagittal plane. The arm didn't confine to this plane. 16 participants were recruited and each of them made 20

trials. Each trial lasted for 30 seconds. The positions (x, y, z coordinates) of 7 markers on the arm and 1 on the ergometer's handle were recorded (sampl. frequency: 100Hz.). For each trial, the time series of each 24 coordinates gave the input to the algorithm. We computed 24×23/2=276 empirical correlation coefficients and arranged them into a 24 by 24 symmetric matrix C. We considered all the 2 by 2 submatrices of C and computed their determinants. We arranged the resulted values into a 276 by 276 symmetric matrix D. Using D we constructed a graph G. The nodes of G correspond the rows of D. If the entry in the i-th row and j-th column is close to 0, then nodes i and j are adjacent in G. The essential point is that locating a clique in G is equivalent to identifying a group of time series that forms a 1D structure. A clique with k vertices corresponds to k data channels that can be substituted by one reference time series. Each of the k time series is obtained from this reference time course by multiplying it with a scalar. We run this algorithm for each participant's each trial. The largest and most common clique, which was found in 92% of the trials, was a 4-clique. This clique corresponded to the data channels of the y coordinates (upward-downward movement) of 4 markers: on the styloid process of the ulna and of the radius, on the caput of metacarpal of the fifth digit and on the handle of the ergometer. This shows that upward - downward movements of these spatial points have the same time profile. In less trials, but similar results were found for the forward-backward movements of these markers. Although, in the lateral direction their movement were not in phase and didn't relate to a clique with k>1. They were neither in phase with coordinates of markers at the elbow and shoulder. This result was not surprising in arm cycling. The found cliques were associated to that coordinate time series which naturally have the same task specific time profile in this periodic motor task. This is an example of the applicability of our novel method, that offers a research tool to be used on large data sets to discern less obvious kinematic and muscle synergies in neural control of multi-joint movements.

Disclosures: J. Laczko: None. **L. Botzheim:** None. **S. Malik:** None. **M. Mravcsik:** None. **S. Szabo:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.12/II7

Topic: E.04. Voluntary Movements

Support: AHA (American Heart Association) 16GRNT31010001

Title: Sex differences in wrist diodochokinesis

Authors: *G. A. SRINIVASAN[1], R. L. SAINBURG[2]
[1]Kinesiology, Pennsylvania State Univ. Univ. Park, University Park, PA; [2]Penn State Univ., University Pk, PA

Abstract: Previous research has indicated sex differences in the extent to which the human nervous system might be lateralized for different neurobehavioral functions, such as visual spatial analysis (Lejbak, L. et. al., 2011; Voyer, D. et. al. 2017), and language (Shaywitz, S. et. al. 1995). We now examine potential sex differences in motor lateralization. Our laboratory has previously proposed a hypothesis of motor lateralization which attributes predictive coordination of limb dynamics to the dominant hemisphere, and specialization for control limb impedance to the non-dominant hemisphere. Consistent with this hypothesis, we recently showed dominant arm advantages in coordination across multiple muscles for single joint movements. Specifically, radial-ulnar deviation movements of the wrist require coordination between multiple muscles that have moment arms at more than one degree of freedom (coupling) by taking advantage of the redundancy in control of each degree of freedom. Our findings showed that movements performed within the instructed degree of freedom were symmetric between arms, while motions perpendicular to this degree of freedom were substantially asymmetric, with the non-dominant arm showing greater out-of-plane motion, as well as substantially greater circumduction of the wrist. We now exploit this task to examine potential differences in motor lateralization between male and female participants. Each participant performed this radial-ulnar deviation task at 3 instructed frequencies, paced to a metronome (0.5 Hz, 1Hz, and 2 Hz) with each hand. Our findings revealed a main effect of sex and a main effect of instructed frequency on out-of-task motion. However, we did not find an interaction between sex and hand, indicating that females and males do not show differences in motor lateralization for this task. Instead, males showed a substantial advantage in performance across frequencies, regardless of hand. Previous literature in human and non-human primates has suggested an evolutionary bias which favors male performance in overhand throwing behaviors (Watson, N.V. 2001). However, it has been difficult to untangle the influence of nature vs nurture by examining throwing, which is more often practiced by male primates. Similar to throwing, our task requires precise coordination across many muscles to account for the moment arms of muscles across multiple degrees of freedom; yet is not part of the repertoire of daily activities in either males or females. Our findings suggest an overall male advantage for coordination of mechanically coupled effectors, which might reflect a male bias associated with the evolution of throwing behaviors.

Disclosures: G.A. Srinivasan: None. **R.L. Sainburg:** None.

Poster

224. Voluntary Movements: Interlimb and Bimanual Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 224.13/II8

Topic: E.04. Voluntary Movements

Support: AHA (American Heart Association) #16GRNT31010001

Title: Isometric force generation in one hand facilitates long latency, but not short latency reflexes in the opposite wrist

Authors: *J. SCHAFFER[1], R. L. SAINBURG[2]
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Abstract: Although interhemispheric inhibition via transcallosal pathways is a well-known phenomenon, recent studies have found that when forces exceed approximately 70% of MVC, these interhemispheric interactions can result in increased cortical excitability in the opposite hemisphere (Perez and Cohen, 2008; Long et al., 2016). A recent study from our lab showed that when participants resisted a strong force at the finger of one arm, vigor (speed and frequency) of rhythmic radial-ulnar deviation movements in the contralateral arm increased, and this effect scaled with isometric force generated by the opposite arm. We now ask if the mechanisms mediating this increase in movement vigor are reflected in spinal and supraspinal reflexes. We examined this question using a perturbation task, in which participants were instructed to hold the position of their left wrists against a background flexor load, and on random trials a perturbation was applied to the wrist, eliciting a stretch reflex of the wrist flexors. Similar to the previous experiment, the contralateral force condition required participants to exert isometric force with their right index finger for the entirety of the trial. In a baseline condition required, the right arm did not exert force. EMG activity of the flexor and extensor carpi muscles of the left forearm was recorded and separated into intervals short-latency (M1: 20-45 ms post-perturbation) and long-latency (M2: 45-75 ms) intervals. We compared activity in these intervals to see if the contralateral force of the right arm altered the reflex response of the left arm. Our preliminary results suggest an interaction between contralateral force condition and reflex interval for the flexors, such that the M2 interval showed increased activity in the contralateral force condition compared to baseline, but M1 did not. This indicates a cortical, but not a spinal facilitation from contralateral isometric force generation, and may be related to inhibition of intercortical inhibition reported previously by Perez and Cohen (2008), and Long et al. (2016).

Disclosures: J. Schaffer: None. **R.L. Sainburg:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.01/II9

Topic: E.05. Brain-Machine Interface

Support: NIH Grant NS095123

Title: A Hebbian framework for predicting modulation of synaptic plasticity with tDCS

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Abstract: Transcranial direct current stimulation (tDCS) has recently received attention for its ability to modulate brain function and potentially improve treatments for brain disorders. To date, little is known about how the effects of stimulation at the cellular level translate into changes in cognitive function, particularly long-term changes that outlast stimulation. A common hypothesis is that tDCS alters synaptic plasticity. Indeed, DCS can modulate synaptic plasticity in brain slices and studies in humans have demonstrated effects that resemble canonical synaptic plasticity. However the magnitude, direction, and spatial distribution of the resulting plasticity is not immediately obvious. For example DCS can have opposite effects on synaptic plasticity within a single pyramidal neuron, depending on the dendritic location and temporal pattern of synaptic activity. The often held assumption that one polarity of DC stimulation will boost plasticity while the other inhibits is therefore likely to be an oversimplification that requires refinement. We argue that tDCS generates subtle alterations of endogenous membrane voltage dynamics, which are then stored via endogenous Hebbian synaptic plasticity. One implication of this mechanism is that tDCS effects should exhibit similar characteristics to the Hebbian plasticity, with which it is paired. Moreover, like Hebbian plasticity, tDCS effects should depend heavily on the pattern of underlying synaptic activity. Specifically, we propose that tDCS effects should depend on brain neuromodulatory state, the spatiotemporal distribution of synaptic inputs, and the orientation of the tDCS electric field with respect to neuronal morphology. Here we show with hippocampal brain slice experiments that indeed DC stimulation in vitro (DCS) modulates Hebbian plasticity according to this framework, and that the effects of DCS exhibit canonical Hebbian properties of associativity and specificity. We characterize the interaction between DCS and various synaptic input patterns, and discover input patterns that amplify the magnitude of DCS effects. These experiments are then used to constrain a parsimonious computational model that is equipped with a commonly used voltage-based Hebbian plasticity rule. The model captures a wealth of long term DCS effects. It further generates specific predictions for pairings of brain state and tDCS dosage that may be most effective at modulating synaptic plasticity and conditions under which this type of modulation may be functionally beneficial or detrimental.

Disclosures: G. Kronberg: None. **A. Rahman:** None. **M. Bikson:** None. **L.C. Parra:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.02/II10

Topic: E.05. Brain-Machine Interface

Support: AHA National Innovative Research Grant 16IRG26960017

Title: Embodiment improves performance on an immersive brain computer interface in head-mounted virtual reality

Authors: *J. M. ANGLIN[1], R. SPICER[2], D. SALDANA[1], C. FINNEGAN[1], S. LEFEBVRE[1], K. JANN[3], T. D. ARD[3], E. SANTARNECCHI[4], D. M. KRUM[2], S.-L. LIEW[1]
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Abstract: Brain computer interfaces (BCI) for severe stroke motor rehabilitation aim to 'close the loop' between attempted motor commands and sensory feedback by providing supplemental sensory information when individuals successfully establish specific brain patterns. However, previous stroke BCIs have typically employed feedback techniques with minimal biological relevance, making them difficult and unintuitive to control. Here, we created a novel BCI that provides neurofeedback in virtual reality using a head-mounted display (HMD-VR), which harnesses principles of immersion and embodiment to provide biologically-engaging neurofeedback. The purpose of this experiment was to examine whether this neurofeedback in HMD-VR improves BCI performance compared the same neurofeedback presented on a normal computer screen. Twelve healthy adults were asked to control a virtual arm by imagining right hand movement, which was measured via electroencephalography (EEG) as desynchronized sensorimotor rhythms (8-30Hz) in the left motor cortex. Subjects performed two blocks of 30 trials, one for each condition (Screen, HMD-VR), counterbalanced across participants. The neurofeedback consisted of a virtual arm that moved towards or away from different targets based on the real-time EEG activity (e.g., great desynchronization moved the arm towards the target). After completing each block, participants were asked questions relating to their sense of presence and embodiment in each environment. We found that, while participants showed similar performance on the BCI when performing the task in either environment ($t(22) = -0.47$, $p = 0.642$), there was an interesting positive correlation between performance and reported levels of presence and embodiment only in the HMD-VR environment. Specifically, participants had more control over the virtual arm in HMD-VR when they reported higher levels of realism ($r_s = 0.58$, $p = 0.046$) and spatial embodiment ($r_s = 0.66$, $p = 0.02$). Furthermore, participants reported higher levels of spatial embodiment ($t(22) = -2.12$, $p = 0.045$) in the HMD-VR environment compared to the computer screen. These results suggest that the HMD-VR environment is capable of increasing levels of embodiment compared to a normal screen environment, and that increased levels of presence and embodiment may improve performance uniquely in the HMD-VR environment. Future work will examine the effects of this HMD-VR BCI on motor rehabilitation in a stroke population.

Disclosures: J.M. Anglin: None. **R. Spicer:** None. **D. Saldana:** None. **C. Finnegan:** None. **S. Lefebvre:** None. **K. Jann:** None. **T.D. Ard:** None. **E. Santarnecchi:** None. **D.M. Krum:** None. **S. Liew:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.03/II11

Topic: E.05. Brain-Machine Interface

Title: Intermuscular coherence in adult stroke subjects

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Abstract: We are investigating the use of inter-muscular coherence for the control of neural prostheses. We previously showed that normal subjects are able to use a secondary frequency when electrical stimulation is applied at a frequency at which they showed intermuscular coherence. The purpose of the study was to determine if adults with a prior history of a stroke were able to also show a change in frequency. 15 adult subjects with a previous stroke were recruited. We tested the hemiplegic arm (9 left, 6 right). Subjects performed an isometric contraction, as previously described. Baseline intermuscular coherence was recorded in the absence of stimulation. The peak frequency was calculated. Electrical stimulation at 2 times motor threshold was applied at 1/10 of the peak frequency, and the peak frequency. There was no statistical difference between left and right arms and so these were combined for analysis. As with control subjects we found that subjects showed no change in peak frequency of intermuscular coherence when stimulation was applied at the low frequency. When stimulation was applied at the peak frequency of the intermuscular coherence a 2nd frequency was present in the coherence spectra. This was close to the original frequency, but clearly distinct in the spectra. The study showed that the alteration in coherence spectra in stroke subjects is similar to that seen in control subjects. For control of neural prostheses we think that physiological control, such as that derived from EMG, might promote neurological recovery. Intermuscular coherence offers advantages over time-domain analysis in this setting because of the constraints of the stimulus artefacts in the frequency domain. This study shows that intermuscular coherence may be a good control signal for the prosthesis.

Disclosures: J.A. Norton: None. **S. Haughian:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.04/II12

Topic: E.05. Brain-Machine Interface

Support: NSF Grant 1137172

Title: Accuracy of arm position sense and EEG contingent negative variation potential in blind and sighted people during arm position matching in joint and external space

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Abstract: Visual experience is known to contribute to the formation of the arm spatial sense (Thinus-Blanc, Gaunet 1997) via shaping the body schema that contributes to arm localization in the extrapersonal space (Longo, Haggard, 2010). Specifically, arm position sense may arise from the mapping of joint based, proprioceptive and tactile information onto visual information of arm location in extrapersonal space (Crollen, Collignon 2012). Visual information therefore calibrates joint-based sensory information to the extrapersonal space (Shadmehr and Wise, 2005). As such, a history of no prior visual information, common in long-term visually impaired individuals, could ultimately result in a poor mapping of joint-based information onto the extrapersonal space. Thus, it might take more cognitive effort, and with higher errors, for the visually impaired to perform coordinate transformations from the joint to external space when compared to normally sighted subjects with an imposed loss in immediate visual information. We tested this hypothesis using concurrent 64 channel EEG and kinematic assessments derived from the KINARM robot. We utilized the Contingent Negative Variation EEG potential (CNV) as an indicator of cognitive motor load (Walter et al. 1964). Our study involved 11 normally sighted subjects and 7 visually impaired subjects, all right-handed. All subjects performed 3 arm matching tasks in block design. The three tasks were: (1) joint angle matching (JAM) wherein the subject was instructed to match the final joint configurations of the right arm (in joint coordinates); (2) hand mirror direction and distance matching (MDDM) wherein the subject was instructed to mirror match the distance and direction their right hand moved in external space coordinates; and (3) hand direction and distance matching (DDM) wherein the subject was instructed to match both the distance and direction their right arm moved in external space coordinates. The JAM and MDDM tasks were kinematically identical though instructions for JAM and MDDM were in joint-angle space and extrapersonal space, respectively. The DDM task was kinematically different from the JAM and MDDM. Both groups of subjects demonstrated lower accuracy in the DDM task. The blind group had a larger CNV potential in

the DDM task than in other tasks, whereas no difference in CNV potential between tasks was observed in the sighted group. Our preliminary results support our hypothesis that visual experience contributes to accuracy of arm position sense as coordinate transformations from the joint to external space required greater cognitive motor effort in the blind than sighted individuals, with higher kinematic errors.

Disclosures: K. Oh: None. **N. Natraj:** None. **J.T. Johnson:** None. **L.A. Wheaton:** None. **B.I. Prilutsky:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.05/II13

Topic: E.05. Brain-Machine Interface

Support: BMBF

Title: Expanding and exploring the parameter space of physiological effects of anodal direct current stimulation in the primary motor cortex

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Abstract: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which induces long-lasting neuroplastic changes in the brain. Clinical research involving tDCS in different neuropsychiatric disorders has revealed encouraging results; however, knowledge about optimally suited protocols is missing. This is especially relevant, since non-linear relations between stimulation parameters and physiological effects have been observed. In this study, we systematically explored the parameter space of tDCS regarding stimulation duration and intensity in 16 healthy young adults. Anodal tDCS was applied in three different intensities - 1, 2, and 3mA, for durations of 15, 20 or 30 minutes, and after-effects of stimulation were monitored with TMS-induced motor evoked potentials (MEP) up to the evening of the next day. All intensities of stimulation showed enhanced cortical excitability within most of the first two hour time period post stimulation. For 1mA intensity domain, only 1mA-15min, and 1mA-20min conditions showed significant cortical excitability within the first 30 minutes post stimulation. 2mA-20min was the only condition of 2mA intensity that showed significantly long-lasting after-effects that lasted until the evening of the same day of stimulation. For the 3mA, all durations resulted in significant excitability enhancement mostly outlasting the first two

hours post-stimulation. Stimulation for 20 minutes with all intensities produced more prominent excitability alteration, lasting for more than 2 hours after stimulation. 3mA stimulation for 20 min produced the largest excitability alteration, and lasted until same day evening after tDCS. We conclude that tDCS effects critically depend on intensity and duration of the intervention, and that the effects of increasing respective parameters are not strictly linear. These results thus help to define optimal tDCS intervention protocols.

Disclosures: D. Agboada: None. **M.M. Samani:** None. **M. Kuo:** None. **M.A. Nitsche:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.06/II14

Topic: E.05. Brain-Machine Interface

Support: New Century Scholars Research Grant, American Speech-Language-Hearing Foundation (PI: J. Brumberg)
IMSD NIH R25GM62232

Title: Decoding the neural substrates of intent to speak

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Abstract: In this study we used an artificial neural network (ANN) brain-computer interface (BCI) to decode both the intent and complexity of speech from electroencephalogram (EEG) data. Specifically, we used the contingent negative variation (CNV) and preparatory alpha waves. The CNV is a brain wave that is elicited in anticipation of a motor command like speaking (indicating intent to speak), while alpha waves are generally related to level of attentiveness and effort (perhaps indicating difficulty / complexity of the word), and may be further implicated in inhibition of competing alternatives during cognitive planning. We defined 9 levels of complexity via 3 levels of increasing syllable structure by 3 levels of word frequency in American English. Healthy participants saw the stimulus word (S1) presented in white for 3 seconds and then color coded to green/red (S2) indicating to speak/not speak the word. Each word appeared throughout the experiment in both a “speak” and “don’t speak” condition in randomized order. The ANN was trained on this data from healthy participants to then decode, or predict, when participants had intent to speak and what level of word complexity the stimulus had from brain activity alone. We found that while the CNV is indicative of intent to speak, Alpha waves may be more useful for decoding word complexity. When applied to existing BCI’s

for communication, we hope this will speed up the process of communication by separating decoding of speech intention from speech content.

Disclosures: B. Marsh: None. **J. Kidwai:** None. **J.S. Brumberg:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.07/II15

Topic: E.05. Brain-Machine Interface

Title: Recurrent neural network approach in predicting joint angles from electroencephalography

Authors: *S. NAKAGOME[1], T. P. LUU[2], Y. HE[1], J. L. CONTRERAS-VIDAL, Ph.D.[2]
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Abstract: Neural decoding is a fundamental component of Brain Computer Interface (BCI) that connects intentions from the brain to the external devices. Increasing the neural decoding accuracy is important because it leads to the higher usability of the interface (both continuous and discrete decoding). This is particularly challenging in a continuous sequential decoding where time series of data have to be predicted in sequence or real-time. Previous studies utilized linear decoders such as Wiener filter and Kalman filter. Later, this was extended to non-linear filters such as Extended Kalman Filter and Unscented Kalman Filter (UKF). However, the ideal performance is yet to be reached by the decoders. Recent advances in deep learning have enabled accurate prediction in not only image classification, but also in sequential data such as time series. Recurrent neural network (RNN) is one of the most fundamental deep learning algorithm in this realm. Here, we used Long-Short Term Memory (LSTM), an extended version of the recurrent neural network (RNN), in decoding joint angles of the lower limb offline using electroencephalography (EEG) signals. The architecture consists of 2 LSTM networks with 32 hidden units on each layer and then connected with a batch normalization layer and a fully connected layer. Adam optimization was used with a learning rate of 0.001 with default parameters. Data from 8 subjects with 64ch active EEG electrodes and goniometers to measure joint angles (hip, knee, and ankle) were utilized for training. Subjects walked on a treadmill for approximately 20 mins with data recorded at 100 Hz in a trial. Three trials per subject were used to train the model and test the performance. EEG signals were first processed by the removal of peripheral channels, followed by the rejection of eye-related artifact using H-infinity filter, and bandpass filtering to delta band (0.1 - 3 Hz). The performance was compared against UKF algorithm which was used in the same dataset in prior publications. LSTM outperformed UKF in preliminary research improving the Pearson's correlation values of more than 0.2 in average, showing significant improvement with $p < 0.01$ using Kruskal-Wallis test. The mean squared error between normalized the measured joint angle and the predicted joint angle was also

calculated and LSTM based model showed smaller errors compared to the UKF (LSTM: 0.0336, UKF: 0.0767).

Disclosures: S. Nakagome: None. **T.P. Luu:** None. **Y. He:** None. **J.L. Contreras-Vidal:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.08/II16

Topic: E.05. Brain-Machine Interface

Support: IITP grant funded by the Korea government (No. 2017-0-00451)

Title: Correlation between event-related desynchronization and motor imagery brain-computer interface performance

Authors: *M. KWON[1], H. CHO[2], S. LEE[1], K. WON[1], M. AHN[3], S. C. JUN[1]
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Abstract: Motor imagery brain-computer interface (BCI) is communication pathway between external devices and neurophysiological signals during limb movement imagination without real movements, so the technique is very useful to the locked-in amyotrophic lateral sclerosis patients who cannot move their limbs without other's help. The representative feature of EEG-based system is event-related desynchronization (ERD) or synchronization (ERS). Many neuroscience studies have reported that ERD is showed in contralateral sensorimotor area during motor imagination, however, some researchers have informed larger inter-subject variations of brain activities for motor imagery tasks. These reports doubt sensorimotor ERD is closely correlated to classification accuracy with common spatial patterns (CSP) for feature extraction. In this study, we investigated the correlation between sensorimotor ERD and classification accuracy based on various ERD phenomena.
Nine healthy volunteers (2 females, age 26.6 ± 2.1 years) participated in multiple sessions, a total of 22 sessions were collected using 64 EEG sensors. Subjects were instructed motor imagination one of three pairs - left/right hand, left hand/feet, and right hand/feet - for 3 s after relaxation for 2 s. The data were band-pass filtered 8 - 30 Hz, and selected 28 channels that are covered sensorimotor area. We calculated contralateral, ipsilateral ERD during imagination, and contralateral ERS after imagination as various ERD features, also calculated classification accuracy using CSP and Fisher's linear discriminant analysis. After that, correlation values were obtained from Pearson's correlation analysis.
Regression p-value of correlation between contralateral ERD and classification performance is 0.004, but most of the data were displayed -40 to 0 % of contralateral ERD. Therefore, simple

ERD value does not indicate classification accuracy. Second characteristic is difference of contralateral ERD during imagination and ERS after imagination, in that case, we cannot find trend from correlation analysis (p-value: 0.161). Last correlation analysis was used difference of contralateral and ipsilateral ERD during imagination. The feature was most related to performance (p-value: 0.006), but it is difficult that the values indicate classification accuracy because many data were concentrated at 0.
From these results, characteristics of ERD during motor imagination may not well estimate motor imagery BCI performance because of inter-subject variations. Therefore, multivariate spatial patterns may consider to estimate motor imagery performance.

Disclosures: M. Kwon: None. **H. Cho:** None. **S. Lee:** None. **K. Won:** None. **M. Ahn:** None. **S.C. Jun:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.09/II17

Topic: E.05. Brain-Machine Interface

Support: This work was supported by Institute for Information & Communication Technology Promotion (IITP) grant funded by the Korea government (No. 2017-0-00451).

Title: Relationship between RSVP task EEG features and P300 speller performance

Authors: *K. WON[1], M. KWON[1], S. JANG[1], M. AHN[2], S. C. JUN[1]
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Abstract: Brain-computer interface (BCI) has benefited people who need to operate machines and computers without physical movements by providing a new communication tool using brain activity. BCIs can be divided into several types depending on the characteristics used, and the performance prediction research has been conducted for deeper understanding of the specific BCI mechanism. A previous study found the positive correlation between the rapid serial visual presentation (RSVP) T1% (the behavioral score) and P300 speller performance, and it motivated us to investigate the RSVP task further by inspecting EEG features and compare the correlation with the speller performance. Since RSVP task and P300 speller share the same properties, we expected that RSVP task ERP may also be associated with speller performance.
A total of 55 healthy subjects participated in the experiment, and 50 subject data were used for the analysis. EEG data were collected during a RSVP task and P300 speller. Temporal attention abilities and event-related potential (ERP) features were computed in the RSVP task. RSVP T1% was defined as the temporal attention abilities corresponding to the accuracy of identifying the

pre-defined target among character streams. To compute RSVP task ERP properties, the channel averaged waveform (Fz, Cz, Pz, CP1, and CP2) was selected. The P300 speller performance is defined as the single trial classification accuracy, determining target and non-target, assessed by 10-fold cross validation.
There was a significant positive correlation between RSVP T1% and speller performance as found in the previous study ($r=0.32$, $p<0.05$). In addition, we found a significant positive relationship between P300 amplitude in RSVP and speller performance ($r=0.37$, $p<0.01$). On the other hand, P300 latency in RSVP and speller performance had a negative relation (but not significant $r=-0.25$, $p=0.08$). Regression analysis was used to compare predictability of RSVP T1% and P300 amplitude on speller performance. RSVP T1% yielded an $F=5.53$ ($p<0.05$, $B=0.71$) and P300 amplitude in RSVP yielded an $F=7.83$ ($p<0.05$, $B=0.82$).
The purpose of this study was to find additional correlates of the speller performance in RSVP EEG features. We found that P300 amplitude and P300 latency (but not significant) in RSVP correlated with the speller performance. In addition, RSVP EEG feature showed better correlation than RSVP T1%, so instead of using a single feature to predict the speller performance, we may consider using both the RSVP T1% and EEG features. For the further study, it may be worth investigating whether the advanced predictor combining multiple correlates can enhance the correlation.

Disclosures: K. Won: None. **M. Kwon:** None. **S. Jang:** None. **M. Ahn:** None. **S.C. Jun:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.10/II18

Topic: E.05. Brain-Machine Interface

Support: Deutsche Forschungsgemeinschaft (DFG, BI 195/77-1)
The European Commission (EU) LUMINOUS-H2020-FETOPEN-2014-2015-RIA (686764)
German Ministry of Education and Research (BMBF) 16SV7701 CoMiCon
WYSS Center of Bio and Neuroengineering, Geneva, Switzerland

Title: Brain-computer-interface (bci) based communication in completely locked-in (clis) patients: Replication and extension

Authors: *N. BIRBAUMER[1,2], A. RANA[2], A. TONIN[2], M. KHALILI[2], A. JARAMILLO GONZALEZ[2], S. PATHAK[3], U. CHAUDHARY[2]
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Abstract: Using an auditory Near Infrared Spectroscopy (NIRS) based BCI we reported stable yes-no brain communication to short questions with an average of 70% correct answers in 4 completely paralysed locked-in patients suffering from Amyotrophic Lateral Sclerosis (ALS) (Gallegos-Ayala et al 2014, Chaudhary et al 2017). Simultaneous recordings of vertical and horizontal eye movements (EOG) over more than a year observation period excluded any motor contribution to the brain communication performance. Here we report a re-analysis of the data previously published (Chaudhary et al 2017) by using filters for very low frequencies (below 0.18 Hz of the slow oxygenation changes at 8 head positions over multiple sessions and General Linear Modeling of the wavelet coherence transformation of oxygenation of all channels (comparable to fMRI responses) during the 10 sec yes or no thinking answering period. These off-line analyses demonstrated improved BCI performance above 70% correct answers to questions with a known answer significant over most sessions spanning a whole year with many sessions. Open questions answering performance was judged by the relatives as above 90% correct. Improved performance to open questions may be a consequence of increased attentional focus to these more relevant questions involving personal care and quality of life. In one surviving patient of the original four (CLIS) patients a BCI based on EEG oscillatory responses during the answering period using desynchronisation pattern as features for the support vector machine (SVM) classifier was successfully applied and in a LIS patient at the verge of CLIS the EEG-BCI resulted in more than 90% correct classification: however after removing EOG contribution the classification results were random. This suggests that EEG-BCIs results without adequate EOG control in patients with intact eye movements should be taken with extreme caution. None of the non-invasive BCIs in CLIS allowed flexible verbal communication i.e. by selecting letters or words as demonstrated in several papers with LIS patients with cortical implants using neuronal spike rate and far field potentials of synaptic origin. Thus, voluntary verbal communication in CLIS needs to be shown using cortical implants.

Disclosures: N. Birbaumer: None. **A. Rana:** None. **A. Tonin:** None. **M. Khalili:** None. **A. Jaramillo Gonzalez:** None. **S. Pathak:** None. **U. Chaudhary:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.11/JJ1

Topic: E.05. Brain-Machine Interface

Support: NIH AT009263
MH114233
EB008389
NSF CBET-1264782
DGE-1069104

Title: Mind body awareness training improves learning of sensorimotor rhythm based brain computer interfaces

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Abstract: A major challenge facing the widespread adoption of non-invasive brain-computer interfaces (BCIs) is variable user proficiency. Previous work has suggested that long-term mind-body awareness training (MBAT) can improve the performance of sensorimotor rhythm (SMR) based BCIs, in which electroencephalography (EEG) signals are used to control an external device through motor imagery. However, whether these procedures can work over the shorter term remains unknown. To assess the effects of MBAT on BCI proficiency, 41 randomly assigned subjects attended an 8-week mindfulness-based stress reduction class. BCI learning was compared between these MBAT subjects and 34 wait-listed controls, across several days of SMR based BCI training sessions. In this study, subjects performed motor imagery of hand movements while EEG mu rhythms were extracted and used to decode subjects' intention to move a computer cursor. Subjects were instructed to imagine left (right) hand movement to move the cursor left (right), movement of both hands to move the cursor up, and a voluntary rest to move the cursor down. In separate blocks of trials, subjects attempted to steer the cursor to a target that required left/right (LR) movement only, up/down (UD) only, and combined 2D movement (2D). Accuracy was quantified by a percent valid correct (PVC) metric, calculated as the number of hits divided by the total number of non-timeout trials. This was done separately for 2D performance, and 1D performance, which was defined as the best 1D task performance for a given session. In order to examine whether MBAT facilitated BCI learning, analysis focused on subjects that were not initially proficient in any of the BCI tasks (MBAT N = 29, Control N = 20). During the early learning period, defined as the first 5 sessions, improvement in BCI performance was greater for MBAT subjects (M = 15%, 11%, SD = 14%, 12%) than control subjects (M = 7%, 3%, SD = 11%, 6%) when compared to a baseline assessment in both 1D ($p = 0.03$), and 2D ($p = 0.02$) paradigms. A major contributing factor to this improvement was that MBAT subjects made fewer errors compared to their baseline assessment. Out of 25 trials per run, the reduction of missed targets by MBAT subjects (M = -2.74, -2.35, SD = 2.67, 2.16) was more pronounced than in control subjects (M = -0.48, -0.44, SD = 2.16, 2.46) in both 1D ($p = 0.003$), and 2D ($p = 0.03$) paradigms. MBAT subjects demonstrated enhanced learning in our study, suggesting short-term mindfulness meditation training can improve the efficiency of SMR based BCI training. Work is ongoing to examine whether cognitive, behavioral, or electrophysiological measures can suggest explanations for the observed results.

Disclosures: J.R. Stieger: None. **C.C. Cline:** None. **C. Coogan:** None. **B.S.R. Murakonda:** None. **S.J. Sherman:** None. **A. Huynh:** None. **D. Hammond:** None. **K. Breshears:** None. **T. Boyle:** None. **M. Kreitzer:** None. **S.A. Engel:** None. **B. He:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.12/JJ2

Topic: E.05. Brain-Machine Interface

Support: NIH T32 grant (5T32HD007414-24)

Title: Transcranial direct current stimulation in pediatric physical rehabilitation: A systematic review and meta-analysis

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Abstract: **Background:** Recent studies have reported that transcranial direct current stimulation (tDCS) improves physical functioning in pediatric motor disorders. To date, no systematic review has comprehensively synthesized the findings of literature in pediatric motor disorders.
Objective: To systematically examine the safety and effectiveness of tDCS interventions in pediatric motor disorders.
Methods: Systematic review and meta-analysis of tDCS randomized, sham-controlled trials (RCT) and observational studies in pediatric motor disorders from the first date available to March 30, 2018. The following databases were searched: PubMed, EMBASE, Cochrane, CINAHL, Web of Science, and ProQuest. Two authors independently assessed each identified study's risk of bias using the Cochrane tool and extracted data. PROSPERO ID: CRD42018085341.
Results: Of the initial 1396 references identified through electronic searching, 23 studies were included, involving a total of 413 participants [Mean (SD): 17.95 (14.05), range: 1 - 56]. Patient diagnoses included cerebral palsy (CP; 18 studies), dystonia (3 studies), involuntary movement (1 study), and delayed neuro-psychomotor development (1 study). There was no difference in the drop-out rates in the active (1/144) and sham (1/144) tDCS groups, risk difference 0.0, 95% CI [-0.05, .0.04]. The most common adverse effects in the active group across studies were tingling (17.2%), discomfort (8.02%), itching (6.79%), and skin redness (4%). Across 3 studies, tDCS significantly improved gait velocity (MD = .23; 95% CI [0.13, 0.34], $p < .0005$), stride length (MD = 0.10; 95% CI [0.05, 0.15], $p < .0005$), and cadence (MD = 15.7; 95% CI [9.72, 21.68], $p < .0005$). Mixed effects were found on balance, upper-extremity function, daily task performance, and functional participation.
Conclusion: Based on this sample, tDCS is a feasible and tolerable technique in children with motor disorders. This review found that tDCS might enhance gait measures. Due to the limited

number of studies with small sample sizes, our results need to be interpreted with caution. To understand if tDCS is beneficial for children with motor disorders, more well-designed long-term RCTs are needed. Current rehabilitation techniques in pediatric motor disorders have limited effectiveness in improving performance and participation in daily activities. tDCS may serve as a potential adjunct to pediatric rehabilitation.

Disclosures: G.T. Saleem: None. **J.E. Crasta:** None. **B. Slomine:** None. **G.L. Cantarero:** None. **S.J. Suskauer:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.13/JJ3

Topic: E.05. Brain-Machine Interface

Support: FP7-PEOPLE-2012-CIG-334201
NIDILRR grant 90RE5010-01-01
NIH/NICHHD grant 1R01HD072080.

Title: A body-machine interface based on autoencoder networks: Mapping movements and muscle activities into a control signal

Authors: *F. RIZZOGLIO, C. PIERELLA[1], A. SCIACCHITANO[2], A. FARSHCHIANSADEGH[3,4], M. CASADIO[2], F. A. MUSSA-IVALDI[3,4]
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Abstract: Body-machine interfaces - B(o)MIs - are a viable option to control assistive devices and promote the recovery of movements after spinal cord injury, stroke or other neurological disorders that impair motor functions. B(o)MIs translate signals from the body into the lower dimensional control space of external devices. Our goal is to develop B(o)MIs that provide the user with the ability to identify and coordinate a convenient subset of movements and/or muscle signals to achieve task objectives with a flexible and adaptable motor behavior. For this reason, we developed a hybrid B(o)MI based on the linear and nonlinear mapping of body motion sensors and/or EMG signals onto the control of a computer cursor. The B(o)MI used in this study had four small-size inertial measurement units (IMUs) and/or eight EMG electrodes to capture motions and muscle activities. The data were used to control the cursor and to analyze the performance of healthy subjects. The interface map was created by asking subjects to engage in free upper-body movements and by extracting low-dimensional latent spaces from the IMU and/or EMG signals. The latent spaces were extracted with autoencoder networks (AEs). Two

types of AEs were considered: a linear AE, performing principal component analysis (PCA) on the input signals, and a nonlinear AE. Three types of B(o)MIs were developed and compared: IMU-based, EMG based and hybrid. In the IMU and EMG-based B(o)MI, cursor coordinates were taken from the IMU and EMG latent space respectively. In the hybrid system, the EMG body space was mapped by nonlinear regression over the IMU latent space. A convex combination of the latent signals obtained from the EMG's regression and from the IMU's was used as the hybrid control signal. Results showed that subjects performed significantly better with motion only and hybrid control than with EMG alone. The use of the nonlinear mapping induced better performances than those obtained with PCA in terms of time, accuracy and smoothness of movement especially during the first exposure to the use of the B(o)MI. These preliminary findings encourage us to exploit nonlinear dimensionality reduction algorithms as well as hybrid movement and muscle controllers to purse a new and effective clinical approach for controlling assistive devices and for facilitating the recovery of motor function in people with high level of paralysis.

Disclosures: C. Pierella: None. **A. Sciacchitano:** None. **A. Farshchiansadegh:** None. **M. Casadio:** None. **F.A. Mussa-Ivaldi:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.14/JJ4

Topic: E.05. Brain-Machine Interface

Title: Identification of noninvasive neuromodulation targets for pediatric stroke rehabilitation

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Abstract: Ischemic perinatal stroke affects as many as 1 in 2,300 live births and may result in lifelong burden of care. Thus, better rehabilitation techniques are indicated to improve quality of life for individuals and families. Implementing interventions early in life can harness neuroplastic potential to promote recovery. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have shown promise as noninvasive cortical assessment and neuromodulation techniques for stroke rehabilitation; regaining motor control and function can be facilitated through the induction of plasticity. While mostly studied in adult populations, recent efforts have been made to translate these methods to pediatric populations. This is challenging because, in addition to the presence of a lesion, stimulation fields vary significantly due to head anatomy and size differences. Here, we explore the integration of individual realistic head models to identify stimulation targets for synergistic neuromodulation and rehabilitation. Combining TMS motor mapping data with FEM models allows precise

identification of motor representations in both affected and unaffected brain hemispheres. Using our computational motor mapping method, we are developing a system to predict individualized neuromodulation stimulation targets for stroke rehabilitation. We have successfully created pediatric stroke FEM head models (Fig. 1B) and have found that the electric field distributions in unaffected hemispheres are comparable to healthy participants (Fig. 1C and D).

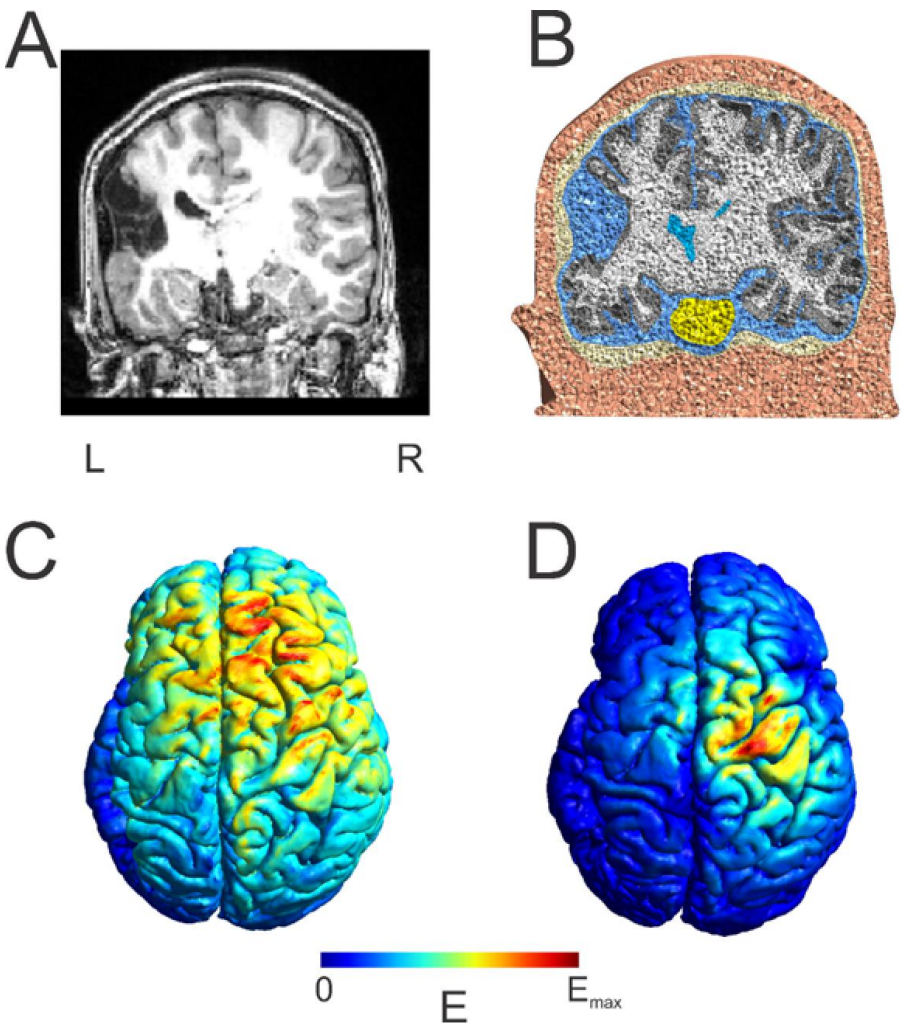

Figure 1. Models and simulations demonstrate that electric fields are relatively unaffected by the lesion in the contralesional hemisphere. A) Anatomical T1 Image showing a lesion volume in the left hemisphere. B) Anatomical realistic FEM model with the lesion volume accounted for. C) Electric field simulation for the tDCS electric field with the cathode placed over contralesional M1 and the anode over the left forehead. D) Electric field simulation for the TMS electric field with stimulation over M1.

Disclosures: K.E. Mantell: None. **S.T. Nemanich:** None. **B.T. Gillick:** None. **A. Opitz:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.15/JJ5

Topic: E.05. Brain-Machine Interface

Support: NIH NINDS NS072342-01
NIH NINDS UH3NS100541

Title: A wearable electrode array for recording volitional and stimulation-evoked myoelectric signals from extrinsic hand muscles

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Abstract: In recent years, brain-machine interfaces have enabled humans with paralysis to control assistive devices with just their thoughts. However, the invasiveness of this technology is not a trivial consideration, particularly for individuals with residual motor function. To address this limitation, we developed a wearable electrode array covering extrinsic hand muscles of the entire forearm. The array consists of 160 electrodes (12 mm diameter) spaced 15 mm apart and embedded in a stretchable fabric. Using this wearable electrode array, we recorded volitional EMG from a neurologically-intact participant who performed individual digit flexion movements. Power of the raw EMG signal was calculated as root-mean-square (RMS) every 100 ms. The average RMS values during the digit-flexion epochs were used as input features in decoding algorithms trained to classify the EMG activity on 32 channels as rest or flexion of one of the five digits. Two decoding algorithms were tested, Linear Discriminant Analysis (LDA) and Support Vector Machines (SVM). LDA is a simple linear decoder, whereas SVM is more effective when channels are highly correlated and relationships are non-linear. We found that both models were highly accurate (LDA 96.4%, SVM 96.7%) for strong digit flexion movements. The participant also performed weak flexion movements to mimic impaired muscle activation. Decoding algorithms were slightly less accurate, as expected, with the SVM showing greater accuracy (LDA 82.4%, SVM 87.2%). Examination of confusion matrices for the decoders revealed that most errors were due to predicting rest at the very beginning or end of a movement. In another participant, we measured motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation of primary motor cortex. We stimulated over optimal sites for eliciting MEPs in wrist extensors and flexors while the participant maintained an isometric force during precision and power grip. Muscle maps were qualitatively similar when stimulating over the wrist extensor or flexor optimal sites. However, areas of densest evoked activation were over

the extensor muscles during precision grip. Flexor muscles exhibited negligible evoked activation during precision grip but high activation during power grip. Our findings indicate that the wearable electrode array detected myoelectric signals that were distinct and spatially localized during individuated finger movements. Evoked responses in wrist flexor and extensor muscles were distributed differentially along the forearm depending on grasp type.

Disclosures: D.J. Weber: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Battelle Memorial Institute. F. Consulting Fees (e.g., advisory boards); Battelle Memorial Institute. **M. Urbin:** None. **D.A. Friedenberg:** None. **S. Colachis:** None. **M. Zhang:** None. **P. Ganzer:** None. **D. Sarma:** None. **A. Sethi:** None. **G. Sharma:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.16/JJ6

Topic: E.05. Brain-Machine Interface

Support: HiPEDS, Grant Reference EP/L016796/1

Title: Mutually informed dynamical models for fNIRS denoising based on EMG and EEG

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Abstract: Functional near-infrared spectroscopy (fNIRS) is a wearable, non-invasive brain imaging technique that can be deployed in unconstrained human motor control experiments. It offers a direct window to assess the oxygenation of cortical areas with greater spatial resolution than Electroencephalography (EEG), however the signal is subject to variations of systemic origin, such as breathing and pulse rates, that covary with motor activity and hinder the neuronal specificity of the signal.
Multi-modal (EEG+fNIRS) wearable neural sensors can allows us to study human sensorimotor control and learning by exploiting the specificity of the EEG signal to brain activity and that of fNIRS to the location. Moreover, the specificity of both signal to motor activity can be increased by means of their shared information with additional motor activity sensory modes such as electromyography (EMG) and force.
However, it is often unclear how to exploit shared information in such multi-modal data spanning fast, low spatial resolution EEG and EMG and slow, higher spatial resolution fNIRS. Furthermore, the relationship between these two measures have not been related to motor activity (EMG) and behavioural output (force).We develop a principled probabilistic estimation approach that allow us to integrate these disparate measures that reflect multiple levels of biological organisation and time scales.EMG is used as a ground truth of motor activity to train black box

models that learn the mutually informed dynamical structures of such motor activity to multimodal brain activity (EEG + fNIRS). In particular, since EEG is not affected by the same systemic noise sources than fNIRS we aim at deriving a hierarchical black box architecture that denoises fNIRS time series by exploiting covariations with both EMG and EEG.
Our advances promise to reduce in confounding effects, large variability, and drift in the signals that undermine the specificity of fNIRS and EEG specially during motor activities. In addition, the exploitation of the mutually informed dynamical structure of the signals allows the prediction of denoised cortical fNIRS signals at each sampled value of the observed modes. This enables us to quantify faster and in higher precision than before the neural basis of goal-directed sensorimotor control where it really matters - in the wild and outside, outside of constrained laboratory and clinical settings.

Disclosures: P. Ortega: None. **A. Faisal:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.17/JJ7

Topic: E.05. Brain-Machine Interface

Support: NIBIB 1P41EB018783
NIBIB EB00856
NCMRR/NICHD HD30146
Fondazione Neurone

Title: Creating an eyes-closed binary SSVEP-based brain-computer interface (BCI) for the bedside: A comparison of foveal centered and off-centered stimulus presentation

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Abstract: Brain-computer interfaces (BCIs) can restore communication and control to people with severe motor disorders such as amyotrophic lateral sclerosis (ALS) (e.g., Wolpaw et al., *Neurology*, in press). However, visual impairments (e.g., ptosis, diplopia, nystagmus) prevent many such individuals from using a vision-based BCI (e.g., McCane et al., *Amyotroph Lateral Scler Frontotemporal Degener* 15:207-215, 2014). In these individuals, a steady-state visual evoked potential or SSVEP-based BCI that relies on electroencephalographic (EEG) signals

might be used to determine binary (YES/NO) intentions. Our system delivers SSVEP stimuli via LEDs embedded in custom eyeglasses and records EEG signals from locations F3, Fz, F4, T7, C3, Cz, C4, T8, P3, Pz, P4, PO7, PO8, and Oz, using BCI2000. The present study examines the effect of LED placement on the classification of binary signals. In studies to date, six people (five women and one man, ages 46.8 ±23.4 (median age 59)) performed 40 5-sec trials (20 left and 20 right) with glasses fixed with foveal-centered and off-centered LEDs with stimulation frequencies of 23.75 Hz (f1) in one eye and 31.15 Hz (f2) in the other. We analyze the EEG data for the 5-sec trial to determine which of the two eyes (i.e., which stimulation frequency) the subject was attending. EEG is bandpass filtered into 0.4-Hz wide bands centered on the two stimulation frequencies. We derive a linear classifier using a regularized least-square fit to determine the relationship between the spectral power in these bands and the attended eye. The results to date show that the spectral power of the EEG is higher for the attended frequency band and lower for the unattended frequency band for both the foveal-centered and off-centered conditions. The accumulated output of the linear classifier over 5 sec for foveal-centered and off-centered LED placements predicts the attended eye with accuracies of 92.9(SD11.7)% and 95.8(SD4.2)% correct, and ideal bitrates of 10.7(SD5.9) and 13.7(SD7.1) bits/min, respectively. These initial results suggest that taking advantage of the specific geometries of foveal off-centered placement may improve SSVEP binary classification and that, with further development, a binary SSVEP-based BCI could prove useful for people with severe neuromuscular disorders and impaired vision.

Disclosures: T.M. Vaughan: None. **M. Aslam:** None. **B. Zoltan:** None. **P. Brunner:** None. **J.J. Norton:** None. **C.S. Carmack:** None. **D.J. Zeitlin:** None. **J.R. Wolpaw:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.18/JJ8

Topic: E.05. Brain-Machine Interface

Support: Alessia Cacace is part of the ITN 'Perception and Action in Complex Environments' (PACE). The PACE project has received funding from the European Union's Horizon 2020 research innovation program under the Marie Sklodwska-Curie No.642961

Title: Functional magnetic resonance imaging reveals reduced imagined movement-related activation in quadriplegic patients as compared to healthy controls: Implications for early onset training for brain-machine interface array implant participants

Authors: *A. CACACE[1], M. PRASAD[2], J. D. CONNOLLY[1]
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Abstract: A substantial degree of overlap in cortical activation when carrying out real or imagined reaching movements is well established in healthy participants. There exists critical overlap when imagining movements - but not generating them - in the posterior parietal, premotor and motor areas of the human cerebral cortex. Based upon these findings, rehabilitative brain-machine interfaces for paralysis have focused implants on the same relevant constellation of cortical areas. There is a paucity of evidence, however, with regard to long-standing functional changes in individuals living with paralysis following a complete spinal cord injury (in this case vertebrae C3-C4). Here we compared via functional Magnetic Resonance Imaging 4 patients (C3-C4) with quadriplegia and 4 healthy age-matched control participants. We used an 'around the clock' paradigm that is typical for saccade topographic mapping experiments, but with light emitting diodes that flashed 'around the clock' and in sequence. Healthy participants were required to: 1) fixate while the light emitting diodes were flashed 'around the clock' (fixation condition); or 2) imagine reaching movements to these same diode locations (imagine condition); or 3) generate real reaches in the scanner to these very same locations (movement condition). In the paralyzed patient group, we had only the first two conditions: fixation or imagined reaching. We then compared cortical activation patterns on segmented surface renderings for fixation and imagined reaching movements across quadriplegic patients and healthy controls. Although similar overall activation patterns are reported across both groups (quadriplegic and controls), participants who suffer from C3-C4 paralysis exhibit substantially lower activation levels (less voxels that passed the critical threshold in movement-related areas and reduced levels of activation in coincident voxels) across inferior and superior parietal cortex, dorsal and ventral premotor areas, primary motor cortex and in the supplementary motor area. These findings provide support for imagery-based training immediately following paralysis onset to retain sufficient movement-related cortical activation/function for those who will require assistive brain-machine interface array implants.

Disclosures: M. Prasad: None. **J.D. Connolly:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.19/KK1

Topic: E.05. Brain-Machine Interface

Support: MOST-106-2410-H-008-054
MOST-105-2410-H-008-054

Title: Accuracy of single-trial motor imagery detection based on the alpha power suppression features for on-line real-time bci application

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Abstract: In the past studies, motor imagery (MI), motor execution (ME), and motor observation (MO) have been reported sharing similar EEG dynamics in the motor-related cortex. The mu EEG power suppression associated with the motor imagery has been widely used in the brain computer interface (BCI) applications. Recently, our group has worked on the reliability of the EEG alpha power suppression in an EEG experiment using the MI, ME, and MO and used independent component analysis (ICA) to find the EEG alpha suppression in the same motor-related cortex for a side-by-side comparison. In this study, we would like to further look at the individual trial performance to see how accurate the alpha power suppression EEG feature can be used to determine the performance of the motor imagery task. To check the accuracy of the alpha power suppression for detecting the motor imagery performance across all trials, we first extract the alpha power time course using time-frequency decomposition and used 150-ms time sliding window to compare the alpha power to the alpha power during the baseline using a t-test for each MI trials. If the alpha power in the sliding window was significantly lower than that during the baseline, the time window was labeled with successful detection of MI. The sliding window would cover the entire trial and give the comparison result for each sliding window. Finally, the single trial results would be further summarized window by window across all MI trials. Although the participants were asked to perform the task with different motor conditions using the non-dominant hand so that the alpha power suppression of motor-related brain areas on the contralateral hemisphere should be the primary feature to consider, combining the alpha power suppression feature on the ipsilateral hemisphere could increase the MI detection accuracy by about 8%. Furthermore, we also realized that the individual difference in the time window, which gave the best MI detection accuracy, could not be negligible. For example, among all the time windows involved in the MI detection accuracy comparison, the accuracy could go as high as 100% for some participants but only 40% maximally for some other participants. The MI has been largely used in the BCI application, however, the accuracy of how the MI performance can be detected at the single-trial level should be further determined. By using the ICA, we were able to focus the alpha feature extraction based on only the motor-related independent EEG component, which should give the best accuracy estimation possible. This study was partially sponsored by the Ministry of Science and Technology, Taiwan (Grant no.: MOST-106-2410-H-008-054 and MOST-105-2410-H-008-054).

Disclosures: Y. Huang: None. **K. Xu:** None. **J. Duann:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.20/KK2

Topic: E.05. Brain-Machine Interface

Support: JSPS KAKENHI 18H03784

Title: Influence of electrical stimulation patterns on velocity of the third-finger joints

Authors: *A. HIRATA, H. MURAMATSU, Y. ITAGUCHI, S. KATSURA
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Abstract: Introduction: The present study aimed to clarify the relation between the electrical stimulation patterns and finger movements for precise control of them. Stimulating the superficial flexor muscles induces flexion of proximal interphalangeal (PIP) joint; however, it could flex also the metacarpophalangeal (MP) and distal interphalangeal (DIP) joints at the same time. To achieve high precision control of hand movements by functional electrical stimulation, we investigated how patterns in electrical stimulation influence the movements of the PIP, MP and DIP joints.
Experimental method: A voltage-control-type electrical stimulator, that generates a symmetric biphasic pulse wave, was used. Its interphase interval was set to 0.10 ms. Amplitude of the pulse, pulse width, and pulse frequency were changed to examine the influence. A pair of surface electrodes connected to the electrical stimulator was put on the forearm such that the third finger moved. The angles of the DIP, PIP and MP joints were measured by a motion capture system. The elbow and wrist were put on a table so that the thumb was on the upper side. Each trial started with a straightened and then relaxed state, stimulated for 1 s.
Results: The average angular velocity was calculated in the transient response. When pulse amplitude was increased from 8.6 V to 20.6 V, there was a positive correlation ($r=0.775$, $p<.001$) in PIP, and the increase in average angular velocity was 530.2 deg/s. On the other hand, there were no significant correlation on MP and DIP ($r=0.291$, n.s., $r=0.300$, n.s.), and the increases were 76.94 deg/s and 37.35 deg/s, respectively. When pulse width was increased from 0.020 ms to 0.55 ms, there were no significant correlation on PIP, MP and DIP ($r=0.342$, n.s., $r=0.117$, n.s., $r=0.0628$, n.s.). When pulse frequency is increased from 10 Hz to 130 Hz, there were positive correlation on PIP and MP ($r=0.825$, $p<.001$, $r=0.836$, $p<.001$), and the increases in average angular velocity were 769.5 deg/s, 367.7 deg/s respectively. On the other hand, there was no significant correlation on DIP ($r=0.0999$, n.s.), and increase was -1.291 deg/s.
Discussion: We found that (1) the pulse amplitude would be the best to control the velocity of the PIP joint without changes in movement velocity of the MP and DIP joints, (2) the velocity of

the PIP joint was independent of the pulse width, and (3) the pulse frequency may be suitable to control the velocity of the PIP joint if movements of the MP joint are allowable.

Disclosures: A. Hirata: None. **H. Muramatsu:** None. **Y. Itaguchi:** None. **S. Katsura:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.21/KK3

Topic: E.05. Brain-Machine Interface

Support: Keio Institute of Pure and Applied Sciences (KiPAS) research program

Title: Promoting excitability of corticospinal tracts from a targeted hemisphere through interplay with EEG-based brain-computer interface

Authors: *M. HAYASHI[1], S. KASUGA[2], J. USHIBA[3,4]
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Abstract: The event-related desynchronization (ERD) of sensorimotor rhythm recorded over sensorimotor area is known as a typical motor-related electroencephalogram (EEG). It has been shown that contralateral ERD (c-ERD) during hand motor imagery involving distal muscles reflects excitability of the contralateral corticospinal tract (CST), and ipsilateral ERD (i-ERD) reflects excitability of the ipsilateral CST that mainly innervates proximal muscles (Takemi et al. 2013; Hasegawa et al. 2017). Such ERD is often exploited in brain-computer interface (BCI)-based neurorehabilitation, aiming at functional maturation of CST (Shindo et al. 2011). In these conventional BCIs, however, it is not designed to promote ERD only from the targeted hemisphere, and the treatment focus is unclear. Here, we developed bivariate BCI which controls contralateral and ipsilateral ERDs to investigate whether BCI users can volitionally promote ERD from the targeted hemisphere. To verify whether ERD shifting is influenced by a neuroanatomical property of CST, we compared the effectiveness of BCI training for shoulder and finger motor imageries.
Fifteen healthy individuals participated in this study with a double-blind crossover design. Nine individuals participated in experiment 1 consisting of a shoulder imagery task, and 6 individuals participated in experiment 2 consisting of a finger imagery task. Each experiment comprised of two types of BCI training: (A) to facilitate either contralateral or ipsilateral ERD, (B) to facilitate the opposite side to Training-A. All individuals performed 120 trials of shoulder/finger imagery task while a 128-channel EEG was recorded. Visual feedback was provided as a movement of a computer cursor in the two-dimensional coordinate, in which each axis corresponded to

contralateral or ipsilateral ERD amplitude. The ERD amplitudes and spatial patterns in both experiments were evaluated. In experiment 1, only i-ERD increased in Training-A, and only c-ERD increased in Training-B ($p < 0.05$, paired t-test). There was a significant change in hemispheric dominance which evaluated with the laterality index in both training types ($p < 0.05$). In experiment 2, however, only c-ERD increased in Training-B ($p < 0.05$), whereas i-ERD did not increase in Training-A ($p = 0.46$). We also found that i-ERD showed significant difference between shoulder and finger motor imageries ($p < 0.05$, student t-test), and implied neuroanatomical constraints on BCI learning. These results indicate that ERD from the targeted hemisphere can be promoted through the bivariate BCI, and it has a potential to be applied to stereotaxic BCI therapies aimed for reorganization of targeted CST.

Disclosures: M. Hayashi: None. **S. Kasuga:** None. **J. Ushiba:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.22/KK4

Topic: E.05. Brain-Machine Interface

Support: US Army Center for Agent Soldier Teaming

Title: Quantifying performance of pliable, dry polymer EEG electrodes

Authors: *W. HAIRSTON[1], J. C. BRADFORD[2], R. A. MROZEK[2], G. A. SLIPHER[2]
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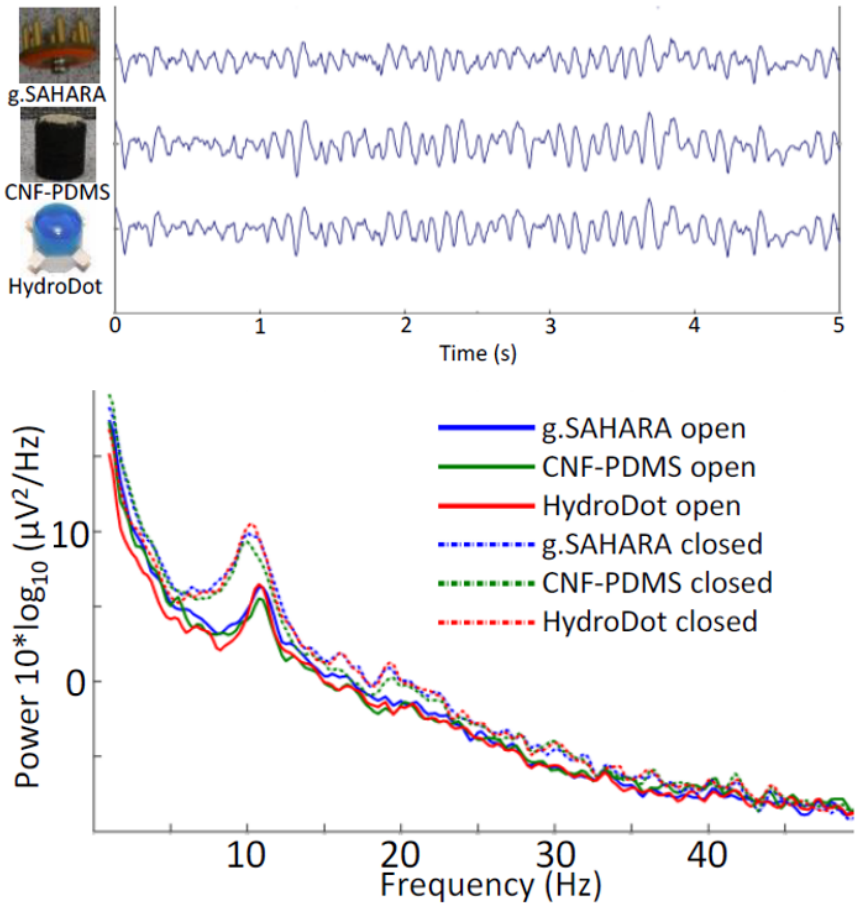
Abstract: There is much interest in so-called “real world neuroimaging”, where neuroscience experimentation occurs outside of conventional lab settings. While electroencephalography (EEG) is the best-poised imaging modality, it remains hampered by the necessity for electrolytic gel or metal-pin electrodes which are messy, uncomfortable, or unstable. To address this challenge, we have recently developed a conformable solid state material solution (carbon nanofiber filled polydimethylsilisoxane, CNF-PDMS) for EEG electrode applications. Prior work has demonstrated our formulation to provide a stable conductive profile even while under substantial mechanical strain, where most other nonmetallic materials fail, suggesting viability for ambulatory applications where flexibility, compression and movement will be common. In this study, we tested the efficacy of electrodes to record well studied neural phenomena using a battery of standard laboratory tasks, including both stationary and walking in place, with a sample of human subjects. Qualitatively, event related potential (ERP) and spectral results for a number of tasks (including RSVP, eyes open/closed, and directed motions) show performance matching that of commercially available metal-pin based dry EEG electrodes (g.SAHARA).

Additionally, we propose objective, quantifiable summary statistics to be applied outside of event-related domains (correlation and RMSE), which show matched and even improved ability to track local and global fluctuations in EEG. Ongoing work focused on artifact susceptibility during motion, as this is a critical challenge with dry electrodes. Together, these results present baseline data that demonstrates CNF-PDMS is a viable solution for conformable, safe, dry EEG electrodes, and hold the promise for improved future real-world neuroimaging.



Disclosures: W. Hairston: None. **J.C. Bradford:** None. **R.A. Mrozek:** None. **G.A. Slipher:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.23/KK5

Topic: E.05. Brain-Machine Interface

Support: NIH Grant UL1TR000114
University of Minnesota's MnDRIVE (Minnesota's Discovery, Research and Innovation Economy) initiative
University of Minnesota Doctoral Dissertation Fellowship

Title: Assessing and modulating intracortical and transcallosal inhibition in cervical dystonia

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Abstract: Introduction: Cervical dystonia (CD) is a debilitating movement disorder characterized by involuntary neck muscle contractions. Intracortical inhibition has been shown to be impaired in people with CD, primarily by assessing the silent period evoked in contralateral muscles (cSP) following transcranial magnetic stimulation (TMS) over the motor cortex. However, stimulation also evokes inhibition in ipsilateral muscles (iSP) and this pathway not been studied in people with CD. The purpose of this exploratory study is to: 1) compare cSP and iSP between CD and controls (CTL), and 2) assess the effects of cerebellar transcranial direct current stimulation (tDCS) on cSP and iSP.
Methods: A two group (CD vs CTL), randomized, double-blind design was conducted with planned enrollment of N=66 (current: 14 CTL, 14 CD). Bilateral electromyographic recordings were collected in the active upper trapezius in response to TMS over the left or right primary motor cortex. Ten trials of cSP and iSP responses were collected using stimulation intensities 110%, 120%, 130% and 140% of cSP threshold. Cerebellar tDCS (anodal, cathodal or sham) was delivered at 2mA for 25min with a unilateral montage (reference was placed on the buccinators). Other measures collected but not discussed here include brainstem response curve and eye-blink classical conditioning blink count. Interim analysis was performed using a mixed model ANOVA.
Results: Preliminary results of baseline data analysis are reported. There was no effect of Group on cSP duration, suggesting normal intracortical inhibition and input-output properties in the cohort with CD compared to CTL. In contrast, there was a significant effect of Group ($p = 0.019$) for the left iSP duration, but not for the right iSP ($p = 0.136$). Transcallosal inhibition from the left to the right hemisphere was reduced in the cohort with CD compared to CTL. These preliminary findings suggest participants with CD have a decreased iSP compared to healthy matched controls. Results of tDCS modulation effects on cSP and iSP will be reported.
Conclusion: The preliminary analysis suggests there is asymmetric involvement of transcallosal inhibitory pathways in the people with CD, while the duration and input-output properties of intracortical inhibition appear to be unaffected.

Disclosures: R.L. Summers: None. **M. Chen:** None. **C.D. MacKinnon:** None. **T.J. Kimberley:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.24/KK6

Topic: E.05. Brain-Machine Interface

Support: NIH AT009263

Title: Asynchronous ballistic finger imagery based brain-computer interface utilizing EEG

Authors: *D. SUMA, J. MENG, B. HE
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Abstract: Brain computer interfacing (BCI) is a promising method for replacing brain-body connections disrupted by injury or disease, potentially improving the quality of life of disabled individuals. Extensive invasive and non-invasive BCI work has been done, but many systems involve continuous, constant effort by end users. Because practical control cannot require continuous focus, novel paradigms which involve asynchronous control signals need to be investigated, especially in noninvasive strategies involving endogenous control, which typically use non-specific control signals. In order to investigate EEG based asynchronous BCI control, 10 healthy, right handed subjects underwent four sessions of experimentation, where they were asked to either execute a single rapid extension and immediate relaxation of the index finger associated with a written prompt after receiving an auditory cue, or to imagine the same. These sessions were conducted using the CREMedical tri-polar EEG (tEEG) system, in hopes of measuring more focal brain activity. All experiments contained 1-2 runs of execution and imagery without feedback, with each run consisting of 50 trials. Sessions 2-4 also included a novel feedback task. During evaluation with feedback, subjects imagined single extensions and relaxations of the appropriate index finger when constant velocity targets entered a pre-defined hit zone in either a left or right column. Three of the ten subjects also completed one run of execution and two runs of imagery during high-density standard EEG recordings with optical digitization. Across online evaluation sessions, subjects demonstrated improvements in percent total correct and number of missed targets while maintaining similar percent valid correct scores (58.3%, 56.2%, 54.3%), suggesting that tEEG electrodes can effectively record underlying neural activity during BCI applications. Further offline analysis discerned spatio-temporal electrophysiological changes associated with rapid imagery and movement and generated superior decoding strategies for both detection and classification. Primarily, these methods demonstrated class dependent contralateral motor cortical activity and onset dependent medial, laterally oriented dipoles, determined through trial averaged source localization and ICA, in the time surrounding the assumed onset of ballistic imagery, based on execution reaction times, during non-feedback trials. These results suggest that EEG based asynchronous control is a

promising future direction for BCI, potentially as an on/off switch for more robust continuous control strategies. This work is supported by NIH AT009263.

Disclosures: D. Suma: None. **J. Meng:** None. **B. He:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.25/KK7

Topic: E.05. Brain-Machine Interface

Support: NSF IIS 1302339
NIH 1F99NS105210-01

Title: Noninvasively recorded human cortical dynamics during level-ground, incline, and stair locomotion

Authors: *J. A. BRANTLEY, T. P. LUU, S. NAKAGOME, F. ZHU, J. L. CONTRERAS-VIDAL
Dept. of Electrical & Computer Engin., Univ. of Houston, Houston, TX

Abstract: Currently available prosthetic devices lack the inherent inability to interpret the user's intent during locomotion. Volitional control of lower-limb prostheses using electromyography (EMG)-based controllers allows for activation patterns of the muscles of the lower-limb to be mapped to various movement patterns. However, although robust during continuous locomotion, EMG-based systems (which rely only on peripheral nervous signaling) lack the ability to predict locomotion mode transitions (e.g., level ground to stairs, stairs to level ground) with significant advanced notice. In this study, we investigated the cortical correlates of dynamic human walking during walking on various terrains in able-bodied individuals. Second, we assessed the feasibility of detecting user locomotion modes (i.e., level-ground walking vs stair ascent) from non-invasive electroencephalography (EEG) signals. Subjects were instrumented with full-body mobile brain-body imaging (EEG, EMG, motion capture) while walking on an experimental gait course involving locomotion on level-ground, stairs, and ramps. A systematic EEG processing method was implemented to reduce artifacts (e.g., eye blinks/movements, muscle artifacts) and estimate the underlying source activity through dipole fitting. The results revealed that spectral changes in the PPC and SMC were aligned to events in the gait cycle and appeared to be associated with the level of motor task demand. Additionally, we observed significant differences in spectral power between level-ground and stair walking, likely indicating heightened cortical involvement prior to the terrain transitions. These significant cortical activations can be detected in advance of the transitions and may be used to improve the state-of-the-art myoelectric controllers. These findings have implications for developing a neural

decoding paradigm that is capable of predicting, rather than responding to, the user gait intentions. This work is a further step toward the development of a multimodal neural-machine Interface (NMI) that fuses EEG and EMG signals for intuitive and flexible control of powered prosthetic legs.

Disclosures: J.A. Brantley: None. **T.P. Luu:** None. **S. Nakagome:** None. **F. Zhu:** None. **J.L. Contreras-Vidal:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.26/KK8

Topic: E.05. Brain-Machine Interface

Support: Fortune Uni Tuebingen (2422-0-0)
BMBF MOTORBIC (FKZ 13GW0053)
BMBF AMORSA (FKZ 16SV7754)
Gipuzkoa Provincial Government Science Network (INKRA-TEK: OF 215/2016)

Title: Synergistic combination of EEG and EMG activity for detecting movement intentions of stroke patients with complete hand paralysis

Authors: *E. LÓPEZ-LARRAZ[1], N. BIRBAUMER[2], A. RAMOS MURGUIALDAY[3]
[1]Univ. Of Tuebingen, Tuebingen, Germany; [2]Eberhard-Karls-Univ, Tubingen, Germany; [3]Univ. of Tubingen, Tubingen, Germany

Abstract: Brain-machine interfaces (BMI) have been demonstrated as a feasible therapeutic tool to facilitate motor recovery in chronic stroke patients with severe paralysis. Electroencephalography (EEG)-based BMIs can detect the attempts of movement of the patients and link those mental commands with a contingent peripheral feedback. By this means, these BMIs aim at promoting activity-dependent plasticity and subsequent motor recovery. However, the EEG contains limited information to accurately detect the movement intentions, especially in stroke patients, whose brain damage significantly affects the measured brain activity. Some stroke patients with complete paralysis can still generate measurable EMG activations during the attempt of movement of a paralyzed limb. Therefore, this residual EMG activity can be also considered to detect the intentions of movement, combining electrical activity coming from brain and muscles as a hybrid BMI. This study evaluates the improvement in performance of a hybrid BMI based on EEG and EMG compared to a BMI that relies on EEG only to detect movement intentions. Thirty-five chronic stroke patients were recruited, and their EEG and EMG activity were recorded while they attempted to open and close their completely paralyzed hand. A pseudo-online linear-discriminant analysis classifier was used to differentiate between resting

activity and movement intention. EEG features consisted of the average power spectra in the alpha and beta frequency ranges over the ipsilesional electrodes, while EMG features consisted of the waveform length of the electrodes placed over the extensor carpi ulnaris and extensor digitorum muscles. The performance of the classifier was measured as the average accuracy between resting detection and movement intention detection. The potential significant difference between the performance obtained with the hybrid BMI and the EEG-based BMI was evaluated with a Wilcoxon signed-rank test. The results show that the hybrid BMI provided an improvement in accuracy of almost 10% with respect to the EEG-based BMI (69.5% vs 61.2%), being this difference statistically significant ($p = 0.0001$). These results encourage the integration of hybrid BMI strategies for motor rehabilitation of severely paralyzed patients due to stroke.

Disclosures: E. López-Larraz: A. Employment/Salary (full or part-time):; University of Tuebingen. **N. Birbaumer:** None. **A. Ramos Murguialday:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.27/KK9

Topic: E.05. Brain-Machine Interface

Support: BMBF Grant 13GW0095D

Title: BOLD signal is more reliable than sensorimotor EEG signals in decoding hand movements

Authors: *C. REICHERT[1,2], S. DÜRSCHMID[1,3], H. HINRICHS[1,3,2,4], H.-J. HEINZE[1,3,4], C. M. SWEENEY-REED[3]
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Abstract: Sensorimotor rhythms (SMR) are often used to control a brain-computer interface (BCI). However, the degree of SMR modulation varies between participants, such that some people are not able to achieve control and hence are termed BCI illiterate. It has been hypothesized that BCI literacy is associated with an ability to recruit motor areas. Here we investigated the relationship between the detectability of hand movement in fMRI and in EEG recordings from the same participants to assess whether illiteracy is specific to participants or to the recording technique. The fMRI/EEG sessions followed a crossover design with 6 right-handed and 5 left-handed healthy participants. In intervals of 20s duration, participants moved their left hand, right hand or rested. EEG signals were recorded at 27 locations primarily covering motor areas. We classified 2s intervals of ongoing α/β activity (8-15Hz) using a CSP

filter and a naïve Bayes classifier. Classification of fMRI data was performed in anatomical ROIs (AAL template) using principal component analysis and a naïve Bayes classifier. While classification accuracy of movement and rest based on EEG data showed an SMR-typical heterogeneous distribution (mean = 81.9%; 59.1-98.4% SD = 14.4%), the BOLD signal of single scans in the contralateral precentral gyrus was classified with accuracies above 89% (mean = 93.9%; SD = 2.2%) in all participants. Further ROIs yielding high accuracies were postcentral gyrus (93.4%), SMA (90.6%), cingulum (88.9%), paracentral lobule (86.1%), Rolandic operculum (88.7%); ipsilateral cerebellum (91.9%) as well as vermis (91.1%). Accuracy could not be explained by handedness in either EEG or fMRI classification. Importantly, fMRI and EEG classifier accuracy did not correlate significantly ($|r|<0.4$, $p>0.05$). However, in contrast to previous studies of motor imagery (MI), the EEG decoding accuracy in most ROIs correlated negatively with the BOLD signal, with significant correlations in ipsilateral SMA ($r=-0.43$) and cerebellum ($r=-0.49$), in contralateral SMA ($r=-0.44$) and cingulum ($r=-0.43$) as well as in the vermis ($r=-0.48$). Our finding of a higher, more homogeneous classification rate using fMRI suggests that the lack of SMR discrimination in EEG-based BCIs is not due to a lower ability of individual users to recruit motor areas as postulated based on MI studies. In participants with low SMR modulation, high γ activity, which is not detectable with surface EEG but is reflected in BOLD recordings, might be more prominent. Our study supports the notion that noninvasive SMR-based BCIs are applicable only to a limited group of users, but access to high γ activity might extend the user group.

Disclosures: C. Reichert: None. **S. Dürschmid:** None. **H. Hinrichs:** None. **H. Heinze:** None. **C.M. Sweeney-Reed:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.28/KK10

Topic: E.05. Brain-Machine Interface

Support: BMBF MOTORBIC (FKZ 13GW0053)
BMBF AMORSA (FKZ 16SV7754)
Gipuzkoa Provincial Government Science Network (INKRA-TEK: OF 215/2016)
Fortune Uni Tuebingen (2422-0-0)

Title: Influence of head and eye movements on the decoding of arm movements from low-frequency EEG

Authors: *C. BIBIÁN[1], E. LÓPEZ-LARRAZ[2], N. BIRBAUMER[3], A. RAMOS MURGUIALDAY[4]

[1]Kuniversity Of Tuebingen, Tuebingen, Germany; [2]Univ. of Tuebingen, Tuebingen, Germany; [3]Eberhard-Karls-Univ, Tubingen, Germany; [4]Univ. of Tubingen, Tubingen, Germany

Abstract: Electroencephalography (EEG)-based brain-machine interfaces (BMI) have been proven as an effective tool for motor rehabilitation of severely paralyzed patients. Brain activity is translated into a start/stop feedback under the premise that an accurate feedback promotes better motor learning. Being able to decode different movements from brain activity could allow creating richer BMI-based therapies (i.e., patients performing different functional movements), maximizing the rehabilitative potential. However, this dynamic scenario might negatively affect the quality of the brain signals recorded with EEG, as it gets easily contaminated. In this study we analyze how involuntary compensatory movements associated with the task (i.e., eye or head movements) influence the performance of an EEG-based decoder for several reaching movements. Ten healthy subjects were enrolled in a cross-over study in which they performed reaching movements towards 4 different directions under two conditions: one in which the subjects avoided head and eye movements during the task, and other in which they could perform the task freely, following their arm movements with their gaze and/or head. To characterize ocular and head movements, electrooculography and acceleration of the head were recorded. A linear classifier was trained to decode the 4 different reaching directions using low frequency features [0.05-2] Hz. Then, we studied the relation between eye and head movements with the performance the classifier for each subject. To do so, a linear regression was fitted to predict the classification accuracy based on the EOG and the accelerometer signals. The results show that the performance could be accurately predicted only in the condition in which subjects were moving the head and eyes freely ($p = 0.009$, $r = 0.77$). This finding reveals the effect of eye and head movements in the EEG-based decoding and underscores the importance of taking them into account when designing or analyzing further studies that rely on low frequency movement decoding based on EEG.

Disclosures: C. Bibián: None. **E. López-Larraz:** None. **N. Birbaumer:** None. **A. Ramos Murguialday:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.29/KK11

Topic: E.05. Brain-Machine Interface

Title: How much is too much: Cognitive load on BCI success

Authors: *M. L. SCHIMMEL[1], E. K. MILLER[2], S. E. BLITZ[1], Y.-C. YU[2], L. A. GABEL[1]
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Abstract: Brain-Computer Interface (BCI) devices create an alternate means of control and communication for those with severe motor impairment. Non-invasive BCI methods use EEG detected neural activity as control signals of external devices or computers, bypassing manual motor control. Mu rhythm, a sensorimotor rhythm that is synchronized or desynchronized in response to imagined movement or rest, can be controlled by the participant through biofeedback training. Due to the wide range of imagined motor activities that can be detected across the sensorimotor cortex, mu rhythm (8-13 Hz) has been particularly useful for a variety of diverse BCI applications. While BCIs continue to develop, most of this research has focused on creating technologically sound systems with improved signal acquisition features, with little work investigating how to improve participant control of the neural signals. In addition, it is important that the participant be able to control mu, as opposed to producing a strong signal for a minimal period of time, in order to maximize the usefulness of the mu-based BCI device. Recently we demonstrated that improved training procedures, focusing on participant instructions and motivation, improved accuracy and reliability of BCI control using imagined hand motion, and imagine relaxation. Using these improved methods we found that a single training session is just as effective as multiple training sessions carried out over three consecutive days. By examining different types of individualized instruction and continuous neural control in a gaming environment, we found that 91% of participants learned successful control of the device when provided with individualized instructions as opposed to 50% of control participants. Using these methods we aimed to increase the degrees of freedom associated with cursor control with additional imagined motor activities. The results of this study enhance our understanding of limits of increased cognitive load on BCI performance as we aim to improve participant success, accuracy and flexibility of the BCI device.

Disclosures: M.L. Schimmel: None. **E.K. Miller:** None. **S.E. Blitz:** None. **Y. Yu:** None. **L.A. Gabel:** None.

Poster

225. Brain-Machine Interface: Neurophysiology and Methods Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 225.30/KK12

Topic: I.07. Data Analysis and Statistics

Support: CRES fellowship (UCSD)
INC fellowship (UCSD)

Title: An open-source graphical environment for the rapid development of animal and human brain-computer interfaces

Authors: A. OJEDA[1,2], N. BUSCHER[1,3], S. SILVEIRA[1], V. MARIC[1], *D. RAMANATHAN[1,3], J. MISHRA[1]

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Abstract: An important goal of clinical neuroscience is to move towards personalized therapies that can target specific neural circuit dysfunctions that lead to neuropsychiatric disorders. To accomplish this goal, it is necessary to understand brain function across multiple scales, from single neurons to large-scale brain networks, and their interaction with the environment, hence, requiring neurophysiological investigations across animals (single-cell and local-field-potential recordings) and humans (whole-brain recordings). Furthermore, to translate this knowledge into therapies, we need closed-loop real-time systems that can extract contextually-relevant neurophysiological markers from noisy data and use these as feedback and control signals to intervene specific brain circuits, ultimately leading to the improved performance of these circuits and emergent cognitive behaviors. To address these needs we have developed SimBCI, an open-source graphical environment for the rapid prototyping of animal and human brain-computer interfaces (BCIs). SimBCI is designed as a library on top of the graphical programming environment of Simulink (MATLAB), with three goals in mind. 1) To provide a flexible cognitive platform for developing human and animal experiments by using Simulink's Stateflow programming. 2) To allow for flexible data acquisition by including multiplatform drivers for standard instrument communication protocols (including the Lab Streaming Layer). 3) To allow for real-time analysis and control of neural circuit dynamics by leveraging Simulink's DSP and Control toolboxes in addition to a customized neuroimaging module. With this library, we hope to ease the development of individualized BCI-based therapies while contributing a tool for deepening our understanding of the neurobiological and environmental basis of neuropsychiatric disorders.

Disclosures: A. Ojeda: None. **N. Buscher:** None. **S. Silveira:** None. **V. Maric:** None. **D. Ramanathan:** None. **J. Mishra:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.01/LL1

Topic: E.05. Brain-Machine Interface

Support: JST PRESTO JPMJPR1506
KAKENHI JP24700419
KAKENHI JP26560467
KAKENHI JP22700435
KAKENHI JP17H06032
KAKENHI JP15H05710

AMED Brain/MINDS

Title: Decoding natural scenes in semantic space from electrocorticography signals

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Abstract: Recent brain decoding studies have utilized semantic space as a medium for modeling and decoding brain activity. A prior study has shown that a semantic space, derived from a natural language processing model word2vec, could be used to build a brain decoder that could infer perceptual contents in words (Nishida and Nishimoto, 2017). This study explores the potential use of the semantic modeling approach to realize practical brain–machine interface (BMI) by applying it with electrocorticography (ECoG), which has a higher temporal sampling rate than the functional magnetic resonance imaging used in the prior study.
Three patients under clinical monitoring for epileptic seizures participated in this study. During ECoG recording, the patients were shown a 60-min training video and a 10-min evaluation video, both composed of short films or animation clips, with no overlapping scenes between the two videos. Movie scenes were extracted as still images once per second from the videos, and annotated manually using a natural language. Based on vector representations learned by word2vec using a Wikipedia dump, *scene vectors* were constructed by averaging 1,000-dimensional vector representations of the words in the annotation to each scene. The scene vectors were then decoded using ridge regression, and powers of the ECoG signals in four frequency bands (α, β, low-γ, high-γ). Nested cross-validation was applied during decoding to optimize the penalty term. A *word score* was calculated based on the correlation between the vector representation of the word and the scene vector for the 10,000 most frequent words in the Wikipedia dump. The significance of the decoding was tested by comparing the Pearson's correlation coefficients between predicted and true scene vectors to those expected by chance as well as by comparing word-wise correlation coefficients between predicted and true word scores for each movie scene to those expected by chance.
For both the training and evaluation video, correlation coefficients between the predicted and true scene vectors were significantly higher compared to those expected by chance for all patients (unpaired two-tailed Student's *t*-test, $P < 0.001$). Word-wise correlation coefficients were also significant for both videos for all patients ($P < 0.001$).
This study demonstrated that the vector representation of movie scenes could be decoded from the ECoG signals in the semantic space of the word2vec model. The decoder could also infer scenes that were new to both the patients and the decoder. The combination of the semantic space and ECoG could be a promising approach to realizing practical BMI.

Disclosures: R. Fukuma: None. **T. Yanagisawa:** None. **S. Nishimoto:** None. **M. Tanaka:** None. **S. Yamamoto:** None. **S. Oshino:** None. **Y. Kamitani:** None. **H. Kishima:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.02/LL2

Topic: E.05. Brain-Machine Interface

Title: Decoding visual attentional state using eeg-based bci

Authors: *S. BORHANI[1], R. ABIRI[4], S. PARVANEZADEH ESFAHANI[2], J. KILMARX[3], Y. JIANG[5], X. ZHAO[3]
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Abstract: Visual attention facilitates processing visual input by rapidly focusing on perceptually salient information and at the same time ruling out irrelevant information. We developed a Brain Computer Interface (BCI) platform to decode brainwave patterns during sustained attention and collected scalp electroencephalography (EEG) signals from the whole brain in real time using a wireless headset. Concurrently, we collected behavioral data. Our experimental materials included a series of composite images which were made by combining a scene (i.e., indoor vs outdoor) image and a face (i.e., female vs male) image. Luminance values of all images were initially equated in terms of mean and standard deviation. There were four blocks, each comprising of 50 composite images. Two blocks began with priming faces and the other two blocks began with priming scenes. During the experiment, each participant was asked to press buttons on keyboard to distinguish between indoor and outdoor scene subcategories in blocks primed with scenes and discriminate between male and female face subcategories in blocks primed with faces. We developed an individualized model using machine learning techniques to decode visual attention based on EEG signals. Our model demonstrates an instantaneous visual attention towards face and scene categories. So far, six adult participants have partaken in the study. Having extracted EEG spectral and temporal features, we filtered out the most significant features using iterative step-wise feature reduction algorithm. The results show that the average decoding accuracy of our model is highly correlated with the behavioral data. The average behavioral response was about 85%. The average categorization between scene and face sets was 77%. Further, the EEG data accuracy is comparable to previous findings using functional magnetic resonance imaging (fMRI) [1]. Findings of the present study may have clinical implications in diagnosing attention deficit in early stages of dementia or Mild Cognitive Impairment (MCI) in elderly people [2] as well as Attention Deficit Hyperactivity Disorder (ADHD). Further, the platform may have potential applications in assessing visual attention and closed-loop brainwave regulation in future.

Reference:
[1] Cohen, Jonathan D., et al. "Closed-loop training of attention with real-time brain imaging." Nature neuroscience 18.3 (2015): 470.
[2] Jiang, Yang, Reza Abiri, and Xiaopeng Zhao. "Tuning up the old brain with new tricks: attention training via neurofeedback." Frontiers in aging neuroscience 9 (2017): 52.

Disclosures: S. Borhani: None. **R. Abiri:** None. **S. Parvanezadeh Esfahani:** None. **J. Kilmarx:** None. **Y. Jiang:** None. **X. Zhao:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.03/LL3

Topic: E.05. Brain-Machine Interface

Support: Eurostars RapidMaps

Title: Online detection of real-world faces in ECoG signals

Authors: *C. KAPELLER[1], F. CAO[2], K. KAMADA[3], C. GUGER[2]
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Abstract: A large body of research has provided evidence that various visual categorization areas exist on the ventral temporal cortex (VTC). Examples include cortex regions specialized for visual word, number, object or face processing, which can be identified by electrophysiological markers like broadband gamma activity in the Electrocorticogram (ECoG). Especially a cortex region on the fusiform gyrus, the so-called fusiform face area (FFA), is well known and has been shown to be specific and causally involved in face processing. However, most electrophysiological studies are based on visual presentation through a monitor and thus cannot be generalized to real-world scenarios. Here, previous findings about face and kanji selective regions are extended by a real-world experiment that aimed in online detection of face and kanji perception by two patients (S1 and S2) with implanted intracranial electrodes who underwent neuro monitoring prior to epilepsy surgery. The brain-computer interface (BCI) was calibrated with presented computer stimuli and then tested with printed kanji characters and images of faces, real faces from surrounding persons and a mirror. Asynchronous online detection of spontaneous face and kanji recognition was possible with an accuracy of 79.9% and 28.4%, and showed a mean latency of 447 ms with respect to the stimulus. This is smaller than the achieved accuracy of 89.8% for faces and 73.5% for kanji when the BCI was tested with the calibrated computer stimuli, but still highly significant ($p<0.0005$) after a bootstrapping test. Notably, both subjects reached a high decoding performance for real-world face detection (S1:

72.4%; S2: 87.4%), whereas only one subject could keep the performance for the printed kanji (S1: 52.9%; S2: 3.9%). Hence, the VTC cortex elicits similar responses to both faces presented on a monitor and real-world faces, leading to a new brain-computer interface that can track a person's attention in an uncontrolled environment.

Disclosures: C. Kapeller: A. Employment/Salary (full or part-time):; g.tec. **F. Cao:** A. Employment/Salary (full or part-time):; g.tec. **K. Kamada:** None. **C. Guger:** A. Employment/Salary (full or part-time):; g.tec.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.04/DP11/LL4

Topic: E.05. Brain-Machine Interface

Support: Alpert Medical School seed grant

Title: Object localization and reaching with a visual prosthesis: Comparing auditory cues and simulated phosphenes

Authors: *M. B. TALBOT, M. A. PARADISO
Brown Univ., Providence, RI

Abstract: A wide range of assistive technologies are currently available to blind people, ranging in complexity from canes to brain implants that electrically stimulate the retina. However, there are few practical technologies that assist blind people with object localization tasks. The long-term goal of our project is to develop a hybrid visual prosthesis that restores a visual sense through brain stimulation, while also using auditory cues to enable precise object recognition and localization. The device takes advantage of recent developments in computer vision and machine learning to identify behaviorally relevant features in the user's environment, particularly the locations of obstacles or user-specified objects of interest. Once these locations are known, auditory or visual cues may be issued to enable localization, reaching, and grasping of a target object. Here we present the results of virtual reality psychophysical experiments conducted with sighted but blindfolded participants, who were asked to localize and reach for a target object using either auditory cues or visual cues that simulate input from an implanted retinal prosthesis (the Alpha IMS). The goals of the study were to compare object localization and reaching performance between auditory and visual cueing systems, and to compare performance when auditory or visual localization cues were delivered in coordinates relative to the head or reaching hand. We find that localization and reaching are faster, but not more precise, with auditory cues than with a currently available visual prosthesis. This is primarily due to the small visual field (10 x 10 degrees) of the simulated retinal implant. Our results also show that reaching

movements are more precise (roughly by a factor of two) when they are based on hand-relative cues than head-relative cues, for both auditory and visual cue modalities. We conclude that auditory cueing is a viable strategy for assisting blind people with precise object localization and grasping, one that can be exploited in a hybrid auditory-visual prosthesis or a device that uses auditory cues alone.

Disclosures: M.B. Talbot: None. **M.A. Paradiso:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.05/LL5

Topic: E.05. Brain-Machine Interface

Support: Fulbright Foundation in Greece
William M. Wood Foundation

Title: A longitudinal study showing the effects of training in a simulated artificial vision reading task

Authors: K. E. K. RASSIA[1], *J. S. PEZARIS[2,3]
[1]Univ. of Athens, Athens, Greece; [2]Massachusetts Gen. Hosp., Boston, MA; [3]Harvard Med. Sch., Boston, MA

Abstract: How easy is it to adapt to the sensory experience of artificial vision? Here, as part of designing a thalamic visual prosthesis, we performed a longitudinal experiment with a simulation of artificial sight to investigate the effects of daily training on a simple reading task. Spanning 40 sessions, six normally sighted individuals were seated in front of a virtual-reality apparatus that included fully gaze-contingent phosphene pattern presentation, and asked to perform an MNREAD-based reading task where they read simple, three-line sentences out loud under various viewing conditions. Subjects were graduate students in Cognitive Science from the University of Athens, in Athens, Greece, with visual acuity in excess of that required for the research, and excellent reading ability in English. Task performance was assessed on reading accuracy (percentage of words read correctly) and reading speed (number of correctly read words per minute) as the number of phosphenes in the simulation (500, 1000, 2000, clear view) and the size of the fonts (logMAR 1.0, 1.1, ..., 1.4) were varied in a balanced, interleaved sequence. Subjects read 40 sentences per daily session, two from each viewing condition / font size combination. Performance in the first session was consistent with earlier reports (Vurro, et al., 2014); the population mean of reading accuracy decreased with decreasing font size, or decreasing phosphene counts. Performance increased in all conditions over time. By 40 sessions, accuracy had saturated at 100% in many cases, although speed was continuing to improve.

Reading speed at the end of training for both of the two hardest phosphene conditions (500, 1000) was as good or better than for the next-easiest condition at the start of training, equivalent to a doubling of the number of phosphenes. Learning rates scaled with ease of task, consistent with similar work in non-human primates (Killian, et al., 2016). Effective acuity increased by about logMAR 0.3 for each pattern, also equivalent to a doubling of phosphene count, as fitted sigmoidal curves fitted to population accuracy shifted to smaller font sizes over time. In the most evocative representation of this shift, the hardest, 500-phosphene pattern which was impossible to use with the smallest font size initially, provided functional reading under the same condition after training. Given the substantial advantages conferred by training in this task, we conclude that post-implantation rehabilitation of visual prosthesis recipients will be of critical importance to optimize device utility.

Disclosures: K.E.K. Rassia: None. **J.S. Pezaris:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.06/LL6

Topic: E.05. Brain-Machine Interface

Support: Fulbright Foundation in Greece
William M. Wood Foundation

Title: The effects of gaze contingency in a simulation of artificial vision

Authors: *N. PARASKEVOUDI[1], J. S. PEZARIS[2,3]
[1]Dept. of Clin. Psychology and Psychobiology, Univ. of Barcelona, Barcelona, Spain; [2]Massachusetts Gen. Hosp., Boston, MA; [3]Harvard Med. Sch., Boston, MA

Abstract: Despite being considered automatic, perceiving the visual world is a highly complex process that depends on intact visual and oculomotor function. Visual scanning is necessary to efficiently integrate individual glances into more coherent perceptions (Chen, Hallum, Suaning, Lovell, 2007). To date, however, most prosthetic devices do not deliver stimulation based on full gaze position (head direction plus eye position within the head), but instead use a head-steered interface. They, therefore, provide suboptimal visual information to the user and require substantial training to hold the eyes fixed forward while scanning with the head (Gilchrist, Brown, Findlay, 1997). Here, we employed a virtual reality simulation of prosthetic vision to investigate the effects of fully gaze-contingent versus head-only steering of the scene camera. Twenty-three naïve subjects from the University of Athens, the Panteion University, and the general population participated in the study. All participants had normal visual acuity and good reading ability in English. Participants were seated in front of a virtual-reality apparatus that

included head-free gaze tracking (SR Research EyeLink 1000+ in Remote Mode), and head tracking (TrackHat Opentrack software with TrackIR LED clip). Subjects completed a one-session MNREAD-based reading task that allowed us to compare reading with 2000 phosphenes simulating either a head-steered scene camera, or a fully gaze-contingent (i.e., eye-position sensitive) camera. Participants read out loud simple, three-line sentences of varying font sizes (logMAR 0.9, 1.0, 1.1, 1.2, 1.3, 1.4) under three viewing conditions (i.e., head-steered, fully gaze-contingent, and unadulterated text as a control) and assessments were made through reading accuracy (percentage of words read correctly) and reading speed (number of correctly read words per minute, WPM). Our results showed that gaze-contingent performance was as expected from earlier work (Rassia, Pezaris, 2018; Vurro, et al., 2013) for both accuracy and speed, with the population average peaking at 100% accuracy at 60 WPM with logMAR 1.4 text, and tailing off with smaller font sizes. Head-steered performance was substantially lower, peaking at 10% at 2.4 WPM with logMAR 1.4, and tailing off. Subjects informally reported the head-steered condition to be quite difficult. Overall, these findings have strong implications for future visual prosthesis designs that wish to maximize performance in tasks of daily living. We conclude that full gaze-contingency is an essential requirement for visual prostheses.

Disclosures: N. Paraskevoudi: None. **J.S. Pezaris:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.07/LL7

Topic: E.05. Brain-Machine Interface

Title: The threshold of new device for artificial vision by direct optic nerve electrical stimulation (AV-DONE)

Authors: *K. NISHIDA[1], H. SAKAGUCHI[1], M. KAMEI[2], Y. TERASAWA[3], T. FUJIKADO[1], K. NISHIDA[1]
[1]Osaka Univ. Grad. Sch. of Med., Suita/Japan, Japan; [2]Aichi Med. Univ., Nagakute, Japan; [3]Nidek Co., Ltd., Gamagori, Japan

Abstract: Objective: To analyze the threshold of new device.
Methods: The patient was a 44-year-old man with autosomal-recessive RP and bare light perception. The patient had no other ocular diseases or systemic disorders that could have caused the visual loss. After a standard three-port pars plana vitrectomy, the electrode device with wires was inserted into the vitreous cavity through the silicon trocar. Then, the electrode tips were inserted into the optic disc. The biphasic, cathodic-phase-first, electrical pulse trains with a 1-s total duration were applied between one of the stimulation electrodes and the reference electrode from next day to two years after implantation. The duration of the stimulus pulses was 0.25

ms/phase, and the frequency was 320 Hz. The patient was questioned about perception of the phosphenes and the thresholds of each electrodes were measured.
Results: The patient identified electrically induced phosphenes through five or six of the seven stimulating electrodes in long term. The phosphenes was distributed focally in the visual field. The average central position of the phosphenes differed for each electrode.The thresholds of the phosphenes (next day, 9 months and 25 months after implantation) were 165±166μA, 175±69μA and 240±89μA respectively (NS).
Conclusion: The threshold of new device is stable and AV-DONE could provide the blind patients with the phosphenes in long term.

Disclosures: K. Nishida: None. **H. Sakaguchi:** None. **M. Kamei:** None. **Y. Terasawa:** A. Employment/Salary (full or part-time):; Nidek Co., Ltd.. **T. Fujikado:** None. **K. Nishida:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.08/LL8

Topic: E.05. Brain-Machine Interface

Support: NIH Grant EY023336

Title: The pattern of phosphenes perceived with multi-electrode stimulation of human visual cortex

Authors: *W. H. BOSKING, P. SUN, B. FOSTER, M. BEAUCHAMP, D. YOSHOR
Dept. of Neurosurg., Baylor Col. of Med., Houston, TX

Abstract: Electrical stimulation of early visual cortex (V1-V3) produces perception of small flashes of light known as phosphenes. Early research with visual cortical prosthetic (VCP) devices found that stimulation of single electrodes produced phosphenes at roughly the expected location in the visual field based on the location of the electrode in visual cortex. In addition, there were reports that subjects could identify simple patterns of phosphenes when electrodes were stimulated concurrently. Recent research in sighted patients has now provided quantitative data regarding the size and location of phosphenes that are produced by stimulation of single sites in V1. However, we still lack data systematically examining the percepts generated when multiple electrodes are stimulated concurrently, and how these percepts are influenced by stimulation intensity and inter-electrode distance. We examined the percepts generated by simultaneous stimulation of 2-6 electrodes. Subjects were sighted epilepsy patients (n = 8) who had undergone surgery for subdural grid and strip placement. Electrical stimulation was delivered while subjects fixated on a small cross on a touchscreen. Subjects gave a verbal report of the number of phosphenes they perceived, and in some cases drew the pattern of perceived

phosphenes on the touchscreen. The receptive field (RF) of each electrode was determined using flashing checkerboard stimuli. We stimulated 233 pairs, 69 triplets, and 12 groups of four or more electrodes. We found that the median cortical separation distance between pairs of sites that produced 2 phosphenes was much larger (24.4 mm) than the median separation between sites that produced 1 phosphene (7.2 mm). In addition, pairs of sites that produced 1 phosphene had RF centers that were shifted by smaller amounts (0.34 RF widths) than those that produced 2 phosphenes (1.16 RF widths). Similar analyses were conducted for triplets. We found that the median pairwise separation for electrodes within the triplets was 37.2 mm when the subjects saw 3 phosphenes, 23.5 mm when they saw 2 phosphenes, and 11.3 mm when they saw only 1 phosphene. In addition, we found that subjects could effectively discriminate between different patterns of electrical stimulation in 2AFC (n = 12 runs; 85.7% correct) and 3 AFC (n = 2 runs; 51.1% correct) tasks. Cortical activation patterns can be estimated based on the location of the electrode in the map of visual space and the stimulation current delivered. Our results suggest that when two cortical activation patterns overlap, the subject sees one phosphene; and when the cortical activation patterns are well separated, the subject sees two phosphenes.

Disclosures: W.H. Bosking: A. Employment/Salary (full or part-time):; Second Sight Medical Products Inc.. **P. Sun:** None. **B. Foster:** None. **M. Beauchamp:** None. **D. Yoshor:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.09/LL9

Topic: E.05. Brain-Machine Interface

Support: NIH R01 EY023336

Title: Electrical stimulation of visual cortex with dynamic current steering produces useful visual percepts in blind and sighted humans

Authors: *M. BEAUCHAMP[1], W. H. BOSKING[1], P. SUN[1], B. L. FOSTER[1], S. NIKETEGHAD[2], N. POURATIAN[2], D. YOSHOR[1]
[1]Neurosurg., Baylor Col. of Med., Houston, TX; [2]Neurosurg., UCLA, Los Angeles, CA

Abstract: Electrical stimulation of early visual cortex produces percepts of spots of lights, known as phosphenes. In visual cortical prosthetics (VCPs) the visual scene is captured by a wearable camera and transformed into a pattern of phosphenes, bypassing damaged eyes and optic nerves. A key assumption underlying all VCPs is that patients will integrate the pattern of phosphenes into a useable image, like pixels in a display. We tested this assumption and found it to be false: multiple phosphenes are not easily combined into a percept of a coherent form. To overcome this obstacle, we developed a novel stimulation paradigm, termed dynamic current

steering. *Dynamic* refers to rapidly sweeping electrical stimulation across the cortex in a pattern that corresponds to the desired visual object. An analogy with the somatosensory system is helpful: to convey a specific letter, such as "Z", through touch, one could either press a "Z" shape consisting of multiple individual points into the hand (the conventional approach) *or* one could trace a "Z" across the hand using a single point (the dynamic approach). *Current steering* refers to concurrently stimulating nearby electrodes to produce activation at a location in between the electrodes. This is helpful because existing electrode arrays are not dense enough for dynamic stimulation to stimulate every desired location in cortex: current steering allows us to create virtual electrodes that approximate a continuous trajectory.
We tested dynamic current steering in 4 sighted epilepsy patients and one blind patient with electrodes implanted over visual cortex. When subjects received a conventional stimulation paradigm consisting of simultaneous stimulation of multiple electrodes, they never reported perceiving a coherent shape. Instead, they perceived multiple isolated phosphenes. In contrast, subjects always reported dynamic coherent steering stimulation as producing a coherent shape. Guided by the retinotopic organization of visual cortex, we constructed distinct electrical stimulation patterns. Subjects were able to discriminate different patterns at far above change level (93% for the blind patient discriminating between 5 patterns). Many of the patterns were similar to letters, and with no training subjects were able to name the letter most similar to each pattern. Dynamic current requires delivering less current to the visual cortex than conventional stimulation paradigms and results in a superior perceptual experience. Dynamic current steering dramatically enhances the ability of VCPs to produce useful percepts of visual forms and can be readily integrated into VCPs already under development.

Disclosures: M. Beauchamp: None. **W.H. Bosking:** A. Employment/Salary (full or part-time):; Second Sight Medical Products. **P. Sun:** None. **B.L. Foster:** None. **S. Niketeghad:** None. **N. Pouratian:** 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.; Second Sight Medical Products. F. Consulting Fees (e.g., advisory boards); Second Sight Medical Products. **D. Yoshor:** None.

Poster

226. Brain-Machine Interface: Vision-Related

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 226.10/LL10

Topic: E.05. Brain-Machine Interface

Support: MTEC-16-02-BMI-06

Title: Longitudinal stability of epicortical microstimulation for evoking visual sensations

Authors: *D. OSWALT[1], P. DATTA[3], N. TALBOT[3], Z. MIRZADEH[4], B. GREGER[2]
[2]Sch. of Biol. and Hlth. Systems Engin., [1]Arizona State Univ., Tempe, AZ; [3]Second Sight Med. Products, Sylmar, CA; [4]Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Electrical stimulation of primary visual cortex has been shown to elicit visual sensations; proper adaptation of this may be used to create a functional visual prosthesis. For sensory prostheses to remain viable, they must interface at a biologically relevant level and supply sufficient current to evoke perception without degrading the tissue. Epicortical micro-electrodes, which do not violate the blood brain barrier and operate at a behaviorally relevant cortical column scale, may provide such a platform. This study evaluates the longitudinal performance of epicortical microstimulation (ECMS) in evoking visual sensations.
ECMS was evaluated in a nonhuman primate model. Two epicortical arrays (I1 and I2) with 200µm diameter electrodes were consecutively implanted in V1 of an adult male rhesus macaque. Each array was placed in the sagittal fissure facing the right hemisphere, with the caudal-most point placed proximal to the occipital pole. The subject was trained to respond to small flashes of visible light on a CRT monitor by lifting the left hand to indicate perception and the right hand to indicate no perception. Electrical stimulation was applied to individual electrodes to determine if the subjects perceived phosphenes. Simultaneous stimulation on neighboring electrodes was used to determine minimum perceptible difference for electrically evoked percepts via a task where the subject trained to respond to single pulses of light by lifting his left hand and multiple, spatially separated stimuli by lifting his right hand. Tissue damage was assessed by monitoring functional changes in the subject's perception of photic stimuli in the visual field area corresponding to the location of the implant.
ECMS on 200µm electrodes consistently evoked behavioral responses indicating perception of visual stimuli. The average 80% threshold across the array was 441µA for I1 and 325µA for I2. Spatial patterns in thresholds were observed at initial collection, with values tending to increase towards the periphery of the visual field. This was observed for both I1 and I2, but dissipated over months of data collection. Thresholds collected on one electrode for I2 showed consistent values over a 10-month period, with an average of 302±20µA. NHP1 identified concurrent stimulation on electrodes with 2mm center-center spacing as separate percepts in 90% of trials conducted. Photic perception was not observed to be impaired by consecutive implants or stimulation, indicating no significant deficit from explanation, re-implantation, or stimulation-induced neurotoxicity. The data support epicortical microelectrode interfaces as a viable platform for a visual prosthesis.

Disclosures: D. Oswalt: None. **P. Datta:** None. **N. Talbot:** None. **Z. Mirzadeh:** None. **B. Greger:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.01/LL11

Topic: F.04. Stress and the Brain

Support: NIMH grant MH053851
SALSI Postdoctoral Neuroscience Fellowship

Title: Optogenetically-induced plasticity in the rat medial prefrontal cortex can impair or enhance attentional set-shifting

Authors: *S. E. BULIN, K. M. HOHL, D. A. MORILAK
Pharmacol., Univ. of Texas Hlth. At San Antonio, San Antonio, TX

Abstract: Relapse and residual symptoms of stress-related mood and anxiety disorders remain problematic, and a poor understanding of the neurobiology underlying these illnesses has limited new treatments. Imaging studies show reduced activity in the mPFC in both depression and PTSD are associated with deficits in executive functions, including impaired cognitive flexibility, that not only represent symptoms of these illnesses, but also contribute to their development and maintenance. Such changes presumably involve aberrant forms of neural plasticity in the mPFC. Similarly, chronic stress compromises cognitive flexibility, and is likely to disrupt the plasticity that underlies this executive process, which is measured using the attentional set-shifting test. Further, CUS attenuates the response of the mPFC to stimulation of the mediodorsal thalamus (MDT), an excitatory afferent. Thus, we are using optogenetics to investigate if directly inducing long-term depression (LTD) in the mPFC is sufficient to mimic CUS-induced set-shifting deficits, and if directly inducing long-term potentiation (LTP) in the mPFC restores cognitive flexibility after CUS. Glutamatergic neurons in the MDT were selectively transfected with the ChETA variant of channelrhodopsin and allowed 6 weeks for expression and trafficking to terminals innervating the mPFC. First, rats were anesthetized and baseline field potentials evoked by MDT stimulation were recorded in the mPFC for 15 min. Then, optical LTD (900 light pulses, 1 ms at 1 Hz for 15 min) or LTP (10 x 1 s trains of pulses, 1 ms at 250 Hz, over 100 s) were induced by stimulating mPFC terminals with 472nm light and field recordings continued for an additional three hours. The LTD protocol induced a depressed mPFC response to MDT stimulation to 75% of baseline ($n=4$; $p<0.0001$), while the LTP protocol increased the response to 125% of baseline ($n=4$; $p <0.002$). We then used these protocols to test the effect of LTD/LTP on set-shifting in awake rats. ChETA-injected rats that received the LTD protocol 1 hr prior to set-shifting required significantly more trials than either control group ($n=10$-14/group; one-way ANOVA, $p<0.01$). Thus, LTD in the mPFC produced a deficit similar to that observed after CUS. To test if directly inducing LTP in the mPFC is sufficient to restore

cognitive flexibility after CUS, a separate cohort underwent CUS treatment prior to cognitive testing. CUS animals receiving LTP 30 min prior to set-shifting took significantly fewer trials than non-potentiated CUS rats (n=7-13/group, one way-ANOVA $p<0.001$). These data suggest that set-shifting is regulated by plasticity within the mPFC, specifically in response to the MDT afferent.

Disclosures: S.E. Bulin: None. **K.M. Hohl:** None. **D.A. Morilak:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.02/LL12

Topic: F.04. Stress and the Brain

Support: NIH R01MH093981-03
NIH 5T32NS007413-17

Title: Sex differences in paraventricular thalamic neuron function in the adolescent rat

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Abstract: The posterior paraventricular thalamic nucleus (pPVT) comprises a critical component of the stress response, controlling HPA axis adaptation to chronic stress and coordinating corticolimbic responses. Striking sex differences in HPA axis response to stress have been shown, with females displaying greater stress responsivity. However, there is currently little information on sex differences in pPVT neural activity or whether pPVT neural activity changes over development. This study is, to our knowledge, the first to address these questions using whole-cell patch clamp recordings. Adolescent male Sprague-Dawley rats (PD 38-45) were exposed to a single 30-minute restraint stress, 5 days of daily 30-minute restraint stress, or control conditions. Adolescent female stress studies are ongoing, with controls completed. Twenty-four hours after the final restraint, 300µm-thick slices containing pPVT were obtained and pPVT neurons were recorded. Four distinct firing patterns were found in both males and females as previously shown: reluctant (non-firing), bursting, single-spiking, and sustained firing neurons. Stress in males altered the percentages of each firing pattern, reducing overall activity, and female controls had significantly more sustained-firing cells than males, indicating enhanced pPVT activity. Stress in males increased the input resistance, due to changes in single-spiking cells, and a single stress lengthened the half-width of action potentials, due to sustained-firing cells. Female controls had significantly larger afterhyperpolarization amplitudes than males for all cell firing patterns. Restraint stress, either acute or repeated, altered synaptic transmission by

increasing the amplitude of spontaneous postsynaptic currents (sEPSCs) in males. For acutely stressed rats, this change was driven by single-spiking cells, but for repeatedly stressed rats, it was driven by sustained firing cells. Interestingly, female controls had higher sEPSC amplitude than male controls, equivalent to stressed males, and this was driven by single-spiking cells. This study reveals that acute and repeated restraint stress alters pPVT neuronal function by affecting distinct populations of pPVT neurons in adolescent male rats. Females display a more excitable pPVT at baseline, which may underlie heightened HPA axis responsiveness to stress and greater stress susceptibility. Ongoing studies are examining pPVT neural activity in stressed adolescent females and in adult males and females.

Disclosures: K.R. Urban: None. **B. Corbett:** None. **S. Bhatnagar:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.03/LL13

Topic: F.04. Stress and the Brain

Support: JSPS fellowship for overseas Research
JSPS Grant for young scientists (B) 25780454
NIDA Grant DA027764

Title: Differential effects of acute stress on effort and reward sensitivity during decision making

Authors: *N. WATANABE[1,2,3,4], J. B. DENNISON[1], M. R. DELGADO[1]
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Abstract: Calculating the trade-off between potential rewards and effort expenditure is important to maximize individual benefits. Indeed, motivation to exert more effort is typically coupled with a higher potential incentive. An interesting question is how the valuation of reward and effort is influenced by acute stress. The experience of stress can impact reward sensitivity (for review see; Porcelli & Delgado, 2017; Ironside et al., 2018), although it is unclear whether and how stress can modulate the interaction between reward and effort during decision-making processes. One prediction is that stress could serve to increase focus on the required efforts necessary to achieve a reward. Alternatively, the experience of stress may promote a diminished sensitivity to effort, resulting in a more reward-driven value calculation. Here, we evaluate the relationship between acute stress experience and reward-effort balance during decision making. Acute stress was induced using the socially evaluated cold-pressure test (SECPT: Schwabe et al., 2008) and measured with pupillometry and cortisol changes. Preliminary data included

participants (n = 50) randomly assigned to stress (n = 27) and non-stress control conditions (Ctl: n = 23). Within the stress condition, responders (Res: n = 14) and non-responders (NoR: n = 13) were classified using a baseline to peak cortisol increase criteria of 15.5% (Miller et al., 2013). All participants performed a task where they had to accept or reject an offer (e.g. 700 keyboard button presses to earn $1.25) within 6 seconds. Each offer varied with respect to two dimensions: reward ($0.20 ~ $2.00) and effort (100 ~ 1000 button presses). Individual reward and effort sensitivities were estimated from 100 binary choices by logistic multiple regression, and mean beta weights were compared among three groups. Stress responders had significantly lower effort sensitivity compared to controls (Ctl vs. Res: $t = 2.99$, $p_{FWE} = 0.02$), and non-responders (Res vs. NoR: $t = -2.63$, $p_{FWE} = 0.04$), However, reward sensitivity did not vary between groups (Ctl vs. Res: $t = 0.67$, $p_{FWE} = 1.00$, Ctl vs. NoR: $t = 0.39$, $p_{FWE} = 1.00$, Res vs. NoR: $t = -0.29$, $p_{FWE} = 1.00$), that is, stress responders made their decision on the basis of reward size irrespective of physical effort. Further analyses will be conducted aimed at investigating the relationship between individual physiological stress response (pupil or cortisol response) and sensitivity to offers (reward-effort balance).

Disclosures: N. Watanabe: None. **J.B. Dennison:** None. **M.R. Delgado:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.04/LL14

Topic: F.04. Stress and the Brain

Support: NS28912
MH73136

Title: Estrus protects females from impaired learning following multiple acute stresses

Authors: *A. K. SHORT[1], E. T. ADAMS[1], Y. CHEN[1], Y. YU[1], A. PHAM[1], J. MOLET[2,1], T. Z. BARAM[1]
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Abstract: Rationale: Multiple, concurrent acute stresses involving emotional, physical and social components enduringly impair spatial memory in male mice, which is associated with functional loss of synaptic potentiation and structural disruption of synapse-bearing dendritic spines in the hippocampus. Males and females behave differently in response to emotional and social stressors, and sex differences in spatial memory have long been observed in humans and animals. However, little is known about the underlying synaptic and molecular mechanisms responsible for these differences. Here, we subjected female mice to simultaneous multiple acute stresses

lasting 2 h (MAS) and investigated the effects of estrous cycle and MAS on memory function and their underlying molecular basis. Methods: Female C57bl6 mice at 2 months of age were subjected to MAS in either estrus or di-/pro-estrus and trained in a hippocampus-dependent object location memory (OLM) task 2 h following stress. Control, non-stressed animals in estrus or di-/pro-estrus were trained at the same time. Brain slices from stressed mice and non-stressed controls in different stages of the estrous cycle were used to test the different effects of MAS on the dendritic spines. Results: As was previously observed in males, females exposed to MAS in di- or pro-estrus had a significant reduction in spatial memory when tested on OLM. However, when females in estrus were stressed there were no differences in spatial learning when compared to control animals. Studies are underway to determine the underlying molecular mechanisms behind this phenomenon.

Disclosures: A.K. Short: None. **E.T. Adams:** None. **Y. Chen:** None. **Y. Yu:** None. **A. Pham:** None. **J. Molet:** None. **T.Z. Baram:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.05/MM1

Topic: F.04. Stress and the Brain

Title: Chronic social defeat stress reduces nectin-1 mrna levels and disrupts dendritic spine plasticity in the adult mouse perirhinal cortex

Authors: *C. WANG[1], Q. GONG[1], Y.-A. SU[2], C. WU[1], T.-M. SI[2], J. M. DEUSSING[3], M. V. SCHMIDT[3], X.-D. WANG[1]
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Abstract: In adulthood, chronic exposure to stressful experiences disrupts synaptic plasticity and cognitive function. Previous studies have shown that perirhinal cortex-dependent object recognition memory is impaired by chronic stress. However, the chronic social defeat stress effects on molecular expression and structural plasticity in the perirhinal cortex remain unclear. In this study, we applied the chronic social defeat stress paradigm and measured the mRNA levels of nectin-1, nectin-3 and neurexin-1, three synaptic cell adhesion molecules implicated in the adverse stress effects, in the perirhinal cortex of wild-type and conditional forebrain corticotropin-releasing hormone receptor 1 knockout (CRHR1-CKO) mice. Chronic stress reduced perirhinal nectin-1 mRNA levels in wild-type but not CRHR1-CKO mice. In conditional forebrain corticotropin-releasing hormone overexpression (CRH-COE) mice, perirhinal nectin-1

mRNA levels were also reduced, indicating that chronic stress modulates nectin-1 expression through the CRH-CRHR1 system. Moreover, chronic stress altered dendritic spine morphology in the main apical dendrites and reduced spine density in the oblique apical dendrites of perirhinal layer V pyramidal neurons. Our data suggest that chronic stress disrupts cell adhesion and dendritic spine plasticity in perirhinal neurons, which may contribute to stress-induced impairments of perirhinal cortex-dependent memory.

Disclosures: C. Wang: None. **Q. Gong:** None. **Y. Su:** None. **C. Wu:** None. **T. Si:** None. **J.M. Deussing:** None. **M.V. Schmidt:** None. **X. Wang:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.06/MM2

Topic: F.04. Stress and the Brain

Support: DLR Grant 50WB1516

Title: Sleep, cognition and neurophysiological responses during isolation

Authors: *T. KLEIN[1,2], J. WEBER[1], A. ROSSITER[3], T. FOITSCHIK[1], B. CRUCIAN[4], S. SCHNEIDER[1,2], V. ABELN[1]
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Abstract: Space and isolation missions are stressful and negatively impact quality of sleep, mood and cognitive performance of crewmembers. Also important neurotropic factors, BDNF and IGF-1, are reduced with stress. The underlying neurophysiological mechanisms are unclear and efficient countermeasures missing. We aimed to investigate the effect isolation (30 days) on sleep, mood, cognition, neutrotrophic factors and brain cortical activity, to explore possible underlying neurophysiological mechanisms.
16 participants (aged: 37±7y) were isolated in 4 missions. During each mission 4 participants were isolated in the Human Exploration Research Analogue at NASA for 30 days. 17 non-isolated participants (control group, aged: 32±9y) were tested simultaneously. Both groups performed daily physical exercise throughout the interventions. Sleep was assessed with actigraphy (Respironics, Amsterdam). On mission days -5, 7, 28 and +5 sleep and awakening quality questionnaires (SSA), Positive Affect and Negative Affect Scale (PANAS-X), cognitive tasks and a five-minutes resting EEG (Brain Products, Munich) with closed eyes were completed. Intravenous morning cortisol, melatonin, BDNF and IGF-1 was compared between groups. Effects of the groups (isolation vs. non-isolation) and time were determined using

repeated measures ANOVA.
Cortisol was significantly increased during isolation in comparison to non-isolated group ($p<0.01$). Melatonin ($p=0.37$), BDNF ($p=0.92$) and IGF-1 ($p=0.09$) was similar between the groups and remained unchanged over time. No group effects for actigraphy total light exposure during sleep ($p=0.61$), sleep efficiency ($p=0.54$) and subjective sleep quality (SSA, $p=0.10$) were shown. Mood was similar between the groups (positive affect ($p=0.38$), negative affect ($p=0.20$)) and cognitive performance tests unaffected by the isolation (group effects: visuo-perceptual speed, $p=0.22$; arithmetical ability, $p=0.75$; special working memory, $p=0.29$). Frontal cortical current density was similar between the groups ($p=0.40$) and remained unchanged throughout the interventions (interaction, $p=0.72$).
Sleep, mood and cognition were not impaired by 30 days of isolation, although increased levels of cortisol suggest high level of stress. Maintained sleep quality during isolation might have positively affected the CNS, as brain cortical activation and neurotropic factors remained unaffected by the isolation. An ongoing HERA campaign, might allow further analyses and insights into possible underlying neurophysiological mechanisms as well as the effect of physical activity as participants exercise less during isolation.

Disclosures: T. Klein: None. **J. Weber:** None. **A. Rossiter:** None. **T. Foitschik:** None. **B. Crucian:** None. **S. Schneider:** None. **V. Abeln:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.07/MM3

Topic: F.04. Stress and the Brain

Support: National Natural Science Foundation of China (81761138044 and 81471369)
the National Key Research and Development Program of China (2016YFA0501000)

Title: Dorsal CA1 interneurons mediate acute stress-induced spatial memory deficits

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Abstract: Exposure to severely stressful experiences disrupts the activity of neuronal circuits and impairs declarative memory. GABAergic interneurons coordinate neuronal network activity, but their involvement in stress-evoked memory loss remains unclear. Here, we provide evidence that interneurons in area CA1 of the dorsal hippocampus partially modulate acute stress-induced memory deficits. In adult male mice, both acute forced swim stress and restraint stress impaired

hippocampus-dependent spatial memory and increased the density of c-fos-positive interneurons in the dorsal CA1. Selective activation of dorsal CA1 interneurons by chemogenetics disrupted memory retrieval in the spatial object recognition task. In comparison, anxiety-related behavior, spatial working memory and novel object recognition memory remained intact when dorsal CA1 interneurons were overactivated. Moreover, chemogenetic activation of dorsal CA1 interneurons suppressed the activity of adjacent pyramidal neurons, whereas a single exposure to forced swim stress but not restraint stress increased the activity of CA1 pyramidal neurons. However, chemogenetic inhibition of dorsal CA1 interneurons led to spatial memory impairments and failed to attenuate acute stress-induced memory loss. These findings suggest that acute stress may overactivate interneurons in the dorsal CA1, which reduces the activity of pyramidal neurons and in turn disrupts long-term memory.

Disclosures: J. Yu: None. **P. Fang:** None. **C. Wang:** None. **X. Wang:** None. **K. Li:** None. **Q. Gong:** None. **B. Luo:** None. **X. Wang:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.08/MM4

Topic: F.04. Stress and the Brain

Title: Rapid intracellular Zn^{2+}dysregulation via corticosteroid receptor activation affects *in vivo* CA1 LTP

Authors: *M. SUZUKI, T. KOTARO, Y. SATO, H. TAMANO, A. TAKEDA
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Abstract: Glucocorticoid (GC) secretion from the adrenal cortex is increased after exposure to stress and induces cognitive decline. GC readily passes through the blood-brain barriers and binds two types of corticosteroid receptors, i.e., the mineralocorticoid (MC) and GC receptors. Both MC and GC receptors are highly expressed in CA1 pyramidal cells of the hippocampus. Cell membrane-bound MC and GC receptors are linked with rapid non-genomic response and GC readily modifies glutamatergic Schaffer collateral-CA1 pyramidal cell synapse activity via these receptors. Because Zn^{2+} is released from the Schaffer collateral, it is estimated that Zn^{2+} is involved in stress-induced cognitive decline via cell membrane MC and GC receptor activation. Here we tested whether long-term potentiation (LTP) at Schaffer collateral-CA1 pyramidal cell synapse is affected by intracellular Zn^{2+} dysregulation via cell membrane MC and GC receptor activation, in comparison with intracellular Ca^{2+} dysregulation. In anesthetized rats, extracellular Zn^{2+} level was increased under local perfusion of the CA1 with 500 ng/ml corticosterone. In vivo LTP was attenuated by the pre-perfusion of corticosterone prior to tetanic stimulation and the attenuation was canceled by co-perfusion with CaEDTA, an extracellular Zn^{2+} chelator,

suggesting that corticosterone-induced increase in extracellular Zn^{2+} is involved in the subsequent attenuation of LTP. In rat brain slices, corticosterone-induced increases in intracellular Zn^{2+} and intracellular Ca^{2+}, in addition to extracellular Zn^{2+}, were blocked in the presence of spironolactone, a MC receptor antagonist that canceled corticosterone-induced attenuation of LTP. Mifepristone, a GC receptor antagonist, which also canceled corticosterone-induced attenuation of LTP, blocked corticosterone-induced increase in intracellular Zn^{2+}, but not those in extracellular Zn^{2+} and intracellular Ca^{2+}, suggesting that intracellular Zn^{2+} dysregulation in CA1 pyramidal cells is crucial for affecting CA1 LTP. Moreover, corticosterone-induced decrease in phosphorylated CaMKII was restored in the presence of CaEDTA. The present study indicates that glucocorticoid rapidly increases intracellular Zn^{2+} via membrane MC and GC receptor activation and decreases phosphorylated CaMKII level, resulting in attenuating LTP. Membrane MC and GC receptors differentially induce intracellular Zn^{2+} dysregulation. In contrast, glucocorticoid-induced rapid increase in intracellular Ca^{2+} is not crucial for affecting LTP.

Disclosures: M. Suzuki: None. **T. Kotaro:** None. **Y. Sato:** None. **H. Tamano:** None. **A. Takeda:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.09/MM5

Topic: F.04. Stress and the Brain

Support: Michigan Institute for Clinical Health Research (MICHR) Seed Grant U050540
MICHR Postdoctoral Translational Scholars Award UL1TR000433
Cohen Veteran Biosciences Foundation
NIMH K23 K23MH109762

Title: The relationship between cumulative stress exposure and hippocampal activation during contextual memory

Authors: *R. A. JOHN, B. J. KUBAT, A. HICKS, S. A. JOSHI, J. L. ABELSON, I. LIBERZON, E. R. DUVAL
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Abstract: Background: Exposure to stressful events is common, with a wide range of types and number of stressful events endorsed, even within healthy populations. Memory impairments have been reported in people exposed to early life stress and trauma. Literature documents the role of the hippocampus (hpc) in memory processes, including encoding and recall of items and complex contextual scenes. Contextual memory is of particular interest, as recent findings

suggest that deficits in contextual memory could contribute to impairments in fear modulation in post-traumatic stress disorder (PTSD). To further investigate relationships between contextual memory and exposure to stress, we examined hpc activation during contextual memory processing and cumulative stress exposure in a sample of healthy adults. Methods: Eighteen healthy participants, 10 female, aged 20 to 42 years (M = 27.9, SD = 7.18) reported the total number and mode of stressful events experienced throughout their life on the Life Events Checklist (LEC; Weathers et al., 2013). All participants underwent fMRI scanning while completing the Context Separation and Completion (CSC) task to assess memory for complex contextual scenes. Participants encoded two target scenes (living room and office) and then categorized a series of ambiguous images as more like the living room, more like the office, or neither/both, based on their recall of the encoded target scenes. Results: Across all participants, we found a significant positive relationship between number of stressful events reported as "happened to me" and hpc activation during the CSC task ($p < .001$, uncorrected). There was no significant relationship between number of "happened to me" stressful events and accuracy on the CSC ($p = .27$). Discussion: Our results illustrate that hpc activation during contextual memory is associated with cumulative stress exposure in a healthy adult sample. Our findings suggest that greater hpc activation in people exposed to more stressful events may be compensatory since no relationship between accuracy and stress exposure was observed. We will use this paradigm to investigate relationships between PTSD symptoms, fear modulation, and hpc activation during contextual memory.

Disclosures: R.A. John: None. **B.J. Kubat:** None. **A. Hicks:** None. **S.A. Joshi:** None. **J.L. Abelson:** None. **I. Liberzon:** None. **E.R. Duval:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.10/MM6

Topic: F.04. Stress and the Brain

Support: Cohen Veterans Bioscience Foundation

Title: Fear learning in stress vulnerable and resilient rats

Authors: *J. PEARSON-LEARY[1], E. FEINDT-SCOTT[2], S. BHATNAGAR[3]
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Abstract: Chronic stress can have a profound influence on mood and can increase the risk of depression, anxiety, and PTSD. However, not all humans who experience chronic stress develop

these conditions, suggesting some people are specifically vulnerable to the effects of chronic stress. Several rodent models of stress vulnerability and stress resiliency have emerged over the past decade. We have previously shown that a subpopulation male Sprague Dawley rats subjected to chronic social defeat stress show indices of vulnerability including increased anxiety-like and depression-like behaviors. These stress vulnerable rats exhibit passive coping during repeated defeat as evidenced by short-latencies (SL) to be defeated, and we have used this model extensively to study stress vulnerability. Rats with long-latencies (LL) to social defeat are considered resilient to the effects of chronic stress, as they are similar to non-stressed control rats on measures of depression-like and anxiety-like behaviors. There is evidence that learning deficits may emerge in SL rats, including impaired reversal learning, however fear-related learning has not been well- studied in rats exhibiting individual differences in response to repeated social defeat. Here, we tested the hypothesis that SL rats have elevated fear-related memory and decreased fear extinction to a context in which they previously received foot shocks. We used a standard contextual fear training paradigm in which rats were given several foot shocks in a fear condition chamber (context), and then tested for freezing behavior over several days by re-exposure to the chamber (context) in the absence of the shock to test for extinction of the learned freezing response. We found that relative to resilient LL rats, SL rats had increased freezing when placed in the context 24 hours following the initial training trial. 24 h following this extinction trial, SL rats continued to show increased freezing in response to the context, suggesting, persistence of decreased extinction relative to LL rats. Finally, 11 days following testing for retention of extinction, SL rats continued to show increased freezing in response to the context, suggesting decreased retention of fear extinction. These data suggest that decreased fear extinction may accompany stress vulnerability, and these fear extinction deficits may persist long-term.

Disclosures: J. Pearson-Leary: None. **E. Feindt-Scott:** None. **S. Bhatnagar:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.11/MM7

Topic: F.04. Stress and the Brain

Support: NIH Grant 1R15MH108926-01A1
Texas Woman's University Startup Funds

Title: Post- myocardial infarction cognitive and affective deficits: Role of the mineralocorticoid receptor

Authors: *M. J. MORRIS[1], J. FRAYRE[1], E. S. NA[2]
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Abstract: Individuals that survive a myocardial infarction (MI) are more likely to develop depression, anxiety, and cognitive impairments as compared to healthy individuals. The incidence of depression in patients that have survived an MI has been reported to be as high as 45%, while occurring in 2-9% of the general population. We utilized coronary artery ligation to produce MI in rats and subsequently studied behavior in the social interaction test, a validated test of depressive-like behavior in rodents, and in a Barnes Maze task, a test of cognitive function. We found that 3-4 weeks after surgery, rats with experimentally-induced MI (> 30% of the left ventricle) exhibited a significant decrease relative to sham rats in the ratio of time spent with the target (a novel conspecific rat) present versus when the target was absent. Rats with experimentally-induced MI also showed a reduced average bout time with the target present as compared to sham rats. These deficits were not apparent following MI if the rats were given daily treatment with the mineralocorticoid receptor antagonist spironolactone (50 mg/k/day, IP) following MI. In a separate experiment we determined that treatment with the mineralocorticoid hormone aldosterone on its own (0.75 µg/0.25 µl/hr in 0.2% ETOH via osmotic minipump) provokes similar deficits in social interaction as those observed in rats post-MI. Treatment with spironolactone did not prevent deficits in cognitive function in the Barnes Maze task 3-4 weeks after MI. Aldosterone is elevated 4 weeks post-MI in our studies and known to be elevated in post-MI patients as well as in many individuals with major depressive disorder. Our data suggest that aldosterone may be involved in the affective deficits commonly observed in cardiovascular disease patients.

Disclosures: M.J. Morris: None. **J. Frayre:** None. **E.S. Na:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.12/MM8

Topic: F.04. Stress and the Brain

Support: Funded by BlackThorn Therapeutics

Title: The kappa opioid receptor antagonist, BTRX-335140, protects working memory performance from mild stress exposure in rhesus monkeys

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Abstract: The dorsolateral prefrontal cortex (dlPFC) subserves higher order cognitive operations such as working memory and top-down control. However, these circuits are readily disengaged with uncontrollable stress exposure, impairing cognitive and executive functions and exacerbating mental disorders (Nat Neurosci 18:1376,2015). Decades of research in animal models have shown that stress-induced PFC dysfunction can be initiated by amygdala activation of catecholamine release in the PFC (J Neurosci 16:4787,1996). This drives calcium-cAMP-K^+ channel signaling, reducing dlPFC neuronal firing and impairing working memory (Nat Neurosci 18:1376,2015). Loss of PFC working memory function occurs with psychological or pharmacological stressors, including the GABA inverse agonist FG7142, which activates the amygdala (Prog Neuropsych Biol Psych 34:1285-93, 2010). The stress response also involves release of dynorphins, which activate kappa opioid receptors (KOR) on presynaptic glutamate projections from amygdala into the PFC and the bed nucleus of the stria terminalis to increase anxiety circuits (Neuropsychopharm 40; 2856, 2015; Cell Rep 14:2774, 2016). Given that stress-induced PFC dysfunction is a risk factor for a host of mental disorders, there is a great need for nonaddictive treatments that can lessen the stress response and protect PFC cognitive function. The current study examined the effects of BTRX-335140, a potent, selective and reversible KOR antagonist, on stress-induced working memory deficits induced by FG7142 treatment in rhesus monkeys. A dose of FG7142 was identified that specifically impaired working memory performance in each animal without compromising the animal's ability to complete the task. BTRX-335140 (0, 0.1, 0.3, 1.0 mg/kg, im) was co-administered with FG7142 or vehicle 30 min before testing. BTRX-335140 had no significant effect of its own on working memory performance under nonstress conditions. However, BTRX-335140 was able to protect working memory performance from the detrimental effects of FG7142, with no evidence of side effects. These data in rhesus monkeys encourage the utility of the KOR antagonist BTRX-335140 for the treatment of stress-related mental disorders.

Disclosures: T.L. Wallace: A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **W.J. Martin:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. **A.F.T. Arnsten:** 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.; BlackThorn Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Royalties from USA sales of Intuniv (nongeneric) from Shire Pharma.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.13/MM9

Topic: F.04. Stress and the Brain

Support: French Health Service (SSA)
General Delegation for Armament (DGA)

Title: The relationship between allostasis and psychological patterns in a healthy French military population

Authors: *D. CLAVERIE[1,2,3,4,5], D. FROMAGE[2,3], C. BECKER[6,4,5,7], J.-G. HOUEL[8], J.-J. BENOLIEL[4,6,5,9], F. CANINI[2,3], M. TROUSSELARD[2,3]
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Abstract: Repetitive stressor exposure may favor psychopathologies through the increase in allostatic load. However, between the naive state and the pathology, a state of sole allostatic load may exist. Our objective was to identify associations between biological markers of allostatic load and psychological characteristics in non-pathological subjects. We hypothetized that a healthy military population frequently exposed to stress and medically followed may exhibit different levels of allostatic load without pathological signs. We included therefore 405 soldiers aged of 18-50 years and already deployed overseas. High urinary and plasma cortisol, high urinary 8-iso-prostaglandin-F2alpha (8-iso-PGF2alpha) and low serum Brain Derived Neurotrophic Factor (BDNF) were considered as marker of allostatic load. Psychological characteristics were assessed by Hospital Anxiety and Depression Scale (HADS: HAD-A and HAD-D for anxiety and depression respectively), PTSD Checklist (PCL-4), Perceived Stress Scale (PSS) and Spielberger Anxiety Scale (Trait and State : STAI-T and STAI-S respectively). In this population, 42 soldiers had pathological scores at HAD-A, or/and HAD-D or/and PCL questionnaire despite healthy state attested by a physician. High scores at HAD-D were associated with a low BDNF level. High scores at PCL were associated with high level of 8-iso-PGF2alpha and urinary cortisol. Soldiers with low psychopathological scores exhibited lower urinary cortisol and 8-iso-PGF2α than high scoring subjects. A hierarchical clustering performed on these allostatic load markers isolated 4 subgroups : one associated high 8-iso-PGF2alpha level

and low PSS scores and another associated high level of plasma cortisol and high STAI-S scores. Our results showed that in a healthy population, subjects scoring high to HAD/PCL scales also exhibit markers of a high allostatic load while subject scoring low to HAD/PCL scales may also exhibit such biological pattern, although without psychological signs. The existence of such infraclinical states suggests that an evidence based primary prevention could be possible. However, other studies are needed to evaluate predictive power of such states.

Disclosures: D. Claverie: None. **D. Fromage:** None. **C. Becker:** None. **J. Houel:** None. **J. Benoliel:** None. **F. Canini:** None. **M. Trousselard:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.14/MM10

Topic: F.04. Stress and the Brain

Support: Tjallingh Roorda Stichting

Title: The interplay between antidepressants and mitochondria in a mouse model with decreased mitochondrial complex I function

Authors: *T. L. EMMERZAAL[1], L. JACOBS[2], B. GRAHAM[4], E. MORAVA[5], R. RODENBURG[3], T. L. KOZICZ[2]
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Abstract: An increasing body of evidence points toward the involvement of suboptimal mitochondrial function (SMF) in depression and other mood disorders. Several clinical and preclinical studies show that depression is associated with altered mitochondrial structure and function. Furthermore, stress, a major risk factor for depression, directly influences mitochondrial function. Also, it seems that different antidepressants influence the mitochondria in different ways, for better or for worse. It is for example known that fluoxetine (Prozac) can have a negative effect on mitochondrial function while ketamine can have a positive effect. The aim of this study is to investigate the interaction between different antidepressants, fluoxetine and ketamine, and mitochondrial function on the behavior of stressed mice. To test this, a new genetically engineered mouse model was used. These animals have a deficiency of the NDUFS4 protein (Ndufs4def mice), a structural protein of complex I (CI), an essential component of the electron transport chain and oxidative phosphorylation. This deficiency leads to a 25% reduction of CI activity in the brain compared to WT mice. Despite this reduction, Ndufs4def mice exhibited no differences in body weight, physical activity, and motor coordination compared to their WT littermates. These animals, together with their WT littermates, are chronically stressed

for 21 days and are treated with either fluoxetine or ketamine. We will report on depression-like phenotype in the various experimental groups assessed by a battery of behavioral tests as well as physiological and biochemical measures. We will also report on the effect of stress and mitochondrial complex activity with or without the use of antidepressants. Results from these experiments would provide novel insights into personalization in drug choice because they will provide alerts to possible adverse drug events as well as facilitate optimal treatment selection in stress-related mood disorders.

Disclosures: T.L. Emmerzaal: None. **L. Jacobs:** None. **B. Graham:** None. **E. Morava:** None. **R. Rodenburg:** None. **T.L. Kozicz:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.15/DP12/MM11

Topic: F.04. Stress and the Brain

Support: Medical Research Council (MRC) Grant

Title: An fMRI study of emotion during pulsatile glucocorticoid replacement in adrenal insufficiency

Authors: *J. THAKRAR[1,2], K. KALAFATAKIS[3], G. M. RUSSELL[3], C. HARMER[6], M. MUNAFO[4], N. MARCHANT[3], J. BOWLES[3], J. THAI[5], A. WILSON[5], J. BROOKS[5], R. MORAN[7], S. L. LIGHTMAN[3]
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Abstract: The Pulses Study is a clinical trial registered with World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.isrctn.com/ISRCTN67193733). This trial was designed to test whether a subcutaneous pulsatile infusion of hydrocortisone (8 pulses over 24 hours) using an infusion pump is an improved form of glucocorticoid replacement therapy for patients with adrenal insufficiency. Glucocorticoid replacement therapy in patients with adrenal insufficiency is a well-established treatment method. A typical treatment schedule includes three oral doses of hydrocortisone (10mg, 5mg, 5mg; amounting to a total 20mg) administered throughout the day. Regretfully, many patients continue to complain of fatigue, weakness and a severe lack of motivation, despite their daily levels of hydrocortisone being replenished to those expected in healthy individuals. Previous studies in animals and healthy

volunteers indicate that dynamic oscillations of glucocorticoids, are important for healthy neuroendocrine function affecting both fast non-genomic and slow genomic processes and that the ultradian rhythmicity of circulating cortisol is critical for the physiological response of the brain to emotional stimuli.
We conducted a double-blind, placebo-controlled, two-way crossover study in participants with conditions of adrenal insufficiency, 18 participants with Addison's Disease (AD; 16 females, 2 left-handed) and 3 with Congenital Adrenal Hyperplasia (CAH; 2 females). In one of two 6-week long study periods, each participant received one of two hydrocortisone replacement therapies: hydrocortisone oral tablets taken three times per day, or a pulsatile subcutaneous infusion of hydrocortisone delivered via an infusion pump (approximated to follow both the ultradian and circadian variations of cortisol in healthy individuals). Dosage varied from 20-40mg according to the individual's current prescription. At the end of each 6-week period, the patients took part in a functional magnetic resonance imaging (fMRI) study during which they underwent a facial expression recognition (FERT) task. Neuroimaging data are to be analysed using FSL software (fmrib Software Library), Statistical Parametric Mapping and Dynamic Causal Modelling.
Due to the blinding strategy implemented in the clinical trial protocol, data analysis for this study will commence after the agreed data-lock implemented by the data monitoring committee. We will present these results at SFN 2018.

Disclosures: J. Thakrar: None. **K. Kalafatakis:** None. **G.M. Russell:** None. **C. Harmer:** None. **M. Munafo:** None. **N. Marchant:** None. **J. Bowles:** None. **J. Thai:** None. **A. Wilson:** None. **J. Brooks:** None. **R. Moran:** None. **S.L. Lightman:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.16/MM12

Topic: F.04. Stress and the Brain

Support: Dean Faculty of Science Grant, University of Karachi

Title: Taurine supplementation improves spatial & recognition memory in rats sub-chronically exposed to noise stress via normalizing neurotransmitter levels & antioxidant enzyme activity

Authors: *S. HAIDER[1], I. SAJID[1,2], Z. BATOOL, 75270[1]
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Abstract: Abstract
Noise has always been an important environmental factor that induces health problems in general

population. Due to ever increasing noise pollution humans are facing multiple auditory and non-auditory problems including neuropsychiatric and memory disorders. In modern day life it is impossible to avoid noise due to rapid industrialization of society. Therefore, it is necessary to find preventive measures to reduce the deleterious effects of noise exposure. The amino acid taurine is gaining the attention of scientist as one of the powerful biomolecules which plays an important role in brain structure and function. It is involved in a number of important physiological functions such as neuromodulation, neuroprotection, and neurotransmission. The antioxidant property of taurine has also been reported previously which involve the modulation of mitochondrial electron transport chain reaction and inhibiting the production of free radicals. Supplementation of taurine is reported to alleviate psychiatric disorders as well as reverse the age-associated cognitive impairments. In the present study taurine was tested in noise stress-exposed rats to check its potential in amelioration of noise-induced behavioral deficits and impaired dopaminergic, serotonergic, and cholinergic functions. Parameters for oxidative stress including lipid peroxidation, superoxide dismutase, catalase, and glutathione peroxidase were also monitored in taurine supplemented rats exposed to noise stress. The dose was selected after monitoring the dose dependent effects of taurine supplementation on depression- and anxiety-like behaviors and memory function. Noise-exposed (100 db; 3 h daily for 15 days) rats were supplemented with taurine at a dose of 100 mg/kg for 15 days. Spatial and recognition memory were assessed using Morris water maze and novel object recognition task respectively. Results of this study revealed reversal of noise-induced memory impairment in rats. The derangements of catecholaminergic and serotonergic levels and altered antioxidant enzyme activity due to noise exposure were also restored by taurine administration. In conclusion, the present study suggested the role of antioxidant property of taurine on noise-induced neurotoxicity and impaired memory function. Attenuation of noise-induced altered biogenic amines levels and increased acetylcholinesterase activity may involve in protective effects of taurine against noise stress. Therefore, this can be suggested that supplementation of taurine is helpful in reducing the insults of excitotoxicity that occur during exposure to loud noise thereby reduce neuronal damage.

Disclosures: S. Haider: None. **I. Sajid:** None. **Z. Batool:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.17/MM13

Topic: F.04. Stress and the Brain

Title: Earlier onset and higher pace of developing Alzheimer’s disease with prenatal stress

Authors: Z. JAFARI[1], B. KOLB[2], *M. H. MOHAJERANI[2]
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Abstract: Noise is an important environmental health hazard that has been shown to contribute to the risk of pathogenesis and progression of Alzheimer's disease (AD). High levels of distress also increase the proneness and pace of progression of the AD, especially in females. A model of prenatal stress (PS) with enduring neurobehavioral outcomes in rodents has been shown to replicate the cognitive and neural abnormalities in human offspring. There is, however, no information as to the link between PS and the risk of developing AD during the lifespan. Male and female $APP^{NL-G-F/NL-G-F}$ offspring of dams exposed to gestational noise stress were compared with the control offspring in corticosterone alternations, cognitive and motor performances, and the onset age and development of amyloid beta (Aβ) aggregation across age. The corticosterone and spatial memory results were sex-specific showing a higher level of stress and further memory loss in females than males, especially in the PS group. Higher Aβ deposition and larger Aβ plaque size in various brain areas were the early onset impacts of the PS at two months. The PS caused an increased Aβ aggregation across age with a remarkably higher impact on females in some measures. The PS also created a long-lasting anxiety-like behaviour and impairment in cognitive and motor coordination. The findings suggest that there are enduring detrimental impacts of the PS in behaviour and an acceleration of AD-like neuropathological changes (lower onset age and higher Aβ accumulation) that were sex-specific in some measures. The most likely mechanism for the PS effects is hyperactivity of the maternal and fetal hypothalamic- pituitary-adrenal (HPA) axis.

Disclosures: Z. Jafari: None. **B. Kolb:** None. **M.H. Mohajerani:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.18/MM14

Topic: F.04. Stress and the Brain

Support: NIH COBRE pilot funding (IP20GM103653)
University of Delaware Research Foundation

Title: The role of amygdala PI3K-Akt signaling in facilitating persistent fear memory in an animal model of PTSD

Authors: *R. B. DELLA VALLE, N. MOHAMMADMIRZAEI, E. MOULTON, M. CHAMNESS, D. KNOX
Dept. of Psychological and Brain Sci., Univ. of Delaware, Middletown, DE

Abstract: Single prolonged stress (SPS) is a procedure consisting of serial stressors (restraint, forced swim, and ether exposure until anesthetized) applied over a three-hour window which approximates the behavioral and neurobiological symptoms of PTSD in rats. SPS exposure causes deficits in retention of extinguished fear, but it is unclear whether this deficit represents changes in fear memory encoding, or changes in extinction memory retrieval. One hypothesis is that SPS exposure causes subsequent fear memories to be encoded in a manner that is resistant to the inhibitory effects of fear extinction. Previous studies have shown that signaling via the PI3K-Akt pathway, which is critical for fear memory formation, is enhanced with SPS exposure. Thus, in SPS rats, enhanced PI3K-Akt signaling within the fear circuit during fear memory formation may result in formation of a fear memory that is resistant to extinction. To explore this possibility we used c-Fos and c-Jun to measure neural activity throughout the fear circuit during fear conditioning in SPS and control rats. Results revealed that neural activity during fear conditioning is enhanced in the basolateral amygdala (BLA) and central nucleus of the amygdala (CeA) in SPS exposed rats. Next we used western blot to examine PI3K-Akt signaling in the fear circuit during fear conditioning. Results revealed that SPS exposure increases recruitment of this signaling pathway in the amygdala when fear memories are being encoded. Current results suggest that our PTSD model enhances neural activity and PI3K-Akt signaling in amygdala nuclei during fear conditioning, which we hypothesize may contribute to the formation of extinction-resistant fear memories. Ongoing work seeks to determine whether inhibiting PI3K-Akt signaling in the amygdala during fear conditioning attenuates the persistence of fear memory in the SPS model of PTSD.

Disclosures: R.B. Della Valle: None. **N. Mohammadmirzaei:** None. **E. Moulton:** None. **M. Chamness:** None. **D. Knox:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.19/NN1

Topic: F.04. Stress and the Brain

Title: Intermittent fasting alters the effects of stress on water maze and rotarod performance

Authors: D. P. WOOD[1], F. A. WALTER[1], T. M. MILEWSKI[1,2], *P. T. ORR[3,1]
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Abstract: Intermittent fasting (IF) has been previously studied as a method of caloric restriction which protects against age-related memory impairment, but its interaction with chronic stress is complex and potentially understudied. In this study, mice were assigned to either a control diet or an IF diet, during which mice only had access to food on alternate days. After 4 weeks of this dietary manipulation, all mice were subjected to a chronic stressor in the form of restraint for two

hours a day for two weeks. Once started, dietary and stress manipulations continued for the duration of the study. After two weeks of chronic stress, all mice were tested for motor coordination on the rotarod, for anxiety on the open field, and for spatial memory on the Morris water maze. Although there were no differences between groups on the first day of rotarod testing (which consisted of multiple trials at the same acceleration rate), IF mice spent significantly less time ($F(1, 20) = 5.025$, $p = .036$) on the rod compared to control mice on the second day of rotarod testing (which consisted of trials at successively increasing acceleration rates). There were no significant differences in the display of anxiety in the open field. All mice, regardless of dietary condition, improved over the eight trials on the first day of water maze ($F(7, 133) = 2.983$, $p = .006$) and there were no differences in learning between groups ($F(7, 133) = 1.061$, $p = .392$). However, there were group differences in memory for the platform location across days ($F(1, 19) = 5.844$, $p = .026$). Mice in the control group were significantly worse on the first trial of the second day of water maze compared to the last trial of the previous day, whereas a significant change in performance was not observed in IF mice. Dietary condition appeared to have an effect on the time mice spent floating (as opposed to actively swimming) during water maze. Across the eight trials on the first day of testing in water maze, time spent floating increased regardless of condition ($F(7, 133) = 3.35$, $p = .003$). Across all trials, IF mice spent significantly less time floating compared to control mice ($F(1, 19) = 5.072$, $p = .036$). There were no effects of group on time spent floating during the second day of testing. Overall, these results suggest that IF significantly interacts with the behavioral effects of chronic stress. Chronically stressed mice on an IF feeding schedule were significantly less coordinated than stressed mice on a regular diet, but demonstrated improved memory and a decreased propensity to float in the Morris water maze.

Disclosures: D.P. Wood: None. **F.A. Walter:** None. **T.M. Milewski:** None. **P.T. Orr:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.20/NN2

Topic: F.04. Stress and the Brain

Support: CONACYT 238313
CONACYT 221092

Title: Long term effect of gestational stress on working memory and mPFC cellular proliferation of male and female adult rats

Authors: *Y. RUVALCABA DELGADILLO[1], A. AGUILAR DELGADILLO[2], T. MORALES SALCEDO[3], A. GARCÍA ZAMUDIO[3], J. FREGOSO GONZÁLEZ[3], D. FERNÁNDEZ QUEZADA[3], J. GARCÍA ESTRADA[4], F. JÁUREGUI-HUERTA[3], S. LUQUÍN[3]

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Abstract: Adverse experiences during early developmental stages can influence the neurobiological and behavioral mechanisms. One of the most commonly observed alterations in the brains of who suffer intense stressful experiences, is the morphological and functional atrophy of the structures that regulate the stress response such as medial prefrontal cortex (mPFC). The proliferative capacity of some cell lines that inhabit these structures is one of the most widely accepted mechanisms when it is intended to explain this alteration. Stressful experience can be determining if it occurs in early stages of development and these alterations can remain even in the long term. Besides these changes can be different depending on some factors such as sex, age of exposure and evaluation stage. Objective: characterize alterations in working memory(alternation/discrimination) and changes in cell proliferation in mPFC of adult male and female rats produced by exposure to psychosocial stress during pregnancy. Methods: 48 rats (24 females and 24 males) were grouped into two different conditions according to the experience in the prenatal stage: Control Female (CF) n = 12; Control Males (CM) n = 12; chronic stress varied females (CSVF) n = 12 and chronic stress varied Males (CSVM) n = 12. The CF and CM groups remained under standard conditions of the bioterium during the gestation stage and after birth. The group CSVF and CSVM were exposed for 7 days to a Chronic stress variable model (CSV). During the 3 final days to the exposure period, 4 animals from each group received a daily intraperitoneal dose of Bromodeoxyuridine(BrdU). At the end of the exposure period, all subjects remained in normal habitat conditions for a period of 3 months. The brain of rats that received BrdU were processed with immunohistochemical technique to analyze cell proliferation in mPFC. On the other hand, 8 rats from each group were evaluated with T maze. Results: We observed a decrease in the number of proliferating cells in mPFC of adult rats exposed to prenatal stress “CSV”. This stimulus also modified the ability of adult rats to perform a work memory alternation/discrimation task. Both effects being significantly more evident in male compared with females rats.CONCLUSION: Exposure to CSV during pregnancy produces long-term alterations in tasks related to mPFC and its proliferative cellular capacity.

Disclosures: Y. Ruvalcaba Delgadillo: None. **A. Aguilar Delgadillo:** None. **T. Morales Salcedo:** None. **A. García Zamudio:** None. **J. Fregoso González:** None. **D. Fernández Quezada:** None. **J. García Estrada:** None. **F. Jáuregui-Huerta:** None. **S. Luquín:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.21/NN3

Topic: F.04. Stress and the Brain

Support: CONACYT

Title: Volume of the amygdalae correlates with self-reported stress in adult males

Authors: *D. VÁZQUEZ CARRILLO[1], S. ALCAUTER[2], F. A. BARRIOS[3], J. MARTÍNEZ-SOTO[4], L. GONZALES-SANTOS[5], E. PASAYE[5]
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Abstract: Psychological stress is a major cause of disruption of the well-being in society since it has been related with elevated risk for health problems. Smaller volume of the amygdalae have been related with higher stress in clinical population, however fewer studies have explored this relationship in healthy adults (Sublette, et al. 2016). The aim of this study was to evaluate the relation between self-reported stress and the volume of the amygdalae. Participants: 27 healthy men (age mean ± std dev = 33.6 ± 10.4 years). High resolution (1x1x1 mm^3) T1 images were acquired for each subject with a 3 Tesla MRI scanner. The volume of subcortical brain structures (Figure 1) were defined on these images using the automated Volbrain pipeline (Manjón & Coupe, 2016). Subjects completed the "Stress and Activation Adjectives Checklist" (King, *et. al*. 1983) while lying on the scanner previous to the T1 acquisition. Finally, Pearson correlations between volume of the amygdalae and stress were performed. There is a significant positive correlation between the volume of the amygdalae and the self-reported stress, indicating that subjects with higher volume referred higher levels of stress. Our results indicate that larger amygdalae volumes are related with higher levels of subjective stress. This finding contrasts with previous reports showing that smaller amygdalae volumes are related with higher stress levels in clinical populations, including post-traumatic stress disorder, depression and anxiety, although a recent report found similar results for healthy subjects. This finding warrants further research in order to clarify this relationship.

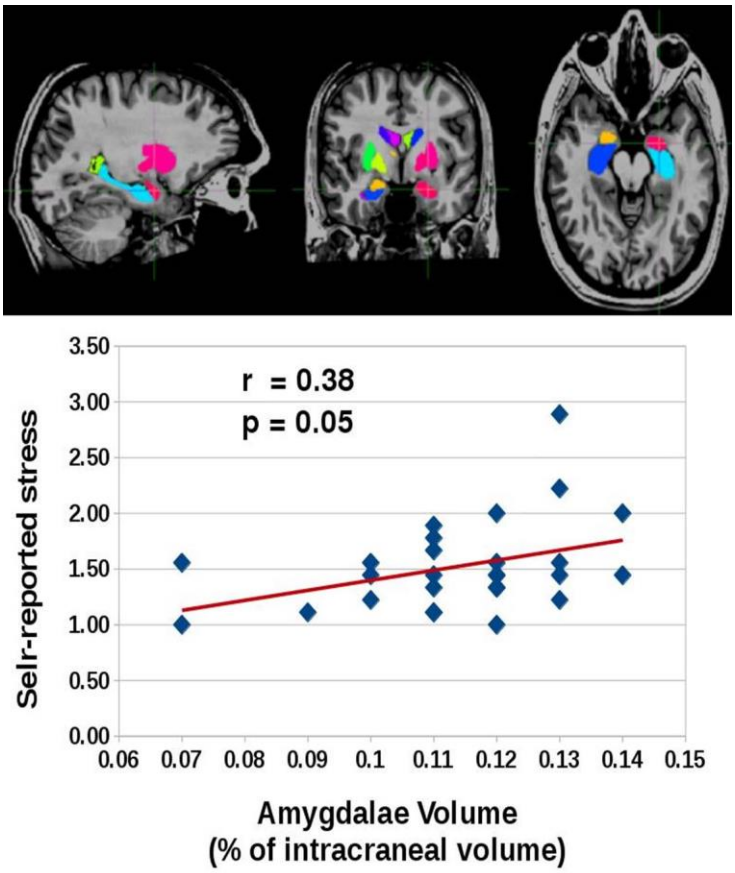

Figure 1. Segmentation of the amygdalae (up) and the correlation between their volume and self-reported stress.

Disclosures: D. Vázquez Carrillo: None. **S. Alcauter:** None. **F.A. Barrios:** None. **J. Martínez-Soto:** None. **L. Gonzales-Santos:** None. **E. Pasaye:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.22/NN4

Topic: F.04. Stress and the Brain

Support: NIH MH103322

Title: The effects of social stress on the neural circuitry of reversal learning

Authors: *E. C. WRIGHT, M. PHAM, S. KUMAR, J. O. ALEXANDER, A. V. WILLIAMS, B. C. TRAINOR
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Abstract: Women are more likely to be diagnosed with anxiety or depression than men, and animal studies show that stress has stronger anxiogenic effects in females than males. However, in some cases specific phenotypes associated with depression may be stronger in males. For example, depression is frequently associated with deficits in cognitive flexibility and there is growing evidence that males may be more susceptible to deficits in cognitive flexibility measures. Previous work in California mice showed that social defeat reduces mu opioid receptor (MOR) binding in orbital frontal cortex of males but not females, and that morphine treatment reduced errors in a reversal learning task. Similarly, male C57Bl6/J mice have impaired cognitive flexibility during morphine withdrawal. Morphine withdrawal induces large increases in cyclic AMP in the ventral tegmental area, which may contribute to deficits in reversal learning. Cyclic AMP inhibits transforming growth factor beta (TGF-β) in VTA, which has been found to promote cognitive flexibility. Preliminary analyses of RNAseq data from female California mouse VTA show that social defeat increases TGF-β expression as well as other transcripts related to this pathway including MAP4K1. PCR analysis found higher levels of TGF-β receptor expression in defeated females that is not seen in defeated males. Continuing work will investigate TGF-β expression itself. If confirmed, these results would suggest that females may be protected from the inhibitory effects of stress on reversal learning via transcriptional responses in the VTA.

Disclosures: E.C. Wright: None. **M. Pham:** None. **S. Kumar:** None. **J.O. Alexander:** None. **A.V. Williams:** None. **B.C. Trainor:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.23/NN5

Topic: F.04. Stress and the Brain

Title: Cognitive diversity in stress-sensitive and stress-resilient animal models is accompanied with marked spatial and temporal alterations in the brain electrical activity

Authors: *I. MICHAELEVSKI[1], M. BAIRACHNAYA[1], A. SHEININ[2], A. PINHASOV[1]
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Abstract: Growing body of evidences indicates the detrimental effects of chronic stress on cognitive function and a higher vulnerability to chronic stress related to brain aging. Using

advantage of social hierarchy-based selectively-bred dominant (Dom) and submissive (Sub) mice model, previously, we have demonstrated a) Sub and Dom mice are stress-sensitive and -resilient, respectively; b) Sub and Dom mice demonstrate diverse pattern of short- and long-term synaptic plasticity; c) stress-sensitive Sub mice show early development reduced cognitive performance in working and reference memory paradigms without exposure to stress; d) Sub and Dom mice exhibit differential protein expression in the functional protein-protein interaction networks of synaptic transmission, circadian regulation and MAPK, NF-kB and ErbB signaling pathways; e) correlation between protein level diversity in Sub and Dom mice and functional link between stress resilience or sensitivity and early appearance of cognitive impairment was shown for synapsin 2b and GluA1 expression. In this report, we show 1) the life expectancy of Sub and Dom mice markedly differ; 2) Chronic mild stress (CMS) differentially affect Sub and Dom mice longevity; 3) CMS deteriorates Sub mice cognitive performance; 4) Sub and Dom mice show markedly different brain electrical activity during free behavior; 5) Sub and Dom mice exhibit differential pattern of the brain spatial and temporal electrical activity evolution during non-spatial memory paradigm.

Disclosures: I. Michaelevski: None. **M. Bairachnaya:** None. **A. Sheinin:** None. **A. Pinhasov:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.24/NN6

Topic: F.04. Stress and the Brain

Support: NSF IOS 1552416

Title: Chronic stress regulation of sustained attention circuitry

Authors: *E. J. ORDOÑES SANCHEZ[1], S. R. ECK[2], M. DUGGAN[2], M. SALVATORE[2], B. WICKS[2], R. D. COLE[2], V. V. PARIKH[2], D. A. BANGASSER[2]
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Abstract: Attentional impairments are common in a variety of different psychiatric disorders ranging from schizophrenia to attention deficit hyperactivity disorder (ADHD). Other shared features of these disorders is that stress can exacerbate their symptoms and attention disruptions in these disorders are worse in males than in females. Although stress can affect attention, the exact mechanisms by which this occurs are not fully understood. The goal of this project is to examine the neurobiological mechanisms by which stress alters sustained attention, the ability to monitor a situation for intermittent and unpredictable events. Sustained attention is mediated by cholinergic neurons in the nucleus basalis of Meynert (NBM), which release acetylcholine (ACh)

into the medial prefrontal cortex (mPFC). Work from our laboratory found that six days of chronic variable stress (CVS) impaired sustained attention in male and female rats and that this effect was greater in males, especially when attentional demands were high. In the present study, we investigate whether CVS disrupts cholinergic transmission and alters synapses forming within the mPFC. *In vivo* amperometric recordings utilizing enzyme-based biosensors were conducted to measure ACh release and the kinetics of exogenously applied choline, in the mPFC of male and female rats exposed to chronic stress. CVS reduced depolarization-evoked ACh release in male, but not female rats. Moreover, choline uptake rate was reduced by CVS only in males, suggesting that the reduction in ACh release in this group is presumably due to reduced density of the choline transporters that might have impacted choline reuptake and constrained the availability of presynaptic choline for ACh synthesis. We are also examining whether CVS induces synaptic plasticity in the mPFC, which could affect attention. To this end, we assessed levels of synaptophysin (SYP), a synaptic vesicle protein, in the mPFC of CVS and control male rats via Western blotting techniques. We found significantly higher levels of SYP in CVS males than in control males, which suggests that stress induces synaptic plasticity at the mPFC. Future studies will determine whether this effect also occurs in females. Collectively, these findings suggest that CVS-induced changes in ACh release and synaptic plasticity in the mPFC contribute to male vulnerability to attention deficits.

Disclosures: E.J. Ordoñes Sanchez: None. **S.R. Eck:** None. **M. Duggan:** None. **M. Salvatore:** None. **B. Wicks:** None. **R.D. Cole:** None. **V.V. Parikh:** None. **D.A. Bangasser:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.25/NN7

Topic: F.04. Stress and the Brain

Support: NSF IOS-1552416
NIDA T32 5T32DA007237-28

Title: Early life stress has lasting effects on development and sex-specific effects on cognition in rats

Authors: *S. ECK, M. SALVATORE, J. KIRKLAND, A. HALL, S. FAMULARO, D. BANGASSER
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Abstract: The experience of early life stress increases risk for a variety of psychiatric disorders, including depression, anxiety disorders, and substance use disorder. In order to study how these risks develop, we utilized a rodent model of early life stress called the limited bedding and

nesting (LBN) model, which mimics the low resource environment that characterizes poverty. In this model, on the pups' postnatal days 2 through 9, dams and pups are separated from bedding by grated flooring, and given only a single paper towel as nesting material. This is compared to the ample bedding and cotton nesting material given to controls (Ivy et al. 2008). To validate the use of the LBN model in our laboratory, we measured how this manipulation affected maternal care behaviors, pup development, and measures of hypothalamus-pituitary-adrenal (HPA) axis activity. Our analysis of maternal behaviors revealed that LBN dams engaged in more pup-directed behaviors (e.g., nursing) and less self-care behaviors (e.g., resting outside of the nest) than control dams, suggesting a behavioral compensation for the lack of resources. Despite this behavioral change, we found that LBN pups showed slower development than control pups in both anogenital distance and body weight, effects that lasted past weaning and into adulthood. Additionally, when male, but not female, LBN pups reached adulthood, they exhibited adrenal hypertrophy as compared to controls, suggesting a persistently heightened HPA axis-mediated stress response. Finally, we present data from a novel two-hit model of stress in which LBN pups are exposed to a 6-day chronic variable stress once they reach adulthood. Our preliminary data suggest that male LBN pups that are exposed to stress in adulthood perform poorly in the novel object recognition task compared to male rats that are only exposed to stress at a single time point, while females' performance remains unimpaired by stressor exposure. Together, these findings indicate that the LBN model of early life stress induces lasting physiological and behavioral changes in rats and that males may be especially susceptible to some of these effects.

Disclosures: S. Eck: None. **M. Salvatore:** None. **J. Kirkland:** None. **A. Hall:** None. **S. Famularo:** None. **D. Bangasser:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.26/NN8

Topic: F.04. Stress and the Brain

Support: Knowledge Enterprise Development

Title: Chronic intermittent restraint (IR) stress has long-lasting effects on fear extinction and anxiety

Authors: V. B. SHAH, J. M. JUDD, E. A. SMITH, *C. D. CONRAD
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Abstract: Chronic stress followed by fear conditioning can be used to model PTSD, as it leads to faster fear acquisition, poor fear extinction, and heightened anxiety. Moreover, chronic stress' effects on heightened anxiety can persist even after a month had elapsed following the end of

chronic stress. Recently, a paradigm in which restraint was administered intermittently (i.e., IR) was used because others reported that it produced greater corticosterone responses than did restraint given daily (i.e., DR). The current study investigated whether chronic IR would lead to poor fear extinction and heightened anxiety six weeks after restraint ended. Young adult, male Sprague Dawley rats underwent restraint stress using wire mesh (6hr/d) for five days with two days off before restraint resumed the next week for three weeks and a total of 23 restraint days. The groups consisted of control (CON), rats that underwent IR and then fear conditioned six weeks after IR ended (IR-W6), and rats that underwent IR and then fear conditioned the next day, or without a lapse in weeks (IR-W0). Fear conditioning involved 3 tone (20 sec, 2kHz, 75db) and foot shock (1 sec, 0.8mA) pairings. Then rats were given extinction training (15 tone only presentations 24 and 48-hr later) in a context that was different from the fear-conditioned training. Finally, rats were tested for anhedonia using sucrose preference (SP), and anxiety using novelty suppressed feeding (NSF) and elevated plus maze (EPM). As expected, all groups acquired fear conditioning rapidly and similarly, as rats were acclimated to the contexts prior to training. For extinction on both days, all groups showed high freezing to the first tone and low freezing to the context prior to the first tone on both extinction days. Group differences arose in subsequent extinction trials, with IR-W6 and IR-W0 discriminating poorly or freezing more to context at various trials than compared to CON. No differences in SP was detected among groups to suggest similar hedonic levels. In contrast, differences in anxiety profile was revealed with EPM and NSF. IR-W0 entered fewer open arms and made fewer total arm entries than did IR-W6 and CON on the EPM. Moreover, IR-W0 and IR-W6 showed more variability in levels of fecal boli excreted on the NSF task compared to CON. In its entirety, we interpret the findings to suggest that the IR groups displayed increased hypervigilance because they discriminated between the tone and context as well as CON on the first trial and then became worse in subsequent trials. The high anxiety profiles of IR-W0 on both tasks, and IR-W6 on one task, suggest that restraint continues to leave a lasting impact on behavior 6 weeks after restraint has ended.

Disclosures: V.B. Shah: None. **J.M. Judd:** None. **E.A. Smith:** None. **C.D. Conrad:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.27/NN9

Topic: F.04. Stress and the Brain

Support: Knowledge Enterprise Development

Title: Does chronic intermittent restraint (IR) disrupt hippocampal function?

Authors: *D. N. PEAY, H. M. SARIBEKYAN, J. M. JUDD, G. F. THORNTON, C. D. CONRAD
Arizona State Univ., Tempe, AZ

Abstract: Chronic restraint stress alters hippocampal morphology and disrupts spatial learning and memory. Restraint is often implemented with rodents because of its ease of use and low cost compared to predator or social defeat stress. One concern is that stress responses become attenuated with repeated restraint. Recently, others reported that restraint administered intermittently (i.e., IR) produced greater corticosterone responses than did restraint given daily. Consequently, the present study examined whether IR could be used to investigate hippocampal function. In experiment 1, young male Sprague-Dawley rats underwent restraint using wire mesh for three weeks. One set was restrained for 6 hrs daily (daily restraint, DR-6hr), another set was restrained for 6hrs/daily or 2hrs/daily for five days with two days off before restraint resumed the next week (IR-6hr, IR-2hr respectively) over the next three weeks. A set of controls (CON) that were not restrained were also included. The day after restraint ended, rats were tested over the next seven days on the radial arm water maze (RAWM), open field (OF), object placement (OP), novel object recognition (NOR) and Y-maze. For the RAWM IR-6hr showed the worst spatial memory deficits compared to CON with IR-2hr making errors that were midway between IR-6hr and CON. In subsequent tasks (OP, NOR) many rats across all treatment groups failed to explore, making cognitive assessments not possible. By the time Y-maze testing occurred, all groups were showing spatial memory ability. Consequently, experiment 2 was performed with task order changed with the least aversive tasks first (Y-maze) and the most aversive task last (RAWM) and without including IR-2hr. In the first task, only the CON rats exhibited significant Y-maze performance to show intact spatial memory, but IR-6hr and DR-6hr showed a non-significant tendency toward spatial ability. On subsequent days, DR-6hr exhibited poor spatial ability on OP, but IR-6hr appeared to avoid the moved object. By the last spatial test on day 7, all groups learned and performed similarly on the RAWM. Performance on the OF and NOR suggest that both IR-6hr and DR-6hr rats exhibited raised anxiety profiles compared to CON. These results suggest that a narrow window of time exists to assess spatial memory from the end of chronic restraint (daily or intermittent), and/or testing order could impact performance. Aversive tasks also appear to negatively influence performance on subsequent tasks and should be used at the end of behavioral batteries. Finally, IR appears to produce spatial memory deficits, but additional studies are warranted to thoroughly understand its impact on cognition.

Disclosures: D.N. Peay: None. **H.M. Saribekyan:** None. **J.M. Judd:** None. **G.F. Thornton:** None. **C.D. Conrad:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.28/NN10

Topic: H.01. Animal Cognition and Behavior

Support: CONACyT 238313
CONACyT 221092

Title: Sex differences in cognition and behavior after chronic exposure to environmental noise

Authors: *D. L. MORAN TORRES[1], D. FERNANDEZ-QUEZADA[2], Y. RUVALCABA-DELGADILLO[1], S. LUQUIN[3], J. GARCIA-ESTRADA[4], F. JAUREGUI-HUERTA[1]
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Abstract: Noise is one of the most important environmental factors affecting cognition and mood. It has also been considered as an environmental stressor that activates the HPA axis. Since females and males show differences in response to stress, we performed an experiment to examine these differences under noisy conditions. To do so, we exposed a group of rats belonging to both sexes, to a fitted adaptation of a noisy environment and compared differences on the execution of three paradigms involving cognition, anxiety and depressive-like behaviors. The short version of the Radial Arm Water Maze (RAWM) was employed to evaluate spatial learning, working memory, reference memory and cognitive flexibility after 21 days of intermittent sounds resembling urban noisy environments. Also, the open field and forced swim paradigms were used to identify changes on anxiety and depressive-like behaviors. Male and female rats exhibited differences in most of the examined items. Execution on RAWM showed that males employed more time than its own control and the exposed females to find the hidden platform at both conditions, during the 5 days training phase, and during the reversal-learning phase. Locomotor activity at the open field and forced swimming test also revealed sex and condition differences. We concluded that females are less sensible to the damaging effects of environmental noise.

Disclosures: D.L. Moran Torres: None. **D. Fernandez-Quezada:** None. **Y. Ruvalcaba-Delgadillo:** None. **S. Luquin:** None. **J. Garcia-Estrada:** None. **F. Jauregui-Huerta:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.29/NN11

Topic: F.04. Stress and the Brain

Support: FRQNT

Title: How studies exclude participants when studying stress? A review of measuring physiological stress in adults

Authors: *V. CHARRON[1], N. F. NARVAEZ LINARES[1], M. BERR[1], V. RANGER[1], P. LABELLE[2], H. PLAMONDON[1]
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Abstract: The impact of stress, especially its effect on the human's hypothalamic-pituitary-adrenal (HPA) axis is a focus of study in Neuroscience. It is acknowledged that different factors can influence HPA axis activation. However, in stress research, there seems to be a lack of consistency regarding exclusion factors (e.g. alcohol) and their operationalization (e.g. frequency of consumption). A Systematic Review was therefore performed examining one of the most widely-used stress paradigm, the Trier Social Stress Test (TSST). Following the application of the PRISMA methodology, procedure-related data available on the TSST protocol was extracted from studies using the latter to induce stress in adults. A total of 30 exclusion criteria were addressed and a greater emphasis was given to the most frequently-used as well as those considerably influential. Despite their effect on cortisol levels, we found no consensus as to exclusion criteria application among study participants. Thereby, this research establishes an inconsistency in the use of exclusion criteria. Apart from basic exclusion criteria that are regularly used in clinical studies, few studies explicitly reported the less common factors or behaviours that could particularly influence cortisol levels in subjects (e.g. night shift work). Unless specificity was desired, the exclusion criteria were generally not discriminating enough to effectively minimize the repercussions of confounding variables. Our findings will allow future stress-related research to consider that exclusion criteria play a significant role on the HPA axis activation, which could result in erroneous data. Furthermore, this research will facilitate accurate replication of studies.

Disclosures: V. Charron: None. **N.F. Narvaez Linares:** None. **M. Berr:** None. **V. Ranger:** None. **P. Labelle:** None. **H. Plamondon:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.30/NN12

Topic: F.04. Stress and the Brain

Title: Psychophysiological aspects of media-based Holocaust reception

Authors: *S. TUKAIEV[1,3], J. GRIMM[5], A. ENZMINGER[5], Y. HAVRYLETS[3], V. RIZUN[4], I. ZYMA[2], M. MAKARCHUK[2]

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Abstract: The studies of the Holocaust are usually focused on the long-term consequences on the survivors. The psychophysiological impact of the Holocaust hasn't been studied previously. Measurements of the real reactions to the traumatic past events present a serious challenge for the researchers in social and clinical psychology and neuroscience. The purposes of this study, a part of the project "Broadcasting History in the Transnational Space", were to investigate the people's reactions to the real cruelty in the historical documentaries and to identify the relationship between different types of documentary sequences (archival footage, witnesses to history and moderators). 51 healthy volunteers (25 women and 26 men, aged 18-35 years, M_{age}=23, SD=2,83), first-fourth year students of the University of Vienna (Vienna, Austria) participated in this study. The first group (26 volunteers) was demonstrated the original Holocaust documentary "Night and Fog" (1955, France, 16.02 min). The second group (25 volunteers) was presented the same documentary with inclusion the witnesses to history and moderators (24.05 min). We estimated the spectral power density of all frequencies from 0.2-45 Hz. Conducted content analysis demonstrated that the viewing of documentary segments depicting war violence, human suffering caused the most pronounced activation changes in the information-analytical cognitive processes of neural networks in the onset of the documentary. We detected the actualization of attention (depression alpha2 rhythm), as well as semantic-cognitive processes (depression alpha3 rhythm). The negative emotional content led to the development of intellectual processes of adaptation (no changes in the theta, alpha and beta rhythms) at the end of original documentary. It was demonstrated the weakening effect of the witness testimonies on the emotional response to video. In this case, the documentary demand less attention and less emotional efforts for emotional evaluation of visual information, analysis, retrieval of information from memory and semantic processes. At the end of the documentary watching, we detected the increase in the spectral power of alpha3, beta2 and gamma bands indicated the active state of the top-down cortical control systems, the activation of emotional-cognitive processes, awareness processes, higher associative processes. Our results suggest that historical violence exert significant influence on the psychological condition of the participants.

Disclosures: S. Tukaiev: None. **J. Grimm:** None. **A. Enzminger:** None. **Y. Havrylets:** None. **V. Rizun:** None. **I. Zyma:** None. **M. Makarchuk:** None.

Poster

227. Stress and Cognition

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 227.31/NN13

Topic: F.04. Stress and the Brain

Support: Grants-in-Aid for Scientific Research from the MECS of Mongolia (In-01/2015)

Title: Psychological issues in patients with diabetes in Mongolia

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Abstract: To determine the psychological issues in patients with diabetes, we assessed quality of life (Short Form 36 Health Survey), depression (Center for Epidemiological Studies Depression Scale), and anxiety (Spielberger's State-Trait Anxiety Inventory) as well physical parameters including a fasting glucose level, a body mass index, and a blood pressure in 82 patients (mean age: 56.14±10.1 years, male/female ratio: 57/42) who were referred to the department of endocrinology at a municipal hospital between January and February, 2016. 39.06% of the participants were overweight. The average blood glucose level of the patient group was higher than the control group ($P<0.001$). The subcutaneous fat and the neck circumference were significantly higher in the patient group than the control group ($p=0.008$, $p=0.032$, respectively). The patients with diabetes had higher scores on both depression and anxiety tests compared to the healthy subjects ($P=0.015$, $P=0.048$, respectively). The total score of the quality of life was much lower in the patient group ($P<0.001$). These findings suggest that Mongolian patients with type 2 diabetes have an increased risk of suffering from depression and anxiety which lead to impaired quality of life.

Disclosures: D. Boldbaatar: None. **E. Nayantai:** None. **N. Namjil:** None. **B. Lkhagvasuren:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.01/NN14

Topic: F.07. Autonomic Regulation

Support: NIH Grant KL2TR001879

Title: Optogenetic inhibition of crh specific neurons in Barrington's Nucleus facilitates micturition

Authors: *J. P. VAN BATAVIA[1], S. BUTLER[2], J. FESI[2], S. VICINI[3], S. A. ZDERIC[4]
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Philadelphia, Philadelphia, PA; [3]Dept Parmacology & Physiol., Georgetown Univ. Med. Ctr., Washington, DC; [4]Pediatric Urology, Children' Hosp. of Philadelphia, Philadelphia, PA

Abstract: Lower urinary tract dysfunction (LUTD) affect 20% of "normal" children and >40% of adults over the age of 40. The neuro-urologic pathways involved in normal and dysfunctional voiding are largely unknown and recent interest has focused on neurons that express corticotropin-releasing hormone (CRH) in Barrington's nucleus (BN), the pontine micturition center. A recent optogenetic study provided evidence for a role of these specific BN neurons in micturition (Hou et al, Cell 2016; 167:73) and we previously presented our work showing that stimulation of these neurons inhibits micturition. Here we examine the effects of optogenetic inhibition of these CRH neurons in BN on the in vivo voiding phenotype and urodynamics in awake mice. We hypothesized that inhibiting these neurons would lead to facilitation of voiding with smaller voided volumes and shorter time between voids.

Double transgenic male mice expressing archaerhodopsin channel (ArchRd) in CRH cells had fiberoptic probes implanted into BN at 8 weeks of age and a catheter secured into the bladder for in vivo cystometry. In vivo cystometry before and during optogenetic inhibition at various frequencies was performed 5 days postoperatively. Saline was perfused at 10µl/min and baseline stable voiding cycles were established. Optogenetic silencing (530 nm at 10, 25 and 50 Hz) of CRH neurons in BN produced a significant decrease in intermicturition interval (time between voids), bladder capacities and voided volumes (Figure 1). Control non double mice showed no effects from optogenetic stimulation.

Our results suggest that optogenetic silencing of CRH-BN neurons at high frequencies elicits bladder contractions and facilitates micturition leading to a voiding phenotype of more frequent and small volumes voids. Further elucidation of the heterogeneous population of neurons in BN are warranted to understand micturition and how it may be manipulated in disease states such as in patients with infrequent voiding or acute urinary retention.

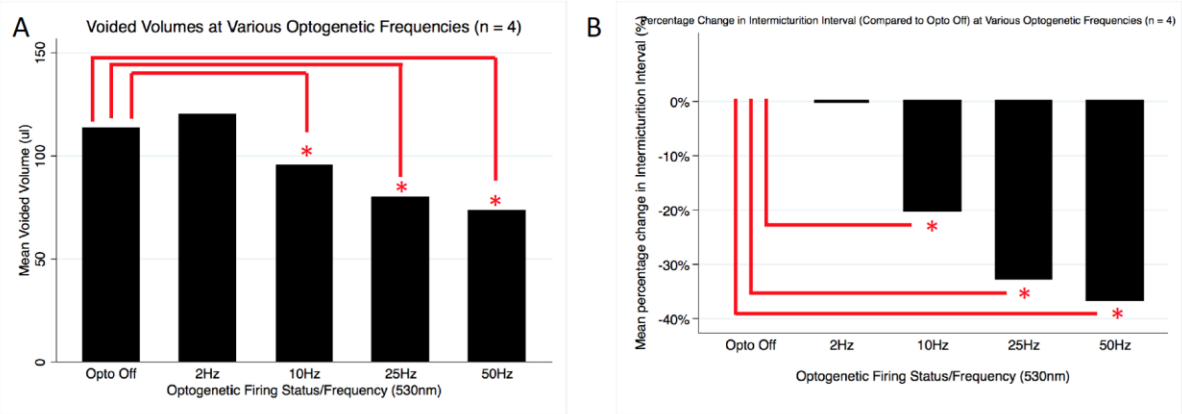

Figure 1. (A) Graph of mean voided volumes at various optogenetic firing frequencies showing decrease in mean voided volume at higher frequencies. Differences in mean voided volumes between baseline (Opto Off) compared with 10Hz, 25Hz, and 50Hz were all statistically significant (asterisks = $p<0.02$). (B) Using intermicturition interval at baseline (Opto Off), the percentage change in IMI at each frequency of optogenetic firing was determined. Comparison of percent change in IMI at 10Hz, 25Hz, and 50Hz with baseline was statistically significant (asterisks, $p<0.02$).

Disclosures: J.P. Van Batavia: None. **S. Butler:** None. **J. Fesi:** None. **S. Vicini:** None. **S.A. Zderic:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.02/NN15

Topic: F.07. Autonomic Regulation

Title: Electrophysiological, morphological, and pharmacological properties of Barrington's nucleus CRF neurons using adult mice brainstem slices

Authors: M. KAWATANI, Jr.[1], K. ITOI[2], K. UCHIDA[3], K. SAKIMURA[4], *M. H. KAWATANI[5]
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Abstract: Barrington's nucleus (BarN) is a small brainstem nucleus, locates in the pons, dorsal tegmentum. Stimulation of this area induces activation of pelvic nerve activity, and induce micturition and/or defecation. Currently, researches has gained momentum by using several lines of transgenic mice. Manipulating specific cellular types of cells link their activities and behavioral outputs. The involvement of the BarN CRF expressing neuron to micturition is determined (Hou et al., 2016, Cell, 167, pp. 73-86.e12.) We conducted in vitro slice patch-clamp recordings from specific neural populations in BarN, using CRF-VenusΔNeo mice, which label 98.0% of CRF expressing neurons in BarN. We used 2~8 month old mice. Slice preparation method was reported previously, and adapted to brainstem. All protocols were approved by the Animal Research Committee of Akita University. Venus(+) neurons has lower membrane resistance and more depolarized resting membrane potentials than Venus(-) neurons. Several types of firing patterns were observed in BarN, however, burst firing types were observed only in Venus(-) neurons. Delayed firing types were existed in the both population, but the times of action potential delay from current injection is shorter in Venus(+) than in Venus(-). Neurobiotin (0.1%) was injected through patch-clamp electrode, and visualized recorded cells by streptavidin-Alexa594. In single cell resolution, Venus(+) neurons progress their long neurites to the 4th ventricle, and lateral or medial side near to the BarN. Next, we investigated the effects of carbachol (Cch), which reported excitedly action in the BarN. Cch inhibits activities of Venus(+) neurons activity with decreasing of input resistance (Rin) in recorded cells, applied in lower concentrations (1~10 μM). However, in higher concentrations (10~100 μM), Cch excited these neurons with the decreasing of Rin. Cch induced inhibitory actions were blocked or reversed by pre-application of Atropine (3~10 μM). Oxotremorine (M2 agonist, 10 μM), mimicked inhibitory

effects. McN-A343 (M1 agonist, 10 μM) does not occurred rapid excitation. Cch induced excitations were totally abolished by mecamylamine (nicotinic receptor antagonist, 3-10 μM). Venus(+) neurons in the BarN demonstrated strong nicotinic excitation and /or muscarinic inhibition. It raises the possibility of modulations of pelvic organ activities by Ach within the brainstem. It could be important for pathophysiological changes of pelvic organ function.

Disclosures: M. Kawatani: None. **K. Itoi:** None. **K. Uchida:** None. **K. Sakimura:** None. **M.H. Kawatani:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.03/NN16

Topic: F.07. Autonomic Regulation

Support: NIH Grant U18EB021793
NIH Grant TR01NS081707
NIH Grant F32DK115122

Title: Optoelectronic system for closed loop optogenetic control of bladder function

Authors: *A. D. MICKLE[1], S. M. WON[4], K. N. NOH[4], J. YOON[5], K. W. MEACHAM[6], L. MCILVRIED[7], B. A. COPITS[8], V. K. SAMINENI[2], P. SRIVASTAVA[2], Y. SHIUAN[2], H. H. LAI[3], J. ROGERS[9], R. W. GEREAU, IV[10]
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Abstract: Millions of people in the United States suffer from diseases that affect normal physiologic function of the peripheral nervous system (PNS), resulting in organ dysfunction and decreased quality of life. In some of these diseases, electric stimulation of PNS can be an effective therapy, however the stimulation is often delivered continually to mitigate symptoms despite undesirable side effects. Automated or closed loop interventions that only stimulate at the onset or during symptoms are desirable but currently technologically limited. One disease where closed-loop neuromodulatory interventions could advance treatments is interstitial cystitis/bladder pain syndrome, a debilitating condition that presents with chronic pain, increased frequency and urgency of micturition. Here we present a fully implantable wireless system for the closed loop modulation of bladder function. The system includes a wireless strain gauge that

wraps around the bladder, enabling measurement of changes bladder size, and integrated microscale light emitting diodes (μLEDs) for optogenetic modulation of bladder function. This approach avoids the use of potentially damaging nerve-interfacing electrodes or implantation of invasive bladder catheters, which can disrupt normal bladder function. The strain gauge and μLEDs operate via an implanted Bluetooth base station that allows for wireless monitoring of bladder activity, and enables closed-loop bladder modulation via optogenetic activation of the light-activated proton pump, archaerhodopsin (Arch). We demonstrate that system can chronically measure bladder activity without overt changes to normal bladder function. We can also clearly identify the onset of altered voiding behaviors associated with bladder inflammation, and activation of Arch in bladder afferents can normalize the enhanced voiding frequency induced by bladder inflammation. We programmed our closed loop software to recognize these changes in bladder frequency and to initiate μLED activation. Finally, the closed loop program activated the μLEDs only during abnormal voiding and activation of Arch reduced void frequency in animals with bladder inflammation. This system and resulting studies provide a framework for potential future closed-loop technology/therapies for treatment of diseases effecting the PNS, offering alternatives to non-specific pharmacological or electrical stimulation approaches.

Disclosures: A.D. Mickle: None. **S.M. Won:** None. **K.N. Noh:** None. **J. Yoon:** None. **K.W. Meacham:** None. **L. McIlvried:** None. **B.A. Copits:** None. **V.K. Samineni:** None. **P. Srivastava:** None. **Y. Shiuan:** None. **H.H. Lai:** None. **J. Rogers:** None. **R.W. Gereau:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.04/OO1

Topic: F.07. Autonomic Regulation

Support: CH Neilsen Foundation PN 460399

Title: Novel high resolution system for continuous urodynamic monitoring of bladder function in chronic rodent studies

Authors: D. ANGOLI[1], A. GERAMIPOUR[1], *Z. C. DANZIGER[2]
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Abstract: The objective of this work is to develop a high-resolution system to monitor the health and function of the lower urinary tract (LUT) in experimental animals for extended periods of time. We accomplish this using a combination of a custom-built metabolic observation system and a mathematical model to estimate urodynamic parameters for every void of each animal. Poor voiding efficiency and high post void residual volumes (PVRs) are common symptoms of

many types of LUT dysfunction. Measuring these urodynamic parameters in experimental animal models of LUT disease provides insight into bladder function and disease progression, but are often very difficult to record in chronic studies. One common way to study LUT function is to measure the PVRs directly during cystometry after each voiding event; however, this requires constant experimenter supervision to remove volume from the bladder after each void. Therefore, continuous PVR data acquisition for long periods of time is currently infeasible.
The aim of this work is to test the feasibility of chronic studies in awake intact animals to continuously obtain all urodynamic parameters at every voiding event for many weeks. We used young female Sprague-Dawley rats to evaluate the PVR and voiding efficiency at each voiding event. Rats were catheterized through the bladder dome in a survival procedure and then kept for the length of the study in modified metabolic cages to maximize the accuracy of collected voided volumes. Rats were housed in a vivarium with enforced 12 hour dark-light phases. Animal activities in the metabolic cages were video recorded and voided volumes were collected and quantified by digital scales in real time. Bladder catheters were tunneled subcutaneously, externalized dorsally, and directly connected by fluid-filled metal tethers to transducers, which enabled monitoring of the bladder pressure and collection of the PVRs twice a day (12 hours apart). All other non-measured PVRs at each voiding event were estimated using our mathematical model constrained by the measured urodynamic parameters.
We validated our custom metabolic cage hardware and mathematical model using healthy control animals for up to one month. We were able to identify habituation behaviors and LUT recovery time courses following catheter implantation. The validation of our new chronic monitoring system will allow us to analyze LUT health in unprecedented detail at single-void resolution in chronic studies. For example, in an SCI model, to help understanding how the bladder reflex could be restored by electrical stimulation or, as another example, in-vivo drug testing for the treatment of overactive or underactive bladder (OAB, UAB).

Disclosures: D. Angoli: None. **A. Geramipour:** None. **Z.C. Danziger:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.05/OO2

Topic: F.07. Autonomic Regulation

Support: NIH/NIBIB 1P41EB018783
NYS Spinal Cord Injury Research Board C32241

Title: Development of targeted vagus nerve stimulation for modifying urinary function in unanesthetized, freely-moving rats

Authors: *J. S. CARP[1], T. F. FULTON[1], M. P. KILGARD[2]
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Abstract: Spinal cord injury (SCI) interrupts the brain's control of external urethral sphincter (EUS) and bladder activity, frequently resulting in abnormal lower urinary tract (LUT) function. Current treatments provide symptomatic relief, but do not address the underlying causes. Vagus nerve stimulation (VNS), when paired with specific behaviors, can induce focused and durable plasticity that produces beneficial effects in animal models of nervous system disorders. We hypothesize that VNS timed to coincide with the appropriate phase of the continence-voiding cycle will induce CNS plasticity that induces long-lasting change in LUT function. The purpose of the present study is to develop methods for applying VNS during cystometry to assess VNS effects on LUT function in freely-moving spinal-intact rats.
Female rats are implanted with a suprapubic bladder catheter, electrodes adjacent to the EUS, and a stimulation cuff on the left vagus nerve at the cervical level; wires and catheter were exteriorized to skull-mounted connectors for infusing saline and measuring bladder pressure, recording EUS EMG, and stimulating the vagus nerve, respectively. After a 1-2 week recovery, rats are placed in a metabolic cage, where urine is collected and weighed continuously during voiding induced by saline infusion into the bladder at 0.25 ml/min. Data are recorded during ~2.5-hour-long sessions in the following sequence: 6-10 voids with no stimulation; 10 voids in which VNS (0.8 mA, 30 pulses at 30 Hz for 0.5-1.5 s) is paired with either the bladder pressure peak during voiding or the EUS bursting activity that precedes the peak pressure; and 6-10 voids with no VNS.
To date, recordings have been made from two rats. Initial results show that VNS applied during peak bladder pressure increased void size and EUS bursting time, while VNS paired with EUS bursting decreased void size and reduced EUS bursting duration. The effects of both VNS pairings persisted for at least 30 min after the end of stimulation. These results suggest that: VNS can affect LUT function in spinal-intact rats; the precise timing of the VNS determines the nature of the effect; and the effects can outlast the period of stimulation. If further studies confirm these early data, targeted VNS could offer a novel approach to treating disorders of LUT function.

Disclosures: J.S. Carp: None. **T.F. Fulton:** None. **M.P. Kilgard:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.06/OO3

Topic: F.07. Autonomic Regulation

Support: 5R21NS086413-02

Saban Research Institute RCDF

Title: MET receptor tyrosine kinase mediates the development of vagal motor neurons in the nucleus ambiguus

Authors: *A. K. KAMITAKAHARA[1], A. L. LANJEWAR[2], H.-H. WU[3], P. R. LEVITT[1]
[1]Children's Hosp. Los Angeles, Los Angeles, CA; [2]USC, Los Angeles, CA; [3]Keck Sch. of Med. of USC/SC CTSI, Los Angeles, CA

Abstract: Vagus nerve connectivity and function have been mapped in great detail in the mature nervous system, however, there remains a substantial knowledge gap regarding mechanisms that guide development of vagal circuitry and specific subsets of neurons based on molecular features. Recent work from our lab has identified three subpopulations of vagal motor neurons that express the autism-associated MET Receptor Tyrosine Kinase (MET) during development: 1) MET+ neurons in the nucleus ambiguus (nAmb) projecting to the esophagus and/or laryngeal muscles, 2) MET+ neurons in the medial dorsal motor nucleus of the vagus (DMV) projecting to the stomach, and 3) MET+ neurons in the lateral DMV projecting to the cecum and/or proximal colon. Because gastrointestinal (GI) disturbances and speech deficits are common in children with autism spectrum disorder, experiments were designed to address the influence of Met expression on development of vagal motor neurons that innervate the GI tract and speech-producing organs. To this end, *Met* was conditionally deleted from developing vagal motor neurons in $Phox2b^{cre}$; $Met^{flox/flox}$ mice. Quantitative analysis of immunostained vagal neurons revealed a significant (38%) reduction in the number of motor neurons in the nAmb on postnatal day (P) 7 in $Phox2b^{cre}$; $Met^{flox/flox}$ compared to wild type mice that persisted into adulthood, indicating MET may participate in nAmb assembly. Deficits in nAmb number were particularly marked in the compact formation of the nAmb known to project to the esophagus and laryngeal muscles. In line with this, projections of nAmb motor neurons to alpha-bungarotoxin labeled innervation sites in the esophagus were reduced in $Phox2b^{cre}$; $Met^{flox/flox}$ mice. $Phox2b^{cre}$; $Met^{flox/flox}$ mice also weighed significantly less than wild type littermates on P7, suggesting that this reduction in nAmb cell number and innervation may impact feeding behavior or GI function. Behavioral assays of GI motility and ultrasonic vocalization are currently being conducted. Ongoing analysis of both DMV and nAmb formation in MET conditional knockout mice will advance understanding of the developmental mechanisms required for proper vagal development.

Disclosures: A.K. Kamitakahara: None. **A.L. Lanjewar:** None. **H. Wu:** None. **P.R. Levitt:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.07/OO4

Topic: F.07. Autonomic Regulation

Support: Colorado College Research and Development Grant
Colorado College Figge-Bourquin Grant
Colorado College Faculty/Student Collaborative Grant

Title: *Bifidobacterium infantis 35624* supplementation in eubiotic adolescent rats increases social interaction independent of vagal nerve signaling

Authors: *L. L. DRISCOLL[1], P. E. ANTON[2], K. TEIGEN[2], Z. SCHULMAN[2], U. SCHARF[2], N. VENKATESWARAN[2], M. TOMHAVE[2]
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Abstract: The composition of the gut microbiome in early postnatal life plays a vital role in shaping neuropsychiatric function, but the relative influences of specific microbial strains, and the mechanisms by which these strains exert their effects, remains to be determined. The aim of the current study was to determine if probiotic supplementation with *Bifidobacterium infantis 35624* (*B. infantis*) in adolescence impacts adult social behaviors in healthy rats, and if these effects are dependent upon vagus nerve signaling. Adolescent male and female Long-Evans rats received a subdiaphragmatic vagotomy or sham surgery and were supplemented daily with *B. infantis* or chocolate pudding vehicle for the subsequent 22 days. One week following supplementation, subjects were placed in an open arena with a same-sex stranger rat for 10 minutes, and the duration of exploring, ignoring, attacking, and freezing behaviors was scored. *B. infantis* supplemented rats demonstrated increased social exploration and decreased ignoring behaviors compared to vehicle supplemented rats. This effect was more pronounced in male than female rats, and it occurred in both sham and vagotomized animals. These results demonstrate that *B. infantis* enrichment in the normal adolescent gut enhances prosocial behaviors, possibly through immune or hormonal mechanisms. The subdiaphragmatic vagotomy procedure itself also altered social interaction and anxiety, suggesting that the vagus nerve plays a unique role in informing these behaviors.

Disclosures: L.L. Driscoll: None. **P.E. Anton:** None. **K. Teigen:** None. **Z. Schulman:** None. **U. Scharf:** None. **N. Venkateswaran:** None. **M. Tomhave:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.08/OO5

Topic: F.07. Autonomic Regulation

Support: NIH Grant DK106181

Title: Spinal cord stimulation over the upper lumbar cord ameliorates detrusor overactivity and bladder hyperalgesia in rats with cystitis

Authors: *H. H. CHANG[1], J.-C. YEH[2], J. MAO[2], D. GINSBERG[2], G. GHONIEM[1], L. RODRIGUEZ[2]
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Abstract: Aim: Interstitial cystitis/painful bladder syndrome/ (IC/PBS) is a chronic inflammation that results in recurring pain in the bladder and surrounding pelvic region caused by abnormal excitability of micturition reflexes. Spinal cord stimulation (SCS) is currently in clinical use for the attenuation of neuropathic pain, and has been identified for amelioration of pain and visceral hyperalgesia in a rodent model of colorectal distention. The present study examined whether SCS at upper lumbar segments modulates detrusor overactivity and bladder hyperalgesia associated with cystitis in a rat model of cyclophosphamide (CYP)-induced cystitis. **Methods:** Cystitis was induced by intraperitoneal injection of CYP (200 mg/kg) in 7 adult female Sprague Dawley rats 48 hours prior to urodynamic recordings. Another 7 rats served as the controls with saline injection. All rats received urethane anesthesia 1 hour prior to the urodynamic recordings. Cystometry and the external urethral sphincter (EUS) electromyography during bladder infusion were evaluated. The latency and area under the curve (AUC) of visceral pain-related visceromotor reflexes (VMR) obtained from the external abdominal oblique muscle were quantified during bladder infusion and isotonic bladder distension (IBD), respectively. After the baseline recordings were taken, SCS was applied on the dorsal surface of the third lumbar spinal segment for 25 minutes. The repeated urodynamic recordings and VMR during bladder infusion and IBD were then obtained 2 hours after SCS. **Results:** CYP resulted in chronic inflammation with significant detrusor overactivity, stronger EUS EMG activation, and an early appearance of VMR during bladder infusion. The VMR AUC induced during IBD was significantly increased in the cystitis rats. SCS significantly reduced non-voiding contractions, prolonged EUS intermittent relaxation, and delayed VMR appearance during bladder infusion in cystitis rats. SCS significantly decreased VMR AUC during IBD in cystitis rats. **Conclusion:** SCS improved voiding function by prolonged EUS intermittent relaxation during voiding, and significantly attenuated visceral pain-related VMR during IBD in rats with cystitis-induced hyperalgesia. SCS may have therapeutic potential for patients with hyperalgesia and IC/PBS.

Disclosures: H.H. Chang: None. **J. Yeh:** None. **J. Mao:** None. **D. Ginsberg:** None. **G. Ghoniem:** None. **L. Rodriguez:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.09/OO6

Topic: F.07. Autonomic Regulation

Support: Dialysis Clinic, Inc.

Title: Urinary K^+ promotes pelvic pain in a rat model of interstitial cystitis/bladder pain syndrome

Authors: *M. D. CARATTINO, S. D. STOCKER, N. MONTALBETTI
Med., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a complex chronic bladder condition that presents with urinary urgency and frequency, nocturia, and pain in the bladder and/or pelvis in the absence of any identifiable cause. While the etiology of IC/BPS remains unknown, clinical studies revealed a strong association between urothelial abnormalities, which range from mucosal ulcerations and urothelial ruptures to denuded epithelium, and symptoms experienced by the patients. Consistent with the notion that increased urothelial permeability contributes to IC/BPS symptoms, we previously reported that the overexpression in the rat urothelium of claudin-2 (Cldn2), a tight junction-associated protein that increases paracellular permeability and is dramatically upregulated in IC/BPS bladder biopsies, reproduces the cardinal features of this disease. In the present study, we investigated the mechanism by which increased urothelial permeability promotes pelvic pain in our rat model of IC/BPS. Our studies show that pelvic afferent nerve discharge and rectified/integrated nerve activity during continuous bladder infusion with saline are significantly greater in rats transduced with an adenovirus coding for Cldn2 (AdCldn2) than GFP (AdGFP). The differences observed between these two groups were exacerbated when bladders were infused with saline supplemented with 100 mM KCl. To determine whether elevated interstitial K^+ promotes sustained neuronal firing and hence triggers voiding and pain at low filling volumes, we examined the response of bladder sensory neurons to electrical stimulation in the presence of increasing extracellular K^+. Significantly, sensory neurons with tetrodotoxin-sensitive action potentials from rats transduced with AdCldn2 display higher firing rate with extracellular [K^+] of 6 and 9 mM than their control counterparts. To assess the contribution of urinary K^+ to the pelvic allodynia seen in rats transduced with AdCldn2, we fed rats a low K^+ diet (0.0015–0.003% w/w K^+ content) or a control diet (1.0 % w/w K^+ content) ad libitum and evaluated mechanical somatic sensitivity with von Frey filaments. Remarkably, dietary K^+ restriction prevented the development of pelvic allodynia in rats transduced with

AdCldn2. Taken together, our studies indicate that in the face of urothelial barrier dysfunction, the diffusion of urinary K^+ in the bladder interstitium sensitizes pelvic nerve afferents, which reduces their mechanical threshold and promotes pain at low filling volumes.

Disclosures: M.D. Carattino: None. **S.D. Stocker:** None. **N. Montalbetti:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.10/OO7

Topic: F.07. Autonomic Regulation

Support: NIH Grant RO1-DK051369
NIH Grant RO1-DK060481

Title: Blockade of VEGR2 in the urinary bladder increased bladder capacity in control rats and in rats treated with cyclophosphamide (CYP)-induced cystitis

Authors: *K. TOOKE[1], M. A. VIZZARD[2]
[1]Univ. of Vermont, Burlington, VT; [2]Neurolog. Sci., Larner Col. of Med. at UVM, Burlington, VT

Abstract: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, inflammatory pain syndrome characterized by urinary urgency, frequency, and pelvic pain. Using a rat CYP model of urinary bladder inflammation, previous studies demonstrated increased vascular endothelial growth factor (VEGF) expression in the urinary bladder with acute (4 hr) and chronic (10 day) CYP-induced cystitis as well as expression of VEGF receptors including VEGFR1, VEGFR2, Npn1 and Npn2. Translational studies demonstrated elevated levels of VEGF in the urinary bladder of women with IC/BPS. Furthermore, high levels of VEGF are associated with immature angiogenesis and vascularization in the bladder as well as visceral hyperalgesia, and pelvic pain. We have determined the effects on bladder function of VEGFR2 receptor blockade using a potent, selective VEGFR2 tyrosine kinase inhibitor (Ki 8751, 1 mg/kg) in the urinary bladder in male and female Wistar rats with 4 hr CYP-induced cystitis as well as littermate controls (no CYP). We used intravesical infusion of the VEGFR2 antagonist coupled with conscious, open outlet cystometry where each rat (control or CYP treated) was evaluated before and after VEGFR2 receptor blockade. With VEGFR2 receptor blockade, bladder capacity increased 31.7% in control female rats ($p \leq 0.01$) and 41.9% in control male rats ($p \leq 0.01$). Voided volume increased 24.8% in control female rats ($p \leq 0.01$) and 33.0% in control male rats ($p \leq 0.05$). After infusion of the VEGFR2 antagonist in female rats treated with CYP, bladder capacity increased by 44.6% ($p \leq 0.05$) and voided volume increase by 32.7% ($p \leq 0.05$). Infusion of the VEGFR2 antagonist in male rats with CYP-induced cystitis exhibited increased

(49.2%) bladder capacity ($p \leq 0.05$), although no change in void volume was observed. The magnitude of change in void volume following VEGFR2 receptor blockade was comparable between control and CYP treatment groups and male and female rats. In contrast, the magnitude of change in bladder capacity in female rats treated with CYP was significantly ($p \leq 0.05$) greater than that in control female rats. The magnitude of change in bladder capacity following VEGFR2 receptor blockade was comparable between male and female control or CYP-treated rats. These data suggest that pharmacological targeting of VEGF/receptor signaling may be a possible intervention for individuals with IC/BPS.

Disclosures: K. Tooke: None. **M.A. Vizzard:** 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.; NIHRO1-DK060481, NIHRO1-DK051369.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.11/OO8

Topic: F.07. Autonomic Regulation

Support: NIH grant R01DK099196
NIH grant R01DK084060
NIH grant P30 - DK079307

Title: Molecular determinants of afferent sensitization in a rat model of interstitial cystitis/bladder pain syndrome

Authors: *N. MONTALBETTI[1], J. ROONEY[2], A. RUED[2], M. CARATTINO[2]
[1]Pittsburgh, PA; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic voiding disorder that presents with pain in the urinary bladder and/or surrounding pelvic region. We previously reported that the overexpression in the rat urothelium of claudin-2 (Cldn2), a tight-junction associated protein that is significantly upregulated in biopsies from IC/BPS patients, reproduces the cardinal features of this disease. The functional changes observed in rats overexpressing Cldn2 were associated to an increase in the excitability of bladder sensory neurons with tetrodotoxin-sensitive (TTX-S) action potentials, which are considered of Aδ origin. In the present study, we combined molecular and functional approaches to define the basis of afferent sensitization in our model of IC/BPS. To determine whether the afferent sensitization seen in our model of IC/BPS reflects changes in the expression of voltage-dependent Na^+ and K^+ channels, we performed a gene expression analysis with acutely isolated bladder sensory neurons from rats

with bladder transduced with an adenovirus coding for Cldn2 (AdCldn2) or GFP (AdGFP). Bladder sensory neurons were sorted on the basis of binding to isolectin IB4, which labels neurons with TTX-resistant action potentials. Gene expression analysis showed a significant upregulation of mRNA levels for subunits Kv2.2 and Kv9.1 in IB4(-) bladder sensory neurons from rats transduced with AdCldn2. No significant difference in mRNA expression for Nav subunits was observed between sensory neurons from rats transduced with AdGFP or AdCldn2. To determine whether the hyperexcitability seen in TTX-S sensory neurons from rats transduced with AdCldn2 reflects changes in the activity of Kv2.2/9.1 channels, we measured whole-cell K^+ currents before and after guangxitoxin-1E (GxTx-1E), a selective blocker of Kv2 channels. GxTx-1E-sensitive currents were significantly larger in IB4(-) sensory neurons from rats transduced with AdCldn2 than AdGFP. In addition, we observed a 3-fold increase in TTX-S Na^+ currents in IB4(-) sensory neurons from rats transduced with AdCldn2, when compared to controls. Significantly, GxTX-1E inhibited repetitive firing in response to electrical stimulation in IB4(-) sensory neurons from rats transduced with AdCldn2. In summary, our data show that urothelial barrier dysfunction increases the expression and activity of Kv2.2 and the activity of TTX-S voltage-gated Na^+ channels in Aδ bladder sensory neurons. These results indicate that afferent sensitization seen in the face of urothelial barrier dysfunction results from changes in the activity of Na^+ and K^+ channels that control neuronal excitability.

Disclosures: N. Montalbetti: None. **J. Rooney:** None. **A. Rued:** None. **M. Carattino:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.12/OO9

Topic: F.07. Autonomic Regulation

Title: Hypoglossal and recurrent laryngeal nerves are involved in swallowing pressure generation in anesthetized rats

Authors: *T. TSUJIMURA, M. INOUE
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Abstract: Introduction: Food and/or liquid bolus are propelled from the oral cavity to esophagus via pharynx during swallowing. Swallowing pressure generation ensures safe transport of an ingested bolus without aspiration or choking. Tongue movement is especially important not only to propel the bolus in the oral cavity but also to generate the oropharyngeal pressure to transport the bolus in the pharynx. The aim of the present study was to clarify the mechanism of generation of swallowing pressure and role of lingual pressure in the pharyngeal swallow. Methods: Experiments were carried out on urethane-anesthetized (1.3 g/kg, ip) Sprague-Dawley male rats. Bipolar enamel-coated copper wire electrodes (0.23 mm diameter, 2 mm inter-polar

distance) were inserted into the left suprahyoid and thyrohyoid (TH) muscles for electromyographic (EMG) recording. A swallow was evoked by punctate mechanical stimulation using a von Frey filament applied to the interarytenoid fold and was identified by EMG burst of the SH and TH muscles. We measured the area under the curve of the oropharyngeal, upper esophageal sphincter (UES) and cervical esophageal (CE) pressures during swallowing using a specially designed manometry catheter. The effects of either transection of hypoglossal (12N) or recurrent laryngeal nerve (RLN) on swallowing pressure were investigated. We also compared the pressure before with and without a palatal plate made of soft acrylic material (AM) (26 mm length × 7 mm width × 1.5 mm thickness). Results: Basically the oropharyngeal, UES and CE pressures during swallowing exhibited high intraindividual reproducibility. Following bilateral hypoglossal nerve transection (Bi-12Nx), oropharyngeal pressure was significantly decreased, and time intervals between peaks of TH EMG bursts and oropharyngeal pressure were significantly shorter. Decreased oropharyngeal pressure and shortened times between peaks of TH EMG bursts and oropharyngeal pressure following Bi-12Nx were significantly increased and longer, respectively, after covering the hard and soft palates with AM. UES pressure was significantly decreased after bilateral RLN transection compared with that before transection. Conclusion: These results suggest that 12N and RLN play a crucial role in the generation of oropharyngeal and UES pressures during swallowing, respectively.

Disclosures: T. Tsujimura: None. **M. Inoue:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.13/OO10

Topic: F.07. Autonomic Regulation

Support: NIH Grant 1U18TR002205-01

Title: Towards closed-loop neuromodulation therapy for gastrointestinal disease: Characterizing gastric myoelectric activity induced by stimulation of the vagus nerve and emetic stimuli

Authors: *A. C. NANIVADEKAR[1], D. M. MILLER[2], S. FULTON[3], A. MCCALL[2], L. WONG[6], J. I. OGREN[6], G. CHITNIS[6], B. L. MCLAUGHLIN[7], L. E. FISHER[4], B. J. YATES[5], C. C. HORN[8]
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Abstract: Gastroparesis is characterized by a diverse pathophysiology that contributes to delayed gastric emptying, symptoms of nausea and vomiting, epigastric pain, early satiety and

weight loss. While gastric electric stimulation (GES) has been used as a therapy for gastroparesis, clinical studies have shown slight or no effect on emesis and several animal studies have shown that GES can result in emesis. Electrical stimulation of the abdominal vagus nerve can provide a more targeted therapy to enhance gastric emptying and prevent emesis. The goal of this study was to evaluate the changes in the electrogastrogram (EGG) leading up to emesis following mechanical, chemical, and electrical emetic stimuli and develop an algorithm to detect early onset of emesis.

To quantify the effect of emetic stimuli, we recorded gastric myoelectric activity in an acute preparation of 6 ferrets. 4-6 multi-contact planar electrodes (200μm diameter, Micro-Leads Inc) were attached to the surface of the gastric fundus and antrum and duodenum. Cuff electrodes (600-700μm diameter, Micro-Leads Inc) were implanted around the ventral abdominal vagus nerve and a balloon was placed in the stomach. Continuous EGG was recorded for each trial and compared to baseline activity. Mechanical stimuli involved gastric distension at 5, 10 and 20 ml volumes. Bipolar electric stimulation of the vagus nerve was delivered between 0.1-5mA and 30ml of intragastric emetine was used as the chemical emetic stimulus. The gastric myoelectric activity was quantified for frequency domain characteristics such as dominant frequency (DF), total power in the normogastric, bradygastric and tachygastric frequency bands and time domain features such the directionality of contractions in the stomach.

The mean baseline DF across all animals was 10.5 cycles per minute (cpm) with the mean normogastric range identified as ± 1.35 cpm around the DF. For 2 ferrets, non-emetic electrical stimulation did not result in a change in the power in the normogastric range. However, supra-threshold electrical stimulation resulted in retching and was accompanied by a decrease in the DF for all ferrets. For gastric distension trials above 5ml, the total power in the 7-17 cpm frequency band showed a significant increase during active increase in volume while the DF remained elevated for the period that the stomach was distended. For emetine infusion trials, the dominant frequency steadily increased post-infusion up to the first retch in 5 of the 6 ferrets. Ongoing work is focused on using these frequency domain features to predict the current state of the stomach and deliver vagus nerve stimulation to suppress the onset of retching.

Disclosures: A.C. Nanivadekar: None. **D.M. Miller:** None. **S. Fulton:** None. **A. McCall:** None. **L. Wong:** None. **J.I. Ogren:** None. **G. Chitnis:** None. **B.L. McLaughlin:** None. **L.E. Fisher:** None. **B.J. Yates:** None. **C.C. Horn:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.14/OO11

Topic: F.07. Autonomic Regulation

Support: University of Michigan MCubed Pilot Grant

Title: Kilohertz frequency stimulation of renal nerves for modulating blood glucose concentration and urinary glucose excretion in a diabetic rat model

Authors: *A. A. JIMAN[1,2], K. H. CHHABRA[3], A. G. LEWIS[4], P. S. CEDERNA[1,5], R. J. SEELEY[4], M. J. LOW[3], T. M. BRUNS[1,2]
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Abstract: Over 400 million people around the world are affected by diabetes. Many diabetic patients struggle with glycemic control and are at high risk of morbidity and mortality. In recent years, the role of the kidney in glucose homeostasis has gained considerable interest. The kidneys are innervated by renal nerves, and renal denervation animal models have shown improved glucose regulation. We hypothesized that kilohertz frequency stimulation, which can block propagation of action potentials, applied to renal nerves would reduce blood glucose concentration levels by increasing urinary glucose excretion. We performed experiments (n = 2) on anesthetized, diabetic streptozotocin (STZ)-induced (50 mg/kg, IV) male Long-Evans rats with stable blood glucose levels above 400 mg/dL prior to surgery. Both kidneys were exposed through a midline abdominal incision. A nerve cuff electrode was placed around each renal artery, encircling the renal nerves that run along the artery. Both ureters were cannulated for collection of urine samples in 10-minute intervals, and colorimetric assays were used to quantify the amount of glucose excreted. Blood samples were obtained from the tail every 10 minutes for blood glucose concentration measurements using a glucometer. Electrical stimulation (50 kHz, 15 V) of the renal nerves was applied for 60 minutes. During stimulation in the two experiments, blood glucose concentration decreased at a rate of -0.6 and -2.8 mg/dL/min, and urinary excretion of glucose increased at a rate of +14.5 and +43.9 µg/min/min. Overall, our results show that kilohertz frequency stimulation of renal nerves is a possible approach for the modulation of blood glucose concentration and urinary glucose excretion. This study suggests that electrical stimulation of renal nerves is a potential treatment modality for glycemic control.

Disclosures: A.A. Jiman: None. **K.H. Chhabra:** None. **A.G. Lewis:** None. **P.S. Cederna:** None. **R.J. Seeley:** None. **M.J. Low:** None. **T.M. Bruns:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.15/OO12

Topic: F.07. Autonomic Regulation

Support: Rådman och Fru Ernst Collianders Stiftelse 2014
Wilhelm och Martina Lundgrens Vetenskapsfond 2015-2017
Carl Gustav och Lilly Lennhoffs stiftelse 2018

Title: A link between the urothelium and caveolae mediated signaling in cyclophosphamide induced cystitis in the rat

Authors: J. STENQVIST, T. CARLSSON, M. WINDER, *P. ARONSSON
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Abstract: Caveolae-mediated signal transduction seems to be vital for healthy bladder function. The expression of the caveolae, i.e. cholesterol stabilized membrane invaginations, appears to be changed by disorders such as bladder hypertrophy and interstitial cystitis/bladder pain syndrome. The latter is an inflammatory disorder during which also the innermost epithelial layer of the bladder wall, the urothelium, is affected in such a way that the expression of receptors as well as the release of neuromodulators from it is altered.
In the present study the effects of caveolae depletion on cholinergic and purinergic signaling in healthy control rats and during cyclophosphamide (CYP)-induced cystitis (100 mg i.p. 60 h before experiment) were examined. A plausible link between ATP-induced release of urothelial acetylcholine and the caveolae was investigated.
A classic organ bath set-up using either bladder strip-preparations (for agonist and electric field stimulation (EFS)) or a whole rat urinary bladder set-up enabling intravesical administration of substances was employed to investigate the effects of caveolae depletion on agonist evoked contractile responses. For the whole bladder preparations the agonist administrations were repeated after removal of the urothelium using collagenase I.
In bladder strip preparations the purinergic part of the EFS-evoked responses was significantly reduced by caveolae depletion by methyl-β-cyclodextrin (10 mM, 60 min). Furthermore, caveolae-depletion significantly reduced the purinergic responses in vitro (from 2.35 ± 0.54 mN to 0.92 ± 0.42 mN at 10^{-3} M ATP, $p< 0.05$, n= 6-7). In the presence of atropine the ATP-evoked responses were significantly reduced in a similar manner. However, when denudation of the urothelium was performed the depletion of caveolae did no longer affect the purinergic response (from 7.83 ± 1.73 mN in denuded bladders to 7.65 ± 0.93 mN after caveolae depletion, n.s, n= 5). CYP-induced cystitis seemed to hamper these effects since caveolae depletion did not significantly affect the purinergic responses during inflammation.
These results suggest a cholinergic part supporting the ATP-induced contractile responses in vitro. A functional link between the urothelium and the caveolae seem to exist, where the caveolae may function as an intermediate signaling step for other transmitters released from the urothelium. Furthermore, the caveolae appear to be vital for neuronal responses as well as purinergic responses in healthy rodents. These effects are absent during inflammation and may be one of the mechanisms affected during interstitial cystitis/bladder pain syndrome.

Disclosures: J. Stenqvist: None. **T. Carlsson:** None. **M. Winder:** None. **P. Aronsson:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.16/OO13

Topic: F.07. Autonomic Regulation

Support: NIH SPARC Award 1OT2OD024908-01

Title: Epidural spinal cord stimulation selectively recruits bladder afferent pathways

Authors: *M. K. JANTZ[1,3], C. GOPINATH[2,3], A. C. NANIVADEKAR[1,3], J. I. OGREN[4], G. CHITNIS[4], L. WONG[4], L. E. FISHER[2,1,3], B. L. MCLAUGHLIN[4], R. A. GAUNT[2,1,3]
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Abstract: Loss of bladder control following spinal cord injury (SCI) has a substantial impact on quality of life, and thus, its restoration is a high priority for people with SCI. Current treatments for lower urinary tract (LUT) dysfunction, including pharmacological interventions and catheterization, are insufficient and people with SCI are frequently rehospitalized due to bladder infections. Recent research suggests that epidural stimulation of the spinal cord can modulate bladder function. Epidural spinal cord stimulators are already regularly implanted to treat back pain, making this a rapidly translatable method to treat loss of bladder control. Here, we demonstrate that localized electrical stimulation through an epidural array can selectively recruit LUT afferents, thereby activating specific reflexes modulating bladder function.
In anesthetized male cats, we placed a high density 16-channel epidural array at several locations above the sacral spinal cord and cauda equina. We implanted nerve cuffs on the pelvic nerve, branches of the pudendal nerve, and on the sciatic nerve to record the antidromic action potentials evoked by stimulation of the spinal cord. Intraurethral and bladder catheters were used to measure bladder and external urethral sphincter contractions. For stimulation at each electrode of the epidural array, as well as for bipolar and tripolar layouts, we determined the recruitment threshold of each peripheral nerve.
Peripheral nerve recruitment due to monopolar stimulation differed for each electrode on the epidural array, both in the peripheral nerve recruitment order and in the amplitude of each response. Bipolar and tripolar stimulation required higher amplitudes to recruit responses, and resulted in different response profiles compared to monopolar stimulation. We observed sciatic nerve coactivation (an unwanted off-target effect) for the epidural array placements over the sacral spinal cord, and were able to reduce these effects with bipolar or tripolar stimulation. For the epidural array placement over the cauda equina, we did not observe these off-target effects. We observed that changes in the intraurethral and bladder pressure were also modulated based on stimulus parameters.

Ultimately, we were able to selectively recruit targeted peripheral nerves and observed that this recruitment also modulated physiological parameters. We believe that being able to control the activity of bladder afferent pathways could be used to systematically modulate function in the LUT. This capability could in turn be an effective treatment to improve LUT function after loss due to SCI or other pathophysiology.

Disclosures: M.K. Jantz: None. **C. Gopinath:** None. **A.C. Nanivadekar:** None. **J.I. Ogren:** A. Employment/Salary (full or part-time):; Micro-Leads, Inc. **G. Chitnis:** A. Employment/Salary (full or part-time):; Micro-Leads, Inc. **L. Wong:** A. Employment/Salary (full or part-time):; Micro-Leads, Inc. **L.E. Fisher:** None. **B.L. McLaughlin:** A. Employment/Salary (full or part-time):; Micro-Leads, Inc. **R.A. Gaunt:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.17/OO14

Topic: F.07. Autonomic Regulation

Support: NIH NINDS R01NS099076
Morton Cure Paralysis Funds

Title: Stimulating spinal 5-HT_{2A} receptors improves involuntary micturition function in rats following complete spinal cord transection

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Abstract: Central serotonin (5-HT), originating mainly in the raphe nuclei of brainstem, regulates lower urinary tract (LUT) activity. Traumatic spinal cord injury (SCI) interrupts spinobulbospinal micturition reflex pathways, resulting in urinary dysfunction. Approximately 2 weeks later, involuntary micturition is established in rats due to the reorganization of spinal reflex circuitry. Recent studies discovered that small amounts of 5-HT remain detectable and spinal 5-HT receptors are upregulated in the caudal spinal cord following injury. To determine if spinal serotonergic machinery plays a role in the partially-recovered urination, we employed pharmacological interventions of 5-HT_{1A} or 5-HT_{2A} receptors combined with micturition functional assays in SCI rats. Female rats received a complete SCI at the 10^{th} thoracic (T10) level. After 3-4 weeks, bladder cystometry and external urethral sphincter (EUS) electromyography (EMG) were recorded to examine micturition reflexes. Intravenous (i. v.) injection of specific 5-HT_{1A} receptor antagonist WAY-100635 (20 μg-1.0 mg/kg) or 5-HT_{2A} receptor antagonist MDL (20 μg-0.5 mg/kg) did not influence the reflexic parameters. However, delivery of selective 5-HT_{1A} receptor agonist 8-OH-DPAT (20 μg-1.0 mg/kg) increased the

voiding duration and EUS tonic activity; injection of specific 5-HT_{2A} receptor agonist DOI (5.0-100 μg/kg) increased the voiding volume and prolonged the interval. This indicates that spinal 5-HT_{1A} receptors are mainly related to urinary continence, but 5-HT_{2A} receptors enable urinary elimination following SCI. Additionally, the high dosage of DOI induced nonspecific effects, such as elevation of EUS tonic activity and body muscle movements. While measuring spontaneous micturition patters via metabolic cage assays, 8-OH-DPAT (0.3 mg/kg in saline, 300μl) or DOI (60 μg/kg in saline, 300μl) were subcutaneously (s. c.) administered and an injection of the same volume of saline served as a control. Spontaneous urinary parameters were continuously recorded for 12 hrs. The results demonstrated that stimulating 5-HT_{1A} receptors with 8-OH-DPAT did not change urodynamic parameters. In contrast, activation of 5-HT_{2A} receptors with DOI increased the urinary volume per void and decreased the frequency within 6 hrs. Thus, spinal 5-HT_{1A} and 5-HT_{2A} receptors appear to have opposing roles in regulating recovered micturition: the former contributes to urinary continence whereas the latter facilitates voiding. Although these two receptors may not be engaged in physiological control of recovered micturition, stimulating spinal 5-HT_{2A} receptors improves involuntary voiding after SCI.

Disclosures: J.H. Definis: None. **J. Weinberger:** None. **D. Wang:** None. **S. Hou:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.18/OO15

Topic: F.07. Autonomic Regulation

Support: NIH NINDS R01 NS088184

Title: Selective recruitment of sensory afferents in the lower urinary tract through microstimulation in the sacral dorsal root ganglia

Authors: *C. GOPINATH[1], M. K. JANTZ[2], A. C. NANIVADEKAR[2], L. E. FISHER[3], R. A. GAUNT[3]
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Abstract: The normal function of lower urinary tract (LUT) is affected by a variety of idiopathic conditions and secondary complications arising from various pathologies. Over the past few decades, peripheral and sacral nerve stimulation has been utilized in clinical setting to modulate LUT function and provide relief to patients through invasive and non-invasive stimulators. One challenge for these clinical systems is their inability to selectively modulate the multiple reflex pathways involved in LUT control. In some of the mixed nerves consisting of sensory and motor fibers, the simultaneous recruitment of efferent and afferent fibers further complicates the problem resulting in activation of undesired reflexes. Here, we report on our effort to selectively

access components of the pudendal and pelvic nerves by stimulating through penetrating microelectrode arrays implanted in the sacral dorsal root ganglion (DRG).
In isoflurane anesthetized male cats, nerve cuffs (Micro-Leads Inc) were implanted on pelvic nerve, pudendal nerve and its branches which included the sensory, caudal rectal and deep perineal nerves. To measure responses evoked from these nerves, intraurethral and transvesical catheters were placed in the urethra and bladder. After a laminectomy of the L5-S4 spinal segments, 32-channel penetrating microelectrode arrays (Blackrock Microsystems) were implanted ipsilaterally into the S1, S2 and S3 DRG. Microstimulation was delivered through individual electrodes and antidromic action potentials were recorded at the peripheral nerve cuffs using a Grapevine neural signal processor (Ripple LLC). A binary search algorithm was used to determine the stimulation threshold for selectively recruiting each instrumented nerve. Stimulation-evoked motor responses were recorded from the bladder, urethra and anal sphincter to confirm the placement of nerve cuffs. Microstimulation of single electrode in the DRG selectively recruited individual nerve branches where the delivered stimulation amplitudes ranged from 2-50 μA. In the tested cats (n=3), the S1 and S2 locations exhibited preferential recruitment of caudal rectal and dorsal nerve of penis respectively. The deep perineal nerve was exclusively recruited through the S2 and S3 locations. Pelvic nerve recruitment was observed through S2 simulation in a single animal. These data enable a preliminary glimpse into the mapping of electrophysiological recruitment patterns of lower urinary tract innervation. Our future experiments will focus on creation of extensive recruitment maps, and testing coordinated microstimulation to produce physiological changes in the function of the bladder and urethra

Disclosures: C. Gopinath: None. **M.K. Jantz:** None. **A.C. Nanivadekar:** None. **L.E. Fisher:** None. **R.A. Gaunt:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.19/OO16

Topic: F.07. Autonomic Regulation

Support: Programa de Becas Postdoctorales DGAPA-UNAM 2018
DGAPA-UNAM IN213418 from Dirección General de Asuntos del Personal Académico UNAM
PAIP 5000-9143 from Facultad de Quimica UNAM

Title: Gastric safety of 3α-hydroxymasticadienoic acid and diligustilide against Indometacin-induced gastric damage in a murine model

Authors: *E. A. PINEDA[1], A. NAVARRETE[1], A. E. CHÁVEZ-PIÑA[2]
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Abstract: *Introduction*. Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin are widely used for the treatment of chronic inflammatory diseases. However, its main limitation is the gastrointestinal toxicity, including ulcers, hemorrhages and gastric perforations. In the pharmaceutical industry, the search for new therapeutic strategies includes the compounds isolated from medicinal plants. Previous studies reported the gastroprotective effect of the extracts of the plants *Amphiptherygium adstringens* and *Ligusticum porteri* Until now, the protective effect of the compounds 3-α-hydroxymasticadienoic acid and diligustilide isolated from these plants against indomethacin-induced gastric damage has not been studied. Therefore, our research aims to |evaluate the gastroprotective effect of 3-α-hydroxymasticadienoic acid and diligustilide against indomethacin-induced gastric damage in Wistar rats. *Methods* male Wistar rats received oral administration of 3-α-hydroxymasticadienoic acid or diligustilide separet (at doses of 1,3,10 and 30 mg/kg, respectively). 30 minutes later, gastric damage was induced by a single oral dose of indomethacin (30 mg/kg). Three h later, animals were euthanized by cardiac puncture. The stomach was removed,and a macroscopical analysis was performed to obtain the total sum of the lesión área (mm^2) for each rat . *Results and Conclusions.* 3-α-hydroxymasticadienoic acid and diligustilide exerts a gastroprotective effect in a dose-dependent manner against indomethacin-induced gastric damage, it is important to note that this effect is comparable with the effect that omeprazole has. Therefore, the gastric safety of both compounds and their potential use in the clinic is evident.

Disclosures: E.A. Pineda: None. **A. Navarrete:** None. **A.E. Chávez-Piña:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.20/OO17

Topic: F.07. Autonomic Regulation

Support: NIH SPARC OT2 OD-023864

Title: Sympathetic innervation of the kidney and liver

Authors: *A. DERBENEV[1], H. TORRES[2], D. BURK[2], H.-R. BERTHOUD[2], H. MUNZBERG[2], A. ZSOMBOK[1]
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Abstract: The sympathetic nervous system (SNS) plays a crucial role in the regulation of renal and hepatic functions. Sympathetic nerves to the kidney and liver have been identified; however, the specific details including anatomical, neurochemical and functional information is lacking, particularly in the mouse. Furthermore, in the absence of detailed information of sympathetic innervation of specific organs, selective manipulation of a particular function will likely remain challenging. Therefore, we aimed to develop tools necessary to comprehensively map the sympathetic innervation of the kidney and liver. Here, we injected the trans-synaptic viral tracer (pseudorabies virus 152) into the left kidney or into the main lobe of the liver to identify kidney- and liver-projecting postganglionic neurons. Following dissection of the ganglia iDISCO method was used to detect pseudorabies virus labeled and tyrosine hydroxylase positive neurons, and then imaging of the tissue was performed with light sheet microscopy. Kidney-projecting neurons were identified in multiple ganglia including the suprarenal and renal ganglia, while only sparse labeling was observed in the celiac complex. In contrast, the majority of liver-projecting postganglionic neurons were observed in the celiac complex. In summary, our study demonstrates that retrograde tracing in combination with iDISCO is a useful tool to map postganglionic neurons innervating the kidney and liver.

Disclosures: A. Derbenev: None. **H. Torres:** None. **D. Burk:** None. **H. Berthoud:** None. **H. Munzberg:** None. **A. Zsombok:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.21/OO18

Topic: F.07. Autonomic Regulation

Support: K12 DK100024-04

Title: Neuromodulation evokes distinct sympathetic mechanisms following cyclophosphamide-induced cystitis

Authors: *E. J. GONZALEZ, W. M. GRILL
Biomed. Engin., Duke Univ., Durham, NC

Abstract: Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) is a major unresolved health concern with a considerable economic burden in lost productivity and health care. Neuromodulation has recently become a therapeutic option to treat patients refractory to standard care. However, the mechanism(s) underlying the effects of nerve stimulation on bladder function are unknown. The objective of this study was to determine the efficacy and mechanisms of neuromodulation in a preclinical model of BPS/IC. Female rats were administered saline or cyclophosphamide (CYP, 150 mg/kg IP) and acute experiments were conducted under urethane

anesthesia (1.2 g/kg SQ, supplemented as needed) 48 hours after injection. The bladder was exposed through a midline abdominal incision and a flared PE-60 catheter was inserted into the bladder dome for cystometry. The catheter was secured and connected via a 3-way stopcock to a pressure transducer and infusion pump. A paddle with platinum iridium contacts was placed between the pubic symphysis and the external urethral sphincter (EUS) to record EMG signals. Pressure and EMG signals were amplified, filtered, and sampled on a PowerLab acquisition unit with LabChart 7 Pro. Electrical stimulation of the sensory branch of the pudendal nerve increased bladder capacity in control and CYP-induced cystitis rats ($p \leq 0.01$). Bilateral transection of the hypogastric nerves (HGNT) had no effect on stimulation-induced increases of bladder capacity in control rats ($p \leq 0.05$), whereas, HGNT, as well as pharmacological inhibition of beta-adrenergic receptors (propranolol, 1 mg/kg IV), blocked the effects of electrical stimulation in CYP-induced cystitis rats. These studies suggest distinct spinal reflexes contribute to the effects of pudendal nerve stimulation following inflammation. Understanding this neural reorganization in cystitis may enable the development of novel therapeutic approaches.

Disclosures: E.J. Gonzalez: None. **W.M. Grill:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.22/PP1

Topic: F.07. Autonomic Regulation

Support: University of Michigan Host Microbiome Initiative - Microbiome Explorer Program

Title: Effects of peripheral nerve stimulation on organ microbiome across rodent estrous cycle

Authors: M. LEVY[1], C. BASSIS[2], E. KENNEDY[3], K. YOEST[4], J. B. BECKER[4], J. BELL[5], M. B. BERGER[6,5], *T. M. BRUNS[3]
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Abstract: The human microbiome has an important influence on health and disease. One such influence is its association with Vulvovaginal Atrophy (VVA), which, due to reduced estrogen levels, may affect up to 50% of post-menopausal women. VVA can lead to vaginal dryness and is correlated with female sexual dysfunction. VVA is associated with an imbalance of the vaginal bacteria population, such as reduced levels of *Lactobacillus* and increased levels of other bacteria. Pudendal nerve stimulation in rodents can lead to increases in vaginal blood flow, and stimulation of the genital nerve branch of the pudendal nerve has led to an improvement in sexual function in a small cohort of women. These sexual function improvements may be due to

changes in the vaginal microbiome, potentially driven by increases in vaginal blood flow. We hypothesized that genital nerve stimulation can lead to a normalization in the vaginal microbiome over time. Five treatment and four control adult, nulliparous female Sprague Dawley rats were used to test the association between nerve stimulation and microbial community. First, daily lavages were collected across a two-week baseline period to determine the normal variation in vaginal microbiota across the rodent estrous cycle. Next, all rats were anesthetized twice a week with ketamine during a 6-week testing period. In each session treatment rats received 30 minutes of cutaneous genital nerve stimulation (10 Hz at amplitude below visible muscle response) while control group rats had the probe in place with no stimulation applied. Vaginal lavages were performed for each animal prior to and following each 30-minute stimulation/no-stimulation period. Each lavage sample was analyzed for estrous stage and microbiota composition using 16S rRNA gene sequencing. Analysis of preliminary vaginal samples identified dominant bacterial species including Proteobacteria, Lactobacillales, and Firmicutes, all of which are common in the rodent vaginal microbiome. Further analyses are underway to compare the microbiota of treatment and control rats within and across the study duration and against different estrous cycle states. To our knowledge this is the first study assessing the effect of nerve stimulation on organ microbiota. A relationship between genital nerve stimulation and changes in the vaginal microbiota would demonstrate it as potential therapeutic technique for women suffering from VVA and its correlated forms of female sexual dysfunction.

Disclosures: M. Levy: None. **C. Bassis:** None. **E. Kennedy:** None. **K. Yoest:** None. **J.B. Becker:** None. **J. Bell:** None. **M.B. Berger:** None. **T.M. Bruns:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.23/PP2

Topic: F.07. Autonomic Regulation

Support: Galvani Bioelectronics
NIH Grant K12DK100024

Title: State-dependent pudendal nerve stimulation increases bladder capacity and voiding efficiency in rats and cats

Authors: *J. A. HOKANSON[1], C. L. LANGDALE[1], P. MILLIKEN[3], A. SRIDHAR[3], W. M. GRILL[2]
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Abstract: Overactive bladder symptoms including urinary urgency, frequency and incontinence are prevalent, negatively impact quality of life, and are inadequately treated by existing clinical

therapies. Stimulation of the pudendal nerve is a promising therapy that is not yet fully developed.

In a prior study pudendal nerve stimulation substantially increased bladder capacity (BC), but the largest increases were associated with decreases in voiding efficiency (VE). In this study we examined whether state-dependent stimulation - one set of parameters to promote urine storage during bladder filling and another to promote voiding - could increase both BC and VE.

Experiments were conducted in urethane anesthetized female Wistar rats (n=9) and alpha-chloralose anesthetized male cats (n=6). Nerve cuffs were placed on the pudendal sensory branch (rats), dorsal genital branch (cats), and pudendal motor branch (both). A catheter was placed in the bladder for pressure measurement and saline infusion during single-fill cystometrograms. Bladder inhibition was achieved by 10 Hz stimulation of the sensory pudendal or dorsal genital nerve. In some trials stimulation occurred throughout the entire cystometrogram (continuous stimulation); in other trials stimulation was terminated at the onset of voiding. In this latter case either no further stimulation was delivered or a second stimulus was delivered to the pudendal motor branch in bursting patterns (state-dependent stimulation).

In rats, continuous 10 Hz stimulation of the sensory pudendal nerve increased BC and decreased VE to 158% and 19% of control values, respectively. Termination of the inhibitory stimulus during voiding increased VE to 48% of control values. Bursting stimulation of the motor branch during the voiding phase increased VE to 75-117% of control. VE was increased relative to continuous stimulation ($p \leq 0.016$) but was not larger than control values.

Similar results were obtained in cats. Continuous 10 Hz stimulation of the dorsal genital nerve increased BC and decreased VE to 126% and 67% of control values respectively, although the latter trend was not significant ($p = 0.072$, n=5). Termination of the inhibitory stimulus during voiding increased VE to 114% of control values. Bursting stimulation of the pudendal motor branch during voiding increased VE to 479% of control values ($p=0.028$, n=5).

In both rats and cats continuous pudendal nerve stimulation increased BC but decreased VE. State-dependent stimulation increased both BC and VE and may be an effective therapy for voiding dysfunction.

Disclosures: **J.A. Hokanson:** A. Employment/Salary (full or part-time):; Phil Milliken, Arun Sridhar. 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.; Galvani Bioelectronics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Warren Grill, James Hokanson, Christopher Langdale. **C.L. Langdale:** None. **P. Milliken:** A. Employment/Salary (full or part-time):; Galvani Bioelectronics. **A. Sridhar:** A. Employment/Salary (full or part-time):; Galvani Bioelectronics. **W.M. Grill:** 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.; Galvani Bioelectronics.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.24/PP3

Topic: F.07. Autonomic Regulation

Title: Age-related degradation of urinary tract reflexes in rat

Authors: *A. GERAMIPOUR[1], Z. C. DANZIGER[2]
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Abstract: Age-related underactive bladder (UAB) can lead to high healthcare expenses, lower urinary tract (LUT) infection and even death in elderly population. When the bladder is in micturition mode, sensory information from the bladder excites the bladder and relaxes the external urethral sphincter (micturition reflex). Urethra flow activates the urethra-to-bladder reflex (augmenting reflex), which promotes the micturition reflex and helps in complete bladder emptying. The augmenting reflex is only engaged when the LUT is in "micturition mode" and not in "continence mode" (Fowler et al. 2008, Nat Rev Neurosci). Previous work in young, anesthetized rats has found this switch between modes to occur at bladder volumes >74% of the bladder capacity (Danziger and Grill, 2017, J Physiol). We hypothesized that the augmenting reflex is weakened with increasing age and can result in UAB like symptoms.
We used young (n=10, 4-7 month), and old (n=12, 18-24 month) urethane-anesthetized female Sprague-Dawley rats to quantify the effect of aging on the augmenting reflex. One lumen of a double-lumen catheter was suprapubically inserted into the bladder. The second lumen passed through the intravesical space into the urethra to allow infusion of fluid through the urethra and simultaneously prevented the bladder from expelling volume. At 2 minute intervals the urethra was infused at a pseudorandomly selected flow rate to test if the infusion could trigger the augmenting reflex. This was repeated multiple (54) times at a range of urethral flow and bladder fill combinations to ascertain the effects of age on augmenting reflex activation point.
The results show that the augmenting reflex in older animals is functionally weaker than young animals. Remarkably, in 66% of aged animals the augmenting reflex disappeared completely. In 25% of aged animals the augmenting reflex could only be triggered once bladder volumes were large enough to evoke the bladder distention (micturition) reflex, meaning, the augmenting reflex for aged animals was engaged far later in the micturition phase than for young animals. This degradation of the augmenting reflex and urethral sensitivity may be the cause of poor voiding efficiency and large residual volumes, which are UAB-like symptoms. Furthermore, results demonstrated an increase in micturition pressure threshold, and a decrease in micturition pressure peak in older animals, which can be an indicative of possible bladder afferent and efferent weakness, respectively.

Disclosures: A. Geramipour: None. **Z.C. Danziger:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.25/PP4

Topic: F.07. Autonomic Regulation

Support: R01 DK113030

Title: 'Neural networks, the pontine micturition center, and bladder control'

Authors: *A. M. VERSTEGEN[1], N. KLYMKO[2], V. VANDERHORST[3], J. GEERLING[4], M. ZEIDEL[2]
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Abstract: Lower urinary tract symptoms (LUTS) are extremely common and enormously debilitating. A significant component of LUTS is due to failure of nervous control of bladder function, or otherwise failure of neural pathways to compensate for bladder dysfunction. It remains unclear how the brain controls bladder filling and voiding and how the reflex is inhibited at times when voiding is undesirable. The pontine micturition center (PMC) directly controls voiding. PMC neurons provide innervation of sacral spinal cord nuclei that control bladder contraction and sphincter relaxation. Here we identify the neurochemical identity of PMC neurons that contribute to micturition control and we identify a network of afferent neurons, spanning several forebrain and brainstem regions, which directly modulates these PMC neurons to initiate voiding behavior. Micro-injections of adeno-associated viruses, modified Rabies virus, CTb or Diphtheria Toxin, placed into anatomically defined regions of the mouse brain, enabled highly selective expression of proteins in target neuron populations. Video thermography to track voiding behavior in awake-behaving mice was combined with measurement of bladder pressure, optogenetic stimulation or inhibition and recording of neuron population activity. Optogenetically stimulating specific subpopulations of PMC neurons triggered time-locked void responses. Conversely, selective ablation of neurons in the PMC using diphtheria toxin A resulted in urinary retention, and delayed the CMG voiding reflex. Input connections controlling PMC were found in the vlPAG, the preoptic area, the lateral hypothalamic area, and other sites.To test the functional consequence of afferent neuron activity, we light-stimulated axon terminals within the PMC and observed micturition events within seconds (excitatory) or increased inter-void intervals (inhibitory afferents). We recorded Ca^{2+}-dependent fluorescence changes in distinct neuron populations to study the timing of neuronal activity with respect to detrusor contraction and voiding and found that specific subpopulations have distinct activity patterns that may drive particular aspects of bladder control. Our results taken together, identify a

network of neurons that can control urinary voiding and continence by acting on PMC neurons. We have demonstrated facilitatory roles of periaqueductal grey (PAG) and hypothalamic afferents, for voiding and modulating continence. This information helps us with a detailed understanding of how forebrain, brainstem and spinal inputs converge to control bladder filling and voiding, and hence the neurologic mechanisms of LUTS in mice and humans.

Disclosures: A.M. Verstegen: None. **N. Klymko:** None. **V. VanderHorst:** None. **J. Geerling:** None. **M. Zeidel:** None.

Poster

228. Autonomic Regulation: Gastrointestinal, Renal/Urinary, and Reproductive Regulation

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 228.26/PP5

Topic: F.08. Biological Rhythms and Sleep

Support: FNA grant from Dr Ranu Jung

Title: A computational model for functional uncoupling in the stomach

Authors: *M. AHMED[1], R. JUNG[2]
[1]Dept. of Biomed. Engin., [2]Biomed. Engin., Florida Intl. Univ., Miami, FL

Abstract: Interstitial cells of Cajal (ICC) isolated from different regions of the stomach generate spontaneous electrical slow wave activity at different frequencies, with cells from the mid corpus (dominant pacemaker) pacing faster than their antral counterparts. However, in vivo there exists a uniform pacing frequency; slow waves propagate aborally from the proximal stomach and subsequently entrain distal tissues. Under some pathological states, the intrinsic frequency of ICC in the myenteric plexus in antrum become equal or close to that of dominant pacemaker in corpus thus becoming ectopic/local pacemakers. These waves propagate backwards and collide with the waves coming from the corpus most likely resulting in disruption of gastric peristalsis and delayed gastric emptying (gastroparesis). This scenario is called *functional uncoupling* of the contractions of the stomach.
To better understand the mechanisms underlying the functional uncoupling, we have computationally modeled the slow waves as being generated by a chain of interconnected biophysical circuits of networks of cells. This biophysical circuit consists of 6 ICC and 6 smooth muscle cells (SMC) where both of the cell models are based on Corrias and Buist model. ICC are connected to each other through gap junctions and so are the SMC. Gap junctions also connect individual ICC with its corresponding muscle cell. The ICC were modeled with an intrinsic frequency gradient with the rostral most cell having the highest frequency and caudal most cell having the lowest frequency by assigning initial inositol trisphosphate (IP_3) concentration in a linear gradient fashion (600 nM at the top to 595 nM at the bottom). An IP_3 dependent calcium

ion release model was incorporated into the ICC model resulting in an entrained pacing frequency of 3.1 cycles per minute. When an ICC membrane depolarizes, this increases IP_3 receptor mediated Ca^{2+} release by increasing synthesis of IP_3 in that cell cytoplasm. Although, cells have a linear gradient in their initial IP_3 concentration, in time, they all attain a maximum concentration which is almost equal to each other (650.91 nM for rostral one to 650.88 nM for caudal one) and so is the case with minimum concentration (616.56 nM-616.50 nM). In our model, it was assumed that IP_3 diffuses through the gap junctions that connect neighboring ICCs. The diffusion was simulated as initial concentration gradient from the local pacemaker in antrum towards oral pacemaker cells. This gradient has created the functional uncoupling in stomach. By modeling functional uncoupling in stomach, we can use this model to study different gastrointestinal diseases, especially motility related diseases.

Disclosures: M. Ahmed: None. **R. Jung:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.01/PP6

Topic: G.02. Motivation

Support: AMED
KAKEN Grant

Title: Analysis of empathic neural circuits regulated by oxytocin

Authors: *S. YADA[1], K. HORIE[2], S. HIDEMA[3], K. NISHIMORI[4]
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Abstract: Social behavior to communicate with others is essential for the survival for organisms including human. Empathy is a mental function that shares emotional state with others, and it is essential as a motivation for causing social behaviors that help other people such as compassion and comfort. Oxytocin (Oxt) is a peptide synthesized in the paraventricular nucleus and the supraoptic nucleus and is known to be involved in social behaviors and empathy. Recent studies have focused on Oxt and its receptor (Oxtr) as therapeutic drug candidates for mental disorders, especially social disorder symptoms of autism spectrum disorder (ASD). ASD is a neurodevelopmental disorder characterized by repetitive behaviors and deficits in social behavior and empathy, while the etiology and treatments for ASD are poorly understood. Therefore, it is strongly expected that the fundamental elucidation of the neural mechanisms of the sociality by Oxt/Oxtr system. It is also necessary to investigate the mechanism of empathy which is the root

of social behavior, because it is thought that neuroscience study of empathy is widely applicable to treatment of many mental diseases including ASD. However, the empathic neural circuits regulated by Oxt/Oxtr have been still unknown. In this study, we researched how the Oxt/Oxtr system controls empathy. We analyze brain regions and neural circuits of $Oxtr^+$ neurons involved in empathy in the whole brain and aim to contribute to treatment of sociality of mental disorders including ASD in the future. In this study, we performed empathic behavioral tests for Oxt/Oxtr genetic modified mice and prairie voles (*Microtus ochrogaster*), and analyzed the relationship between $Oxtr^+$ neurons and empathy. Prairie voles are rodents which have high sociality such as robust monogamous system and breeding by parents. They are increasingly becoming popular as model animals of social behavior research in recent years. Furthermore, they are expected to be useful as empathic model animals from the report showing empathetic behavior among pairs. We revealed that the Oxt/Oxtr signals are important for empathy, and identified the brain regions related to empathic behavior in the whole brain.

Disclosures: S. Yada: None. **K. Horie:** None. **S. Hidema:** None. **K. Nishimori:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.02/PP7

Topic: G.02. Motivation

Title: The exploration of neuronal circuits underlying rat cooperation behavior

Authors: *M. JIANG, Z. WANG
Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai City, China

Abstract: Cooperation has generally been attributed to a cognitively demanding, complex social behavior that two or more individuals act together to achieve a common goal. The ability of cooperation is key to surviving and has even been thought as which help humans become Earth's dominant vertebrate by some anthropologists. However, the details of how and why cooperation evolved remain unclear. Here we use a temporal coordination task which is a simple form of cooperation to address these questions, namely familiar pairs of SD rats were required to poke nose port synchronously within a short time (3s or 1s) for mutual reward in a automated maze. Rats were trained under various conditions including light or dark condition, with/out physical contact to assess the role of different sensory modalities on cooperative efficiency. We found that SD rats performed better in dark condition compared with the rest conditions. Rats could cooperate well even with route changed. What's interesting is that the social interactions between the two individuals increased with task difficulty, indicating that social communication played an important role in cooperation. The phenomenon that higher reward would promote rats to cooperate from individual action implies the behavior is related to the reward circuit.

Interestingly, we identified a population of neurons which responded differently to the same event in cooperative task (CT) and non-cooperative task (NCT) in prelimbic cortex (Prl) by using extracellular recording, providing important clues about the driving force behind cooperation.

Disclosures: M. Jiang: None. **Z. Wang:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.03/PP8

Topic: G.02. Motivation

Support: Binational Science Foundation
Feil Foundation

Title: Phasic signaling by noradrenergic locus coeruleus neurons during maternal social interactions

Authors: *R. DVORKIN, C. KELAHAN, S. D. SHEA
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Abstract: The Locus Coeruleus-Noradrenaline system (LC-NA) has an established role in arousal, attention and state-dependent behavioral modulation. Tonic firing rates in LC closely track other physiological measures of arousal such as EEG patterns and pupil diameter. In structured operant tasks, LC neurons emit phasic bursts in response to salient stimuli and facilitate goal-directed behaviors. Indirect evidence implies that LC is also engaged in naturalistic social behavior, but there are few reports of LC activity under those conditions. Certain social stimuli such as odors and vocalizations can act as rewards, and their subjective value is powerfully modulated by context and internal state, or “motivational salience.” First-time motherhood, for example, attaches emotional significance, and thereby greater motivational salience, to social cues. This may explain why maternal experience in mice induces robust pup gathering behavior and attraction to ultrasonic pup vocalizations. The neural circuits that facilitate this switch in motivated behavior are poorly understood. Therefore, we are evaluating the potential role of the LC-NA system in modulating social reward value by signaling motivational salience.
We are using chronically-implanted multielectrode arrays (MEAs) and fiber photometry to measure spiking activity from single neurons and bulk Ca2+ signals from neuronal populations in LC of freely behaving, nulliparous female mice, before and after exposure to pups. LC neurons are identified by electrophysiological criteria and by post hoc histology. For fiber photometry, DBH (dopamine-β-hydroxylase)-Cre mice are with injected with a Cre-dependent adeno-associated virus (AAV) driving expression of the Ca2+ indicator GCaMP6s. Our

preliminary results reveal that contact with pups during retrieval events by maternally-experienced surrogates coincided with rapid, transient increases in neuronal firing rate (phasic bursts) and optically-detected GCaMP fluorescence, suggesting that LC may participate in evaluating and responding to rewarding social signals. Ongoing experiments aim to ascertain whether these transients are modulated by cumulative experience with social cues, and to further investigate the influence of LC on social behavior and motivational salience.

Disclosures: R. Dvorkin: None. **C. Kelahan:** None. **S.D. Shea:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.04/PP9

Topic: G.02. Motivation

Support: R01-MH087583
R01-MN099085
R01-MH058616

Title: Consequences of prenatal exposure to valproic acid in the socially monogamous prairie vole

Authors: *L. L. SAILER[1], F. DUCLOT[1], Z. WANG[2], M. KABBAJ[1]
[1]Biomed. Sci., [2]Psych., Florida State Univ., Tallahassee, FL

Abstract: One of the most widely used environmental exposure models of autism spectrum disorders is the valproic acid (VPA)-induced animal model. VPA-exposed rats and mice exhibit deficits in social behaviors that resemble some aspects of autism spectrum disorders. Although significant discoveries on the embryopathology of VPA have been proposed, its effects on social bonding, a complex behavior uncommonly displayed by rats and mice, remains unknown. In this study, we aimed at validating the socially monogamous prairie vole (*Microtus ochrogaster*) model for the study of the effects of prenatal VPA exposure. VPA-exposed prairie voles engage in fewer social affiliative behaviors, exhibit less social interactions with novel conspecifics, and show enhanced anxiety-like behavior, compared to saline-exposed controls. A downregulation of cortical vasopressin receptor (V1aR) and methyl CpG-binding protein 2 (MECP2) mRNA expression coincide with these social impairments. Through chromatin immunoprecipitation, we confirm that reduced mRNA expression of V1aR and MECP2 occur through independent processes. Additionally, prenatal VPA exposure does not alter total dendritic and spine-shape subtype densities during adulthood. Interestingly, adult social bonding behaviors, such as partner preference formation and selective aggression, are not disrupted by prenatal VPA exposure.

Disclosures: L.L. Sailer: None. **F. Duclot:** None. **Z. Wang:** None. **M. Kabbaj:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.05/PP10

Topic: G.02. Motivation

Title: Disrupting endocannabinoid tone during adolescence: Effects on anxiety & sociability

Authors: *H. H. LOPEZ[1], D. COSSIO[2], Z. MICHAS[2], H. STADLER[2], C. JOHNSTON[2]
[1]Psychology, [2]Neurosci., Skidmore Col., Saratoga Springs, NY

Abstract: Animal models suggest that the endocannabinoid system (eCS) helps regulate various aspects of social behavior, including play behavior and social reward, during adolescence. Properly tuned endocannabinoid signaling may be a critical developmental component in the emergence of normal adult social behavior. In the current experiment, we attempted to pharmacologically disrupt endocannabinoid tone during early adolescence, and then measure the behavioral effects during both middle adolescence and early adulthood. 36 male and 36 female Long Evans rats received daily injections of one of three treatments between post-natal day (PND) 25-39: 1) vehicle treatment, 2) CP55,940 (0.5 mg/kg), a potent CB1 receptor agonist, or 3) AM251 (0.4 mg/kg), a CB1 receptor antagonist/inverse agonist. Both in middle adolescence (PND 40-44) and early adulthood (PND 66-70), subjects were tested in an elevated plus maze for general anxiety and a 3-chambered sociability apparatus for social motivation. For the sociability test, the percentage of entries into the social chamber, the percentage of time spent in the social chamber, and the percentage of time spent investigating the social target (a same-sex conspecific) were the primary dependent variables. We hypothesized that both CP55,940 and AM251 treatment would significantly attenuate sociability in both male and female rats, expressed during middle adolescence and early adulthood. This would indicate that disruption of endocannabinoid tone during a critical social-developmental phase has long-term, persistent neurobehavioral effects. Initial analyses indicate a modest effect of CP55,940 but not AM251 on subsequent sociability. There were also main effects of sex (with males expressing greater social motivation overall than females) and age (with subjects expressing greater sociability as adolescents than as adults).

Disclosures: H.H. Lopez: None. **D. Cossio:** None. **Z. Michas:** None. **H. Stadler:** None. **C. Johnston:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.06/PP11

Topic: G.02. Motivation

Support: Department of Science and Technology (DST), India to SI (grant # SR/SO/AS-39/2009)
NBRC Core funds

Title: Role of μ-opioid receptors in the motivation to sing and acoustic features of female-directed songs in male zebra finches

Authors: *S. KUMAR[1], A. N. MOHAPATRA[1], U. A. SINGH[1], S. SHARMA[1], V. ARORA[1], N. KAMBI[1], A. DATTA[1], H. SHARMA[2], T. VELPANDIAN[2], R. RAJAN[3], S. IYENGAR[1]
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Abstract: Objective and rationale: Mu-opioid receptors (μ-ORs) are G-protein-coupled receptors found throughout the nervous system and bind endogenous opioid peptides such as enkephalin and endorphin. High levels of μ-ORs are expressed in different components of the basal ganglia, which receives dopaminergic projections from the VTA/SNc. Dopamine is known to affect the inhibitory output of the basal ganglia and modulate the cortico-basal ganglia-thalamic circuitry. This circuitry is involved in various cognitive functions such as motivational and motor aspects of behaviour, including vocalization across different species of vertebrates. Interestingly, modulating levels of the endogenous opioids or their binding in the basal ganglia can change dopamine release by the VTA/SNc and affect associated behaviours. Songbirds like zebra finches show high expression of μ-ORs in various song control regions. Social context-dependent singing is a direct output of a part of this circuitry (called anterior forebrain pathway or AFP), making songbirds an excellent model system to study the role of opioid modulation in vocal behaviours.
Methods: To study the role of opioid neuromodulation on female-directed (FD) singing in zebra finches which is a male courtship behaviour, we performed site-specific infusions of μ-OR antagonists in the nuclei of the AFP by microdialysis and analysized the neurotrasmitters by HPLC-MS in the dialysate, while simultaneously recording the behaviour of experimental birds. This methodology gave us direct insights (from the molecular to the behavioural level) as to how the endogenous opioid system directs motivational aspects of singing during courtship in zebra finches.
Results: Inhibiting μ-ORs in Area X (a basal ganglia homologue in songbirds of AFP) using antagonists results in a significant dose-dependent increase in the number of FD songs which suggests an increase in the motivation to sing. Interestingly, the same manipulation in the cortical

nucleus LMAN which is upstream of Area X led to a decrease in the number of songs. Further, we found changes in the acoustic features of individual syllables that these birds sang, after the μ-OR system was modulated in Area X.
Conclusions: Our results confirm that μ-ORs in the AFP play a major role in the motivation of male birds to sing FD songs. Also, we report for the first time that μ-OR modulation in different components of the AFP can affect the acoustic properties of songs.

Disclosures: S. Kumar: None. **A.N. Mohapatra:** None. **U.A. Singh:** None. **S. Sharma:** None. **V. Arora:** None. **N. Kambi:** None. **A. Datta:** None. **H. Sharma:** None. **T. Velpandian:** None. **R. Rajan:** None. **S. Iyengar:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.07/PP12

Topic: G.02. Motivation

Support: RO1MH095894
RO1MH108627
R37MH109728
SFARI304935

Title: Does oral acetaminophen affect the sensitivity of neurons in macaque anterior cingulate cortex to the valence of outcomes in a social decision-making task?

Authors: *K. M. SHARIKA, M. PLATT
Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Human imaging studies have implicated both dorsal anterior cingulate cortex (dACC) and anterior insula, areas associated with the affective component of pain and discomfort (Rainville et al., 1997), in empathy (Singer et al., 2004). Oral acetaminophen (active ingredient in tylenol/ paracetamol) reduces BOLD activity in ACC and eases self-reported pain induced by social rejection (DeWall et al., 2016) and also diminishes empathy for others in distress (Mischkowski et al., 2016).These observations suggest acetaminophen, and possibly other pain killers, may interfere with normal processing of negative outcomes for both self and others. One potential cellular substrate for these effects are recently reported neurons in anterior cingulate cortex that have been shown to be sensitive to others' reward (Chang et al., 2013). It remains unknown whether these neurons also process negatively valenced information for other and whether the activity of these neurons is sensitive to acetaminophen. To answer these questions, we recorded the activity of neurons in ACC gyrus (ACCg) in rhesus monkeys choosing between two differently colored targets associated with varying magnitudes of fluid. On each trial, the

fluid on offer was cued to be pleasant (fruit juice) or unpleasant (diluted quinine) for either self or a recipient monkey (sitting across the room and facing the actor monkey). Monkeys rapidly learnt the valence, magnitude and recipient associated cues and showed overall preference for good tasting fluid for both self and other. Neurons in ACCg were also sensitive to outcome valence and recipient. Next, we studied decisions and activity of ACCg neurons following oral acetaminophen. Behaviorally, monkeys showed reduced sensitivity to negative outcomes for both self and the other. Preliminary results also suggest that acetaminophen diminishes the sensitivity of ACCg neurons to positive and negative outcomes for both self and the other.

Disclosures: K.M. Sharika: None. **M. Platt:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.08/PP13

Topic: G.02. Motivation

Support: NIH Grant AA021449
NIH Grant DA023248
NIH Grant DA044749

Title: Neural correlates of reward-directed actions and individual variation in behavioral approach tendency

Authors: *T. M. LE[1], S. ZHANG[3], S. L. ZHORNITSK, 06511[4], W. WANG[1], C.-S. R. LI[2]
[1]Psychiatry, [2]Dept Psychiatry, Yale Univ., New Haven, CT; [3]Yale Univ. Sch. of Med., New Haven, CT; [4]Psychiatry, Yale, New Haven, CT

Abstract: Human and non-human primate studies have reported regional and neuronal responses to incentivized actions as well as restraint of actions. However, it remains unclear how reward may modulate these neural processes differently or how individual variation in approach tendency influences the neural processes. We examined brain activation to go and nogo actions in a reward go/nogo task, with approximately ¾ go and ¼ nogo trials and an individually titrated go response window. Correct go and nogo trials were rewarded with $1 or ¢5 in reward sessions. Behaviorally, reward facilitated go and impeded nogo action. Rewarded go and nogo shared activation in the rostral anterior cingulate cortex (ACC) and right inferior frontal and parietal cortex. Rewarded go as compared to nogo success engaged the medial orbitofrontal cortex, with differential response to reward magnitude, as well as dorsal ACC/supplementary motor area and subcortical structures, all with indistinguishable response to dollar and nickel rewards. In contrast, rewarded nogo as compared to go success involved activation of the right middle frontal cortex and bilateral intraparietal sulci. We derived a behavioral index of approach

tendency for each subject by subtracting the actual from the group predicted nogo error RT in a linear regression against go success RT. A large index reflected higher approach tendency and was associated with less activation of the right superior frontal gyrus during rewarded go action. The current findings distinguished neural responses to rewarded action and restraint of action and characterized a neural correlate of individual variation in approach behavior.

Disclosures: T.M. Le: None. **S. Zhang:** None. **S.L. Zhornitsk:** None. **W. Wang:** None. **C.R. Li:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.09/PP14

Topic: G.02. Motivation

Support: CAN-BIND

Title: Does learning to control an aversive stimulus mitigate the effects of stress on social motivation in rats?

Authors: *S. DANIELS[1], D. LEMAIRE[2], T. LAPOINTE[2], F. LERI[3]
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Abstract: Decreased social motivation is a prominent feature of depression. Stress is known to cause reduced reward motivation in rodents, and this is potentiated when subjects have no control over aversive stimuli. Whether stressor controllability influences the etiology of decreased social motivation has not been tested and has important implications for reducing the detrimental effects of stress on depressive symptomology. The current research tested the hypothesis that exposure to inescapable but not escapable stress causes reduced social motivation. In Experiment 1, a novel procedure to measure social motivation in male Sprague-Dawley rats was developed. Test rats underwent either: one, two or ten training sessions where they had free access to investigate a social conspecific or an object in adjacent arms of a Y-maze. Twenty-four hours after the last training session, rats were tested for a social compartmental preference (SCP), where investigation of the previously paired social and object compartments was assessed. In Experiment 2, the short-term effects of stressor controllability on the expression of social motivation was assessed. Test rats were exposed to escapable or inescapable foot shocks twenty-four hours after the last training session, followed by SCP testing the next day. In Experiment 3, the long-term effects of stressor controllability on the acquisition of social motivation was assessed. Test rats were first exposed to escapable or inescapable foot shocks prior to 10 training sessions and SCP testing. It was found that when test rats underwent at least

two training sessions they spent significantly more time investigating the previously paired social compartment, compared to the object compartment, during the SCP test. Furthermore, while rats exposed to escapable foot shocks demonstrated a significant SCP in both Experiments 2 and 3, this was not seen in rats exposed to inescapable stress. These results suggest that the ability to control an aversive stimulus blocks the detrimental consequences of stress on social motivation. Future research will investigate whether this effect can be mitigated by drugs that increase serotonergic tonicity.

Disclosures: S. Daniels: None. **D. Lemaire:** None. **T. Lapointe:** None. **F. Leri:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.10/PP15

Topic: G.02. Motivation

Support: NIH Grant P01HD064653

Title: Oxytocin modulates neural responses during observation of facial gestures in infant macaques

Authors: *H. RAYSON[1], F. FESTANTE[2], G. TOSCHI[2], S. S. K. KABURU[3], A. PAUKNER[4], C. S. BARR[5], N. A. FOX[6], P. F. FERRARI[1]
[1]Inst. des Sci. Cognitives, Ctr. Natl. de la Recherche Scientifique, Bron, France; [2]Dept of Med. and Surgery, Univ. of Parma, Parma, Italy; [3]Dept. of Population Hlth. and Reproduction, Univ. of California, Davis, Davis, CA; [4]Intramural Res. Program, [5]Natl. Inst. on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD; [6]Dept. of Human Develop. and Quantitative Methodology, Univ. of Maryland, College Park, MD

Abstract: Oxytocin plays a critical role in the social behaviour of many species, and mounting evidence suggests that it also modulates socio-cognitive processes in primates (e.g. Chang & Platt, 2014; Kirsch et al., 2005; Skuse et al., 2014; Simpson et al., 2014; Liu et al., 2015). Suppression of activity in the alpha frequency band is commonly associated with the perception of social stimuli, with administration of oxytocin in human adults modulating alpha suppression during observation of biological motion (Perry et al., 2010). While alpha event-related desynchronization (ERD) is seen during observation of facial gestures in infant human and nonhuman primates (Ferrari et al., 2012; Rayson et al., 2017; Fox et al. 2016), it is not clear whether oxytocin plays the same role in the perception of social stimuli from a very early stage in development. To answer this question, we used electroencephalography (EEG) to investigate alpha ERD in three-month-old rhesus macaques during observation of a human performing different facial gestures (lip-smacking and tongue protrusion), as well as observation of a non-

biological stimulus (a spinning disk). We recorded activity from anteriorly- and posteriorly-placed electrodes, and coded video recordings of the infants' own behavior during the experiment. Each infant took part in the experiment two times: once after administration of saline, and once after administration of nebulized oxytocin. We found that oxytocin increased alpha ERD in posterior electrodes during observation of lip-smacking, the most socially relevant, affiliative gesture for macaques. Behaviorally, oxytocin increased the proportion of time infants attended to the demonstrator's face in the lip-smacking condition, as well as infants' own production of facial gestures during observation of lip-smacking and tongue protrusion. This increase in production was specific to the facial gesture observed: infants performed more lip-smacking themselves during observation of lip-smacking, and more tongue protrusions during observation of tongue protrusion. We also found that the genetic polymorphism of the oxytocin receptor influenced the effects of oxytocin on social behavior. Our findings indicate that oxytocin does indeed modulate the neural processing of facial gestures in infant macaques, increasing both infants' attention to socially relevant stimuli and their own social behavior.

Disclosures: H. Rayson: None. **F. Festante:** None. **G. Toschi:** None. **S.S.K. Kaburu:** None. **A. Paukner:** None. **C.S. Barr:** None. **N.A. Fox:** None. **P.F. Ferrari:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.11/PP16

Topic: G.02. Motivation

Support: R01-MH109450
R01-MH058616

Title: Transcriptomic regulations underlying pair bond maintenance in the socially monogamous prairie voles

Authors: *F. DUCLOT[1,2], L. SAILER[1], Y. LIU[2,3], Z. WANG[2,3], M. KABBAJ[1,2]
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Abstract: Social affiliation is a core characteristic of human social behaviors and related impairments are a common feature in a multitude of neuropsychiatric disorders including schizophrenia and autism spectrum disorders. As a result, understanding the neurobiology of social attachment is of critical importance. In this context, the socially monogamous prairie vole (Microtus ochrogaster) provides an excellent opportunity to study the molecular mechanisms underlying the formation and maintenance of a pair bond. Indeed, in prairie voles, prolonged cohabitation with an opposite-sex conspecific leads to the development of an enduring social bond reflected at the behavioral level by selective aggression towards an unfamiliar conspecific.

At the molecular level, relatively little is known regarding the mechanisms associated with the maintenance of the bond. Indeed, despite the variety of neurotransmitter systems involved in the initial formation of the bond, and despite the enduring nature of the bond, surprisingly few genes have been involved in the maintenance phase of the bond. In this study, we thus aimed at identifying the pattern of gene expression related to pair-bond maintenance by analyzing the global transcriptional profiles in the nucleus accumbens (NAc) by RNA-sequencing. To this end, male and female adult prairie voles were cohabitated for 3 weeks with an opposite-sex partner—or a same-sex conspecific as a control—and tested for selective aggression to verify the establishment of the pair bond. Notably, in order to discriminate regulations specific to the maintenance phase of the bond, a third group of animals were cohabitated with an opposite-sex partner for 24 hours only. Using this experimental design, we will thus be able to investigate the transcriptomic regulations associated with either early (24 hours) or later phase (3 weeks)—or both—of the pair bond maintenance in the prairie vole NAc. Furthermore, the parallel analysis in both male and female voles will highlight the similarities and differences in each transcriptomic profiles between sexes, allowing for the identification of regulations common or specific to each sex. Overall, these data will provide a novel insight into the global profiles of gene regulations underlying the maintenance of pair-bond in the prairie vole NAc, and thus open the way for the identification of novel candidates mediating enduring social attachment.

Disclosures: F. Duclot: None. **L. Sailer:** None. **Y. Liu:** None. **Z. Wang:** None. **M. Kabbaj:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.12/PP17

Topic: G.02. Motivation

Support: Brain Research Foundation
Klingenstein Foundation
National Science Foundation
The Raymond-Sackler Fund

Title: Correlated neural activity across the brains of socially interacting bats

Authors: *W. ZHANG, M. YARTSEV
Univ. of California Berkeley, Berkeley, CA

Abstract: Social interaction is fundamental to our everyday life and that of diverse animals. When two animals interact, they behave in different ways, and each social interaction is inherently unique. Thus, to get a complete picture of the neural activity underlying real-life

social interaction, we need to study the brains of both animals at the same time. Here, we developed an approach to do so in a highly social mammal, the Egyptian fruit bat, using wireless electrophysiology, which allows unrestrained natural social behaviors, and detailed behavioral analysis. We recorded simultaneously from the frontal cortex of pairs of bats, as they naturally interacted with each other and engaged in a wide range of social behaviors. We found neural correlates of the behavioral coordination across bats, at the levels of LFP, single units, and multiunits. Power in different frequency bands of the LFP showed distinct behavior-dependent dynamics, which were remarkably correlated across brains. Activity of single units and multiunits was also modulated by behavior, and exhibited both correlation and anticorrelation across brains. In another set of three experiments, we showed the necessity of social interactions for neural coordination across brains. We simultaneously recorded from two bats in separate, identical chambers, under three conditions: (1) the two bats each being isolated in its own chamber, (2) the two bats each being isolated in its own chamber while listening to identical auditory stimuli, and (3) the two bats each socially interacting with a different bat in their respective chambers. Despite similar sensory environments and behavioral states, LFP and spiking activity showed no correlation across brains in the absence of direct social engagement. In conclusion, our results demonstrate the neural coordination across brains that accompanies the behavioral coordination of social interactions.

Disclosures: W. Zhang: None. **M. Yartsev:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.13/PP18

Topic: G.02. Motivation

Support: NIDA T32 Training Grant

Title: The social brain and μ: Genetic knockout of the mu opioid receptor differentially alters social behavior in male and female mice

Authors: *C. TODDES[1], L. ZUGSCHWERT[3], E. LEFEVRE[1], P. ROTHWELL[2]
[2]Neurosci., [1]Univ. of Minneosta, Minneapolis, MN; [3]Univ. of St. Thomas, Minneapolis, MN

Abstract: The mu opioid receptor is best known for its role in regulating pain, analgesia, and the reinforcing effects of exogenous opiates and other drugs of abuse. Binding of endogenous opioid peptides to the mu opioid receptor mediates various natural rewards, including the rewarding aspects of social interaction. Due to the high density of opioid receptors and peptides throughout the limbic system, the endogenous opioid system is thought to play a key role in social reinforcement and thus modulates social behavior. While social behavior has been well studied

in a variety of animal models, the exact neural mechanisms mediating adaptive and maladaptive social interactions have yet to be fully elucidated. The goal of this study was to determine how heterozygous and homozygous knockout of the mu opioid receptor alters social behavior in male and female mice, using a variety of behavioral assays. Our behavioral battery includes: social conditioned place preference, dyadic social interaction, and the three-chamber social test. Additionally, we have been working with a novel behavioral test examining wildtype social preference between another wildtype mouse or an atypical mouse. These assays focus on different aspects of social behavior including social reward, motivation, affiliation and memory. Our data demonstrate that a genetic knockout of the mu opioid receptor has differential effects on male and female social behavior. We find that while male heterozygous and homozygous knockout animals display social deficits across all social tests, female knockout animals display little to no change and, in one assay, a surprising increase in sociability compared to wild-type littermates. Our results indicate a partial reduction of mu opioid receptor signaling (through heterozygous genetic knockout) is sufficient to alter social behavior in mice and may point to a sexually dimorphic role of the mu opioid receptor in regulating social behavior in males and females.

Disclosures: C. Toddes: None. **L. Zugschwert:** None. **E. Lefevre:** None. **P. Rothwell:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.14/PP19

Topic: G.02. Motivation

Support: NSERC (DRE, SMP)
AIHS (DRE)

Title: Breakdown of context-appropriate vocalizations in rats after prefrontal lesions

Authors: *C. J. BURKE[1], S. M. PELLIS[2], T. M. KISKO[4], D. R. EUSTON[3]
[1]Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Dept Neurosci, [3]Univ. Lethbridge, Lethbridge, AB, Canada; [4]Behavioural Psychology, Philipps Univ. Marburg, Marburg, Germany

Abstract: I**ntroduction:** In rodents the mPFC plays a significant role in social interactions. For example, firing of mPFC cells is selectively modulated when approaching a peer or competing for food. Functional studies also implicate mPFC in social behaviors. Inactivation of ventral mPFC causes a dramatic reduction in play among juvenile rats. Further, inhibition of the pathway from the mPFC to the periaqueductal gray mimics the effects of social defeat, suggesting that the mPFC may have control over brainstem circuits which mediate social behavior. Ultrasonic vocalizations (USV) are tightly coordinated with social interactions. Indeed,

we have found that specific calls in the 50-kHz range, linked to both play and aggression, appear critical for successful interactions. Therefore, the mPFC's role in social interactions could be related to the contextually appropriate usage of USVs. **Hypothesis:** mPFC lesion animals will change the type and usage of ultrasonic calls while anticipating the arrival of a play partner **Methods:** Sixteen juvenile Long Evans males were socially isolated and trained to anticipate a play partner over 7 days. Half of the animals received sham surgery and the other half received NMDA lesions to medial prefrontal (AP-3.5, -2.5; ML +/- 0.75; DV -3.3, -3.2 relative to dura). The animals were given 5 days of recovery and tested in the original play anticipation chamber. Behaviour and vocalizations were recorded and categorized to create detailed vocal-behaviour co-occurrence matrices. **Results:** On the last day of play anticipation, vocal and behavioural analysis revealed no significant differences between future sham and lesion groups in behaviour and call profiles. Further, after surgery there were again no major differences in the type or amount of calls between groups, or their behavioural profiles. However, the lesion animals showed differences in their usage of some calls. Specifically, calls with a flat component had different behavioral correlates in the lesion group. The usage of trill calls, on the other hand, remained the unchanged. **Conclusions:** Our results suggest that the mPFC may influence the contextual usage of some types of 50 kHz vocalizations when anticipating (and presumably calling to) a play partner. The role of mPFC in social interactions may thus include the modulation of vocal communication signals.

Disclosures: C.J. Burke: None. **S.M. Pellis:** None. **T.M. Kisko:** None. **D.R. Euston:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.15/PP20

Topic: G.02. Motivation

Support: NIMH R01MH102456

Title: Activation of the ventral tegmental area supports the expression of social play behavior in juvenile rats

Authors: *C. J. REPPUCCI, R. BREDEWOLD, S. S. POSANI, C. L. WASHINGTON, A. H. VEENEMA
Neurosci. Program; Dept. of Psychology, Michigan State Univ., East Lansing, MI

Abstract: The ventral tegmental area (VTA) is an essential component of the mesocorticolimbic dopamine reward system and an important node of the Social Decision-Making Network (O'Connell & Hofmann, 2011). As such, the VTA is interconnected with brain regions implicated in the expression of social play, a highly rewarding behavior predominately displayed

by juveniles and expressed by nearly all mammalian species. Using juvenile male and female rats, we investigated the recruitment of the VTA following social play exposure (Experiment 1) and how temporary inactivation of the VTA affected the expression of social play (Experiment 2). In Experiment 1, single-housed juveniles were exposed, in their home cage, to an age- and sex-matched unfamiliar juvenile for 10 min ("Play" condition) or received similar handling but no partner ("No Play" condition). Fos and tyrosine hydroxylase (TH) immunohistochemistry was used to determine activation of the VTA and its dopaminergic neurons in response to social play. Subjects in the play condition had greater Fos induction in the rostral and mid VTA than subjects in the no play condition; there was no effect of play exposure on Fos induction in the caudal VTA. Likewise, subjects in the play condition had greater Fos induction within TH-positive VTA neurons than subjects in the no play condition, although the occurrence of double-labeled neurons was very low. In Experiment 2, subjects received, in counterbalanced order, bilateral infusions (0.3 uL/side) of vehicle (aCSF) or the GABA-A receptor agonist muscimol (10 ng/side) into the VTA 20 min prior to exposure to the 10 min social play test (as described for the "Play" condition above). Temporary inactivation of the VTA with muscimol selectively decreased the expression of social play behavior while leaving social investigation intact. Together, these data suggest that activation of the VTA supports the expression of social play behavior in juvenile male and female rats. To better understand the role of the VTA and its dopaminergic neurons in the regulation of social play, we will measure dopamine release in the VTA during the expression of social play behavior using *in vivo* microdialysis.

Disclosures: C.J. Reppucci: None. **R. Bredewold:** None. **S.S. Posani:** None. **C.L. Washington:** None. **A.H. Veenema:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.16/PP21

Topic: G.02. Motivation

Support: NIH R01MH102456

Title: Sex differences in social reward regulation in juvenile rats: Focus on glutamate signaling in the lateral septum

Authors: *R. BREDEWOLD, C. L. WASHINGTON, A. H. VEENEMA
Dept. of Psychology, Michigan State Univ., East Lansing, MI

Abstract: Social play is a highly rewarding behavior, is essential for the development of social skills, and is impaired in children diagnosed with autism, a disorder with a strong sex bias in prevalence. We recently showed that the arginine vasopressin (AVP) system in the lateral septum

(LS) regulates social play behavior in opposite directions in male and female juvenile rats. We further showed that glutamate is involved in the sex-specific regulation of social play by the LS-AVP system. Intriguingly, males show higher LS-glutamate release than females at baseline and during social play while pharmacological blockade of the AVP V1a receptor (V1aR) in the LS eliminates this sex difference by increasing LS-glutamate release in females only. Here, we aimed to determine the origin of the sex difference in glutamate release as well as potential sex differences in the cell types that express the V1aR in the LS. Retrograde tract tracing (using cholera toxin subunit B, CtB) combined with c-Fos (cell activation marker) and *vglut2* (marker for glutamatergic neurons) was used to investigate potential sex differences in social play-induced activation of glutamatergic projections to the LS. We found that females have more glutamatergic projections from hypothalamic subregions to the LS and a higher percentage of c-Fos-positive glutamatergic projections from specific prefrontal cortex subregions to the LS compared to males. CtB-positive neurons were also found in the ventral hippocampus and periaqueductal gray and we are currently examining whether these neurons are potential sources of sex-specific glutamate release in the LS. Additionally, we will measure the amount of excitatory amino acid transporters 2 and 3 in the LS to determine a possible sex difference in glutamate reuptake. Finally, we will determine the extent to which the V1aR is expressed by astrocytes (using *sox9* as astrocytic marker) and by neurons (using *NeuN* as neuronal marker) and whether there is a sex difference in this expression. This research will help elucidate the neural mechanisms mediating the sex-specific regulation of social play, which is an important step towards better understanding the neural basis of sex-biased social disorders such as autism.

Disclosures: R. Bredewold: None. **C.L. Washington:** None. **A.H. Veenema:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.17/PP22

Topic: G.02. Motivation

Title: Sexual experience-induced shifts in paced mating are resistant to change during a 28-day period of abstinence

Authors: *M. A. TOPF, S. H. MEERTS
Carleton Col., Northfield, MN

Abstract: Paced mating enables female rats to control the timing and receipt of sexual stimulations from a male rat. Sexually experienced female rats show shorter contact-return latencies to intromission, decreased percentage of exit after intromission, higher percent time with male, more intromissions, and less total test duration. The stability of the experience-induced shift in paced mating behavior is unknown. We tested whether paced mating behavior of

sexually experienced female rats resembled that of naïve or experienced rats after either a short or long abstinence period. Female Long-Evans rats were mated twice a week for two weeks. One group underwent a 28-day abstinence period and the other experienced a 7-day abstinence period. Paced mating behavior was compared on a fifth paced mating test conducted on the same day for all rats. Sexual experience induced a shift in paced mating behavior between tests 1 and 4, consistent with the previous literature showing the experience-induced shift. No differences in paced mating behavior were observed on the fifth test between the 7-day and 28-day abstinent groups. However, both groups showed a decrease in percent time spent with the male rat from test 4 to test 5, suggesting that some measures of paced mating behavior are sensitive to both a 7- and 28-day abstinence period. Ongoing work is exploring whether activation of mating-related brain areas, such as the medial preoptic area and ventromedial nucleus of the hypothalamus, differs as a function of sexual experience. Expression of ΔFosB, a molecular marker associated with reward, is also a target of investigation in our efforts to identify the neural components underlying experience-induced sexual behavior.

Disclosures: M.A. Topf: None. **S.H. Meerts:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.18/QQ1

Topic: G.02. Motivation

Title: Sexually experienced,but not naive, female rats show a conditioned object preference (COP) after a single training trial

Authors: *T. PIERGIES, J. SCHWARTZ, M. HICKS, S. MEERTS
Carleton Col., Northfield, MN

Abstract: During a mating encounter, female rats control the receipt of sexual stimulations through paced mating behavior, approaching and retreating from the male rat. Paced mating behavior of sexually experienced female rats differs sexually naive female rats, which spend less time with the male rat, exhibit longer contact-return latency to intromission, exit more often following intromissions, and display less proceptive behaviors in the male rat's compartment during the first mating experience. Whether the first mating experience is rewarding for sexually naive rats is unknown. Mating-induced reward has only been assessed in sexually experienced female rats; conditioned preference experiments typically involve 3-5 mating sessions so experimental rats are sexually experienced by the time of the post-conditioning test. Given the differences in paced mating behavior between sexually naive and sexually experienced rats, we hypothesized that the rewarding effects of mating differ as well. We elected to use a single trial conditioned object preference (COP) paradigm to test whether mating-induced reward can be

observed in rats mating for the first time and rats mating for the fifth time. A baseline test was used to determine preference for one of two objects. During training, experienced and naive rats were tested with one object in the chamber for 10 minutes of mating (uncontrolled number of stimulations) or to 15 intromissions (uncontrolled mating duration). On another day rats were exposed to the other object with no associated mating. A control group received exposure to both objects but never mated. After training the rats were again tested for object preference. As anticipated, sexually naive rats versus sexually experienced rats spent less time with the male rat, exhibited a longer contact-return latency following intromission, received fewer intromissions, and displayed fewer proceptive behaviors with the male during paced mating. Sexually experienced, but not sexually naive, rats developed a COP for mating, in agreement with the idea that mating is differentially rewarding based on sexual history. Future research is needed to determine whether peripheral and/or central sensitization underlies the COP for mating in sexually experienced but not naive female rats.

Disclosures: T. Piergies: None. **J. Schwartz:** None. **M. Hicks:** None. **S. Meerts:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.19/QQ2

Topic: G.02. Motivation

Support: NIAAA R01AA013983 (KAM)

Title: Deconstructing the motivational components of natural reinforcers in mice: Critical role for CRF in anticipatory arousal

Authors: *H. E. COVINGTON, III, K. HA, K. CHIEN-YOUNG, M. Z. LEONARD, K. A. MICZEK
Psychology, Tufts Univ., Medford, MA

Abstract: Corticotropin-releasing factor (CRF) is an initial response element of the hypothalamic-pituitary-adrenal (HPA) “stress axis.” Activation of this axis is shared across all mammalian species for the initiation of motivated behaviors, particularly when fulfilling physiological and psychological *needs*. To study motivation in mice, schedules of reinforcement can be useful, whereupon the presentation of natural rewards is contingent on particular patterns of operant responding. A typical “response curve” for patterns of responding during fixed interval (FI) schedules is in the form of a “scallop”, since the majority of behavioral responses that lead to a reinforcement occur towards the end of the interval. Naturally, mice will work during an FI schedule in a predictable manner for the opportunity to fight or to gain access to a sexual partner, indicating that these social stimuli can serve as potent positive reinforcers. Recent

experiments have suggested that CRF receptors play a significant role in this measure of motivation to seek social rewards. The experiments presented here reveal a precise role for CRFR1 receptors during the motivation to engage in divergent social and non-social rewards (including saccharine reinforcements), which can be dissociated from indices of consummatory behavior. In sum, FI schedules are sensitive tools for targeting the neurobiological mechanisms that are involved in the anticipation, but not consumption, of natural rewards. Furthermore, repeated alcohol exposures in the context of anticipating *social* reward outcomes can dramatically affect levels of arousal - as indicated by the FI scallop.

Disclosures: H.E. Covington: None. **K. Ha:** None. **K. Chien-Young:** None. **M.Z. Leonard:** None. **K.A. Miczek:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.20/QQ3

Topic: G.02. Motivation

Support: NIAAA R01AA013983 (KAM)

Title: A new murine model for aggressive motivation: Extrahypothalamic CRF and persistent escalation by alcohol

Authors: *K. A. MICZEK, K. CHIEN-YOUNG, Z. KRAMER, T. ARCHIBALD, E. P. FLEISHER, Y. BARAKATLROUDAINI, E. L. NEWMAN, H. E. COVINGTON, III
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Abstract: Behavioral and neural plasticity resulting from chronic alcohol drinking, in some individuals, can culminate in pathological aggression. The present series of experiments was to determine how alcohol, when orally administered, escalates (1) the motivation to fight, or (2) the execution of fighting performance. We sought to examine if seven daily administrations of alcohol would induce tolerance, and eventually sensitization, of responding for aggressive reinforcements - and whether or not changes in the motivation to initiate aggressive acts occur with, or without, shifts in the topography of fighting behavior. Specifically, responding under the control of a fixed interval (FI) schedule of reinforcement (i.e., “scalloped pattern of responding”) indicated the development of tolerance to the initial disruptive effects of alcohol. Eventually, persistent sensitization to aggressive arousal emerged ca. 4-7 days after successive daily administrations of alcohol. This lasting increase in aggressive motivation occurred without any observed changes in fighting performance, and depended on the activation of CRFR1, NMDA or AMPA receptors. Pretreatment with a CRFR1 antagonist (CP 376395) eliminated the enduring escalation of alcohol-induced aggressive motivation. NBQX, ketamine and dizocilpine prevented

the disruptive effects of acute alcohol administration on the motivation to seek aggressive rewards. Under these conditions, oral administrations of alcohol engender neural and behavioral plasticity that specifically enhance aggression-seeking behavior.

Disclosures: K.A. Miczek: None. **K. Chien-Young:** None. **Z. Kramer:** None. **T. Archibald:** None. **E.P. Fleisher:** None. **Y. Barakatlroudaini:** None. **E.L. Newman:** None. **H.E. Covington:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.21/QQ4

Topic: G.02. Motivation

Support: NSF GRFP
MH109545

Title: Insular cortex projections to the nucleus accumbens core modulate social affective behaviors

Authors: *M. M. ROGERS, A. DJERDJAJ, K. B. GRIBBONS, J. P. CHRISTIANSON
Dept. of Psychology, Boston Col., Chestnut Hill, MA

Abstract: Social animals detect the affect of others to organize appropriate social behaviors. Age-specific responses to social affect are evident when an adult male rat is presented with a pair of unfamiliar male conspecifics, one of which is stressed via 2 footshocks and the other naïve to treatment. Test rats prefer to interact with a stressed juvenile (PN30) conspecific, but will avoid a stressed adult (PN50) conspecific. This pattern depends upon the insular cortex (IC) which is anatomically connected to the nucleus accumbens core (NAc). Prior network analysis of fos immunoreactivity indicated greater involvement for the NAc during social interactions with stressed juvenile conspecifics. Here, bilateral pharmacological inhibition of the NAc (tetrodotoxin 1µM; 0.5ul/side) abolished the preference for stressed juvenile conspecifics, but not naive adults. To explore if NAc projecting IC neurons contribute to social exploration we chemogenetically activated IC terminals in the NAc. After insular transduction of AAV5-hSyn-hM3Dq-mCherry, bilateral microinjection of clozapine-N-oxide (1µM; 0.5ul/side) to the NAc increased social exploration with juvenile, but not adult conspecifics. Ongoing analysis using functional retrograde tracing and chemogenetic inhibition will establish the necessity of this pathway to social approach. The current findings suggest that behavioral responses to stressed juveniles involve the NAc and activation of NAc-projecting IC neurons is sufficient to elicit prosocial behaviors.

Disclosures: M.M. Rogers: None. **A. Djerdjaj:** None. **K.B. Gribbons:** None. **J.P. Christianson:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.22/QQ5

Topic: G.02. Motivation

Support: MH109545
NSF GRFP

Title: Familiarity determines prosocial affective behaviors in female but not male rats

Authors: A. DJERDJAJ, M. M. ROGERS-CARTER, A. CULP, J. ELBAZ, *J. P. CHRISTIANSON
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Abstract: In translational research seeking to identify the neural mechanisms underlying empathic cognition, the sex, age, stress history and familiarity of the interacting subjects modulate the way in which individuals approach each other. In a social affective preference test in which an experimental rat is given the choice to interact with either a naive or stressed (2, 5 second footshocks) conspecific, we reported that adult male and female rats will avoid interactions with unfamiliar stressed adults. To determine if familiarity would influence social affective preference, male or female test rats underwent 2 social affective preference tests with either familiar (cagemates) or unfamiliar adult conspecifics in isosexual triads (experimental rat, naive and stressed conspecifics). As previously (doi: 10.1038/s41593-018-0071-y), both adult and female rats avoided stressed unfamiliar conspecifics. However, in the familiar condition, females approached familiar stressed conspecifics but males avoided the stressed conspecifics. In the presence of stressed conspecifics, both male and female rats exhibited more self-grooming and immobility behavior which may indicate emotional contagion. The findings suggest a sex-specific role of familiarity in social decision making and ongoing work seeks to uncover whether social responses to familiar conspecifics engages the same or different neural circuitry in the insular cortex which mediate responses to unfamiliar conspecifics.

Disclosures: A. Djerdjaj: None. **M.M. Rogers-Carter:** None. **A. Culp:** None. **J. Elbaz:** None. **J.P. Christianson:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.23/QQ6

Topic: G.02. Motivation

Title: Dopamine signaling mediates bias among competing motivations

Authors: *P. CORREA, B. DICKSON
Janelia Res. Campus, Ashburn, VA

Abstract: Mating and eating are both strong innate drives, but for most animals these two behaviors are mutually exclusive. The brain must therefore flexibly prioritize between these two goal-oriented actions to optimize survival and reproduction. However, the neural mechanisms that choose between competing motivational systems remain poorly understood. To address this crucial knowledge gap, I will dissect how hunger adjusts the well-defined Drosophila courtship circuit to conduct context-dependent mating choices. A critical node in the neural circuits controlling courtship behavior are the P1 neurons, which encode a persistent state of courtship arousal. Accordingly, P1 gates sensory-motor transformations to sustain stereotyped behavioral displays throughout the courtship ritual. Since P1 activity likely represents the male sexual drive, we propose that hunger might fine-tune P1 excitability to adjust mating performance according to the animal's nutritional satiety. We monitored P1 calcium transients and found that P1 has decreased calcium responses to chemosensory stimuli in hungry animals, indicating that mating drive is likely reduced during starvation. Consequently, caloric-restricted males take longer to initiate courtship and ingest sucrose instead of pursuing a mate in *food vs. mate* preference test. Thus, the mating ardor is likely decreased to prioritize for nutrient acquisition during starvation. Next we establish causal relationships among changes in courtship network physiology and hunger levels. Since monoamines and peptides are well-known to modulate internal states, we hypothesized that these signaling systems potentially broadcast a hunger signal onto P1. Therefore, we behaviorally tested transgenic males in which these candidate cells were genetically silenced or activated. Our approach identified a pair of dopaminergic (DA) neurons required to decrease courtship during hunger state. Moreover, we find that DA down-modulates P1 through D2-like receptor signaling. Altogether, our findings show that DA modulation diminishes the mating bias when food is scarce, as a necessary survival tactic to indirectly promote nutrient supplementation. Further molecular and physiological elucidation of P1 and dopaminergic neurons interactions, will resolve a potentially conserved mechanism for motivational drive adjustments.

Disclosures: P. Correa: None. **B. Dickson:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.24/QQ7

Topic: G.02. Motivation

Support: NIH Grant 1 U01 AG052564-01

Title: The human connectome project: Investigating gender and age-related differences in reward processing via delayed discounting

Authors: *T. K. LY, T. P. KUHN, A. C. BURGGREN, S. Y. BOOKHEIMER
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Abstract: Background: Motivation is critical in treatment and patient outcomes. Motivation can be studied through reward processing by using neuropsychological assessments, such as the University of Pennsylvania Delayed Discounting task (UPDD), which calculates the rate of reward discounting. This is measured via the discrepancy between selecting a smaller, immediate monetary reward over a greater, delayed monetary reward. Prior studies have shown that older adults performed better than younger adults on such tasks. However, there is uncertainty regarding how aging affects reward processing and whether differences exist between genders. Objective: This study examined trends and differences in reward processing across different age groups and genders. Participants and Methods: As a part of the Mapping the Human Connectome in Typical Aging Project, we analyzed 138 adults (Mean age = 51.3, SD = 11.8; 66.67% F). The sample was divided into two groups: younger (Mean age = 47.56, SD = 7.99; 68.1% F) and older adults (Mean age = 71.8, SD = 5.68; 59.1% F). Reward processing was assessed via the UPDD, where a higher score signals reduced rate of reward discounting. A linear regression analysis was performed on UPDD performance, using age and gender as predictors and covarying for education (Mean = 17.59, SD = 2.1 yrs) and ethnicity. Results: We found a main effect of gender with males performing significantly better on the UPDD than females [$F(1, 138) = 7.73$, $p = 0.006$, partial $\eta^2 = 0.055$]. There was a significant interaction between age and sex [$F(1, 138) = 5.247$, $p = .024$, partial $\eta^2 = 0.038$]. Post hoc comparisons demonstrated that this interaction was driven by older males performing better than older females (Mean $\Delta = 0.224$), younger females (Mean $\Delta = 0.194$), and younger males (Mean $\Delta = 0.186$). Conclusions: Our significant interaction effect results indicate that the main effect of gender on UPDD, where men outperform women, is driven by significantly better performance of older men compared to all aged women and younger men. This suggests that older age, in conjunction with male gender, accounts for enhanced performance. These results lead us to hypothesize that differences in aging trajectories of the reward system could result from neuroendocrine (i.e. menopause), neuroanatomical, (i.e. differences in prefrontal activation), or behavioral differences, (i.e.

depression). Our results are in line with prior studies that found older adults performing better than younger adults. We intend to follow-up on these results by investigating potential differences in functional brain connectivity that might serve as a basis for these reward discounting and motivational findings.

Disclosures: T.K. Ly: None. **T.P. Kuhn:** None. **A.C. Burggren:** None. **S.Y. Bookheimer:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.25/QQ8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Social hierarchy and stress susceptibility

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Abstract: The establishment of social hierarchy is an evolutionarily conserved phenomenon that, in part, determines access to resources such as food, water, and potential mates. Across species, rank within social hierarchy has large effects on health and behavior. In humans, socioeconomic status (SES) is one of the strongest predictors of mortality and morbidity, with low SES associated with a host of diseases, including cardiovascular disease, cancer, and multiple psychiatric conditions. In particular, major depressive disorder (MDD) has been associated with low SES even after accounting for lifestyle factors like smoking, alcohol use, physical activity, and diet. Despite this, little is known about the underlying neural mechanisms between low social hierarchy and MDD. Using isogenic mice, in combination with chronic social defeat stress (CSDS), an animal model of depression, we seek to investigate this relationship and the neural circuitry underlying both dominance and stress susceptibility.

Disclosures: K.B. LeClair: None. **S. Russo:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.26/QQ9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01-MH111604
Whitehall Foundation (APP131146)

Title: Circuit-specific hippocampus Δfosb expression mediates resilience in chronic stress

Authors: *C. MANNING[1], E. S. WILLIAMS[2], A. L. EAGLE[3], P. A. KURDZIEL[4], H. M. LYNCH[1], R. NEVE[7], M. S. MAZEI-ROBISON[5], A. ROBISON[6]
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Abstract: Stress contributes to mood disorders in some individuals while others are resilient. As hippocampus (HPC), and especially its projections to the nucleus accumbens (NAc), plays a crucial role in stress responses, we investigated whether HPC expression of the transcription factor ΔFosB drives resilience to stress. Using the chronic social defeat stress (CSDS) model of depression, we demonstrate that general inhibition of ventral HPC ΔFosB promotes a depression-like phenotype. Using a novel dual-virus CRISPR system, we show that silencing the *FosB* gene specifically in HPC neurons projecting to NAc prevents resilience to CSDS in male mice. Critically, deletion of the *FosB* gene in hippocampal neurons projecting to amygdala did not affect resilience, and the effects in the HPC-NAc circuit could be prevented by overexpressing ΔFosB into the same neurons in which *FosB* was deleted. These data are some of the first to demonstrate the circuit-specific role of a gene in a model of neuropsychiatric disease, and we are now extending this work to study both males and females in an additional stress/depression models, including subchronic variable stress.

Disclosures: C. Manning: None. **E.S. Williams:** None. **A.L. Eagle:** None. **P.A. Kurdziel:** None. **H.M. Lynch:** None. **R. Neve:** None. **M.S. Mazei-Robison:** None. **A. Robison:** None.

Poster

229. Motivation: Social Communication and Behavior

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 229.27/QQ10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Training Grant T32-ES725525
NARSAD Young Investigator Award from the Brain and Behavior Foundation
Whitehall Foundation Research Grant
NIH Grant MH111604
NIH Grant 5DP1DA042078

Title: Cocaine reshapes the physiology of ventral CA1 afferents to nucleus accumbens that underlie drug seeking and reward

Authors: *A. L. EAGLE[1,2], E. S. WILLIAMS[3], M. A. DOYLE[2], C. E. MANNING[2], R. M. BASTLE[4], I. S. MAZE[4], A. J. ROBISON[1,2]
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Abstract: Ventral hippocampus afferent neurons play a critical role in drug behavior, and activation of ventral CA1 glutamatergic projections to nucleus accumbens (NAc) drive seeking for cocaine. However, the mechanism by which cocaine shapes the function of this vCA1-NAc circuit is poorly understood. We propose an innovative role for ΔFosB, a transcription factor, in the activity of vCA1-NAc neurons and cocaine behavior. ΔFosB is induced in HPC by cocaine and we show that regulates HPC function. Preliminary evidence from our lab has also demonstrated that ΔFosB expression reduces hippocampal excitability. Here, we used viral-mediated targeted fluorescent labeling and whole cell patch-clamp electrophysiology to determine cocaine effects on vCA1-NAc physiology. We found that cocaine, similar to ΔFosB expression, reduces vCA1-NAc excitability, suggesting that cocaine induces ΔFosB leading to decreased neuronal excitability. Studies are ongoing to identify the ion channel mechanism underlying this change. We next sought to determine whether ΔFosB expression in vCA1-NAc neurons is necessary for cocaine reward and seeking. We used circuit-specific, viral-mediated CRISPR silencing of the *FosB* gene (FosB KO) in vCA1-NAc and assessed both place preference for cocaine and cocaine seeking after forced abstinence. FosB KO in vCA1-NAc neurons decreased cocaine reward and seeking, which could be rescued by ΔFosB replacement. Circuit-specific TRAP-RNASeq in non-drug-exposed vCA1-NAc neurons indicates that these effects are driven by specific patterns of ΔFosB-mediated gene expression, however future studies will identify the cocaine-specific ΔFosB transcriptional targets underlying vCA1-NAc physiology and behavior. Collectively, these findings demonstrate that cocaine induces ΔFosB expression in vCA1-NAc, leading to functional reshaping of this circuit and driving cocaine-dependent behaviors. Furthermore, they suggest that ΔFosB and its gene targets in hippocampus afferents may serve as promising therapeutic inroads for drug addiction.

Disclosures: A.L. Eagle: None. **E.S. Williams:** None. **M.A. Doyle:** None. **C.E. Manning:** None. **R.M. Bastle:** None. **I.S. Maze:** None. **A.J. Robison:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.01/QQ11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Neurobiology & Behavior Research Training Grant T32 HD007430-19
Coulter Biomedical Accelerator program
NIH DP5 OD017908
New York Stem Cell Science NYSTEM C-021957
For the Love of Travis, Inc

Title: (R,S)-ketamine and (2R,6R)-hydroxynorketamine are prophylactic against stress-induced depressive-like behavior in females

Authors: *B. CHEN[1], C. T. LAGAMMA[2], R. A. BRACHMAN[3], X. XU[3], S.-X. DENG[3], D. W. LANDRY[3], C. A. DENNY[4]
[1]Neurobio. and Behavior, Columbia Univ. Med. Ctr., New York, NY; [2]Integrative Neurosci., Res. Fndn. For Mental Hyg., New York City, NY; [3]Columbia Univ., New York City, NY; [4]Columbia Univ., New York, NY

Abstract: Exposure to stress is a major risk factor for mood disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). However, stress does not universally cause disease. Stress resilience, the ability to adapt to stress without developing psychopathology, varies in individuals. For example, although women experience trauma at significantly lower rates than men, they are twice as likely to develop MDD. We previously reported that a single injection of (*R,S*)-ketamine prior to stress protects against the onset of depressive-like behavior and buffers against a deleterious fear response in male mice. However, the prophylactic efficacy of ketamine and ketamine metabolites in female mice remain largely unknown. Therefore, the goal of this study was to determine whether prophylactics can be developed for use in females and whether metabolites of (*R,S*)-ketamine can have the same prophylactic efficacy as their precursor. Female 129S6/SvEv mice were administered (*R,S*)-ketamine, (2*R*,6*R*)-HNK, or (2*S*,6*S*)-HNK at various doses 1 week before one of a number of stressors, including contextual fear conditioning (CFC), learned helplessness (LH), and chronic immobilization stress (CIS). Prophylactic efficacy was validated using the forced swim test (FST). We found that (*R,S*)-ketamine and (2*R*,6*R*)-HNK, but not (2*S*,6*S*)-HNK, significantly reduced immobility in the FST compared to saline controls. Interestingly, in females, ketamine was prophylactic at a lower dose than previously shown in males. Moreover, (2*R*,6*R*)-HNK was prophylactic at a significantly smaller dose and at a faster rate than its precursor (*R,S*)-ketamine. In a separate set of experiments, we investigated the neurobiological mechanisms potentially mediating these sex-dependent results and found that prophylactic efficacy of these compounds may be mediated by ovarian-derived hormones. Overall, these data indicate that (*R,S*)-ketamine and (2*R*,6*R*)-HNK are effective prophylactics against a variety of stressors in females and that their sex-specific effects may be modulated by gonadal hormones. Our findings offer insights into the prevention of stress-related impairments in a susceptible population and may further elucidate underlying sex-specific neuropathology contributing to the onset of MDD.

Disclosures: B. Chen: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Columbia University. **C.T. LaGamma:** None. **R.A. Brachman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

funds); Columbia University. **X. Xu:** None. **S. Deng:** None. **D.W. Landry:** None. **C.A. Denny:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Columbia University.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.02/QQ12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH DP5 OD017908
Rotary Global Grant GG1864162
NYSTEM C-029157
NARSAD Young Investigator Grant
For the Love of Travis

Title: Prophylactic ketamine protects against fear overgeneralization

Authors: *A. MASTRODONATO[1,2], R. MARTINEZ[3], I. PAVLOVA[1,2], C. LAGAMMA[2], R. A. BRACHMAN[1], A. ROBISON[4], C. A. DENNY[1,2]
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Abstract: Background: Stress exposure is the main cause of mood disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). However, some individuals can successfully adapt to stress, which is known as stress resilience. We previously reported that a single injection ketamine, an NMDA antagonist, prior to stress protects against the development of depressive-like behavior and attenuates learned fear in mice. Recently, we have showed that ketamine induces a prophylactic effect by modulating expression of the transcription factor ΔFosB in ventral CA3 (vCA3). In particular, transcriptional inhibition or overexpression of ΔFosB in vCA3 occludes and mimics, respectively, prophylactic ketamine efficacy, suggesting that ΔFosB expression in vCA3 is necessary and sufficient for ketamine prophylactic efficacy. Here, we sought to identify if prophylactic ketamine protects against fear generalization and which neural alterations correlate to fear generalization. **Methods:** ArcCreERT2 mice were injected with saline or ketamine (30 mg/kg). One week later, mice were administered a pattern separation (PS) paradigm. After an initial training in the context A, where they received a shock, mice were exposed daily to the aversive context A and to a similar, but safe context B, for 10 days. Mice were then sacrificed, and brains were processed. Whole-brain immunolabeling was utilized in order to identify the neural ensembles (e.g., memory traces/engrams) representing fear generalization. **Results:** During PS task, both groups of mice

exhibited comparable levels of freezing following one-shock in the aversive context A. However, prophylactic ketamine mice distinguished between the two contexts more rapidly than prophylactic saline mice, froze significantly less in the similar but neutral context B and had significantly higher levels of discrimination between the two contexts. The ketamine prophylactic effect persists up to 6 weeks following a single injection. **Conclusion:** Our data indicate that a single prophylactic injection of ketamine may be able to prevent fear generalization and protect against stress-induced psychiatric disorders (e.g., PTSD and depression) in a long-lasting, self-maintaining vaccine-like fashion. Prophylactic ketamine treatment in human subjects and PTSD patients might decrease fear generalization and alter similar neural circuits identified in the mouse studies.

Disclosures: A. Mastrodonato: None. **R. Martinez:** None. **I. Pavlova:** None. **C. LaGamma:** None. **R.A. Brachman:** None. **A. Robison:** None. **C.A. Denny:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.03/QQ13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA-MH002857; NCT02049385)

Title: Ketamine downregulates the expression of heat shock protein in patient with treatment-resistant depression

Authors: *B. KADRIU[1], C. FARMER[2], P. YUAN[2], C. A. ZARATE, JR[3]
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Abstract: Heat shock proteins (HSP) are ubiquitously expressed intracellular proteins that function as chaperones, and assist in the synthesis and folding of proteins in the absence of stress. However, evidence from both animal models and human data indicate that HSPs are robustly upregulated in response to physical, cellular and psychological stress. While intracellular HSP expression aids in the repair and stabilization of proteins during stress, the passive (during necrosis or apoptosis) or active release of these proteins into the extracellular matrix leads to increased pro-inflammatory cytokine production. Of the known HSPs that mediate inflammatory responses to stress, HSP70 has been implicated in psychiatric disorders including major depressive disorder. Moreover, multiple studies shown the increased HSP70 serum levels in depressed or at-risk patients. In addition, its increase correlates strongly with symptom severity in patients with chronic negative affect. Pooled data were drawn from previous

double-blind, randomized, placebo-controlled, crossover trials designed to test the antidepressant efficacy of ketamine in subjects with treatment-resistand major depressive disorder (MDD) and as well as healthy controls (HCs). All subjects were medication-free. Initial leads for changes in proteins were derived from an initial pilot proteomic study on HC, MDD responders and nonresponders. Targeted plasma concentrations of heat shock protein 70 were measured at four time points: 60 minutes pre-ketamine infusion (baseline), 230 minutes post-ketamine infusion, on Day 1, and on Day 3 post-ketamine infusion in both ketamine and placebo arm. All data were matched for age, sex and body mass index. Individuals with treatment resistant MDD displayed upregulated baseline HSP70 levels compared to matched HC. Ketamine significantly decreased HSP70 (p=.0002) in both MDD and HC. In addition, ketamine decreased HSP70 in all three time points (230min, day 1 and day 3 post-ketamine). We separately observe that ketamine also decreased depression symptoms severity, however there was no correlation with decrease in MADRS score. This preliminary findings indicate that ketamine does have an effect on HSP70, hypothetically it does so by decreasing the symptoms severity as well as ameliorating stress and inflammation. Taken together, this is the first study to show that ketamine impacts stress regulating factors such HSP 70 in MDD and HC subjects. In addition, data suggests that extracellular HSP70 plays a role in mood regulation and depressive symptoms.

Disclosures: B. Kadriu: None. **C. Farmer:** None. **P. Yuan:** None. **C.A. Zarate:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.04/QQ14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Chronic social defeat mouse model of depression: Acute ketamine rescues social avoidance and modulates inflammatory signalling as well as synaptic marker expression in the hippocampus

Authors: *J. A. PRENDERVILLE, E. SOKOLOWSKA, T. BURKE, M. BIANCHI
Transpharmation Ireland Ltd, Dublin, Ireland

Abstract: Chronic social defeat (CSD) is a stress-induced model of depression involving daily physical interaction and 24h sensory contact with an unfamiliar aggressive male. Following CSD, mice can be classified as resilient or susceptible to stress based on social avoidance behaviour. Growing evidence suggests that changes in neuronal/synaptic plasticity and immune signalling play a role in development and treatment of mood disorders. Here, we investigated social avoidance behaviour in mice subjected to CSD and the effect of a single administration of a low-dose of ketamine (10 mg/kg, s.c.). Cytokine/chemokine expression was measured in plasma. Proteins associated with synaptic structure and plasticity were investigated in the

hippocampus.C57BL/6J mice were subjected to 10 days of CSD paradigm followed by a social preference test (SP) to assess social avoidance behaviour in defeated mice when exposed to an aggressive CD-1 mouse. Baseline SP was measured and then stress susceptible (SUS) mice received either acute vehicle (0.9% NaCl, s.c.) or ketamine (10 mg/kg, s.c.) and 24h later were re-submitted to SP. Proinflammatory Panel 1 Kit (MesoScale Diagnostics, USA) was used to measure plasma levels of cytokines/chemokines. Proteins associated with neuronal plasticity including synaptic proteins (synaptophysin, PSD-95), cytoskeletal proteins (acetylated α-tubulin) and intracellular signalling proteins (GSK-3β, eEF2) were investigated using infrared western blotting (IFWB) in the hippocampus.
A SUS phenotype was identified in 46.4% of mice subjected to CSD as indicated by a significant increase in social avoidance in comparison to stress resilient and control animals. Acute ketamine reversed social avoidance in SUS mice 24h post-administration. Plasma cytokine profile was altered in SUS mice and this was reversed by acute ketamine administration. Changes in neuronal plasticity-related proteins were consistent with the depressive-like phenotype of SUS mice and were modulated by ketamine treatment.
CSD induced depressive-like behaviour in a subset of mice which is here shown for the first time to be reversed by acute ketamine at the low-dose of 10 mg/kg (s.c.). Plasma cytokine/chemokine changes induced by CSD were consistent with immune dysregulation reported in depressed patients and were corrected by ketamine. Deficits in signalling pathways associated with neuronal plasticity reported here following CSD and ketamine treatment were concurrent with the antidepressant efficacy of ketamine. Thus, our CSD protocol represents a translational model of depression sensitive to acute low-dose ketamine treatment.

Disclosures: **J.A. Prenderville:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **E. Sokolowska:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **T. Burke:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **M. Bianchi:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd..

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.05/QQ15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH GM123842
Della Martin Foundation
NARSAD
HHMI
Caltech Innovation Initiative

Title: Genetically encoded biosensors for ketamine inside neurons

Authors: *K. BERA[1], A. KAMAJAYA[1], A. L. NICHOLS[1], A. V. SHIVANGE[1], P. M. BORDEN[2], B. N. COHEN[1], J. JEON[1], J. S. MARVIN[2], L. L. LOOGER[2], H. A. LESTER[1]
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Abstract: **K**etamine-**c**lass **a**ntidepressant **d**rugs (KCADs, our term) include ketamine (Ket) and other antidepressants whose onset of action is 10- to 100-fold faster than conventional antidepressants such as the serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs). Candidate KCADs include individual Ket enantiomers, metabolites, and analogs under investigation. Whether KCADs principally act via blockade of N-methyl-d-aspartate (NMDA) receptors, or via other targets, is presently unknown. It is important to detect and quantify the drugs inside subcellular regions of living neurons.
Therefore, we develop the "**i**ntensity-based **Ket**amine-**S**e**n**sing **F**luorescent **R**eporter" [iKetSnFR] genetically encoded biosensor family for R and S-ketamine. The bacterial periplasmic binding protein (PBP) OpuBC displays a binding site at the interface between two domains, and a ligand-induced "Venus flytrap" conformational change involving relative motions of the two domains. We inserted circularly permuted GFP, flanked by several-residue linkers, within inter-domain hinge regions. Thousands of mutants are tested with computational docking models, site-saturation mutagenesis, bacterial colony growth in 96-well plates, incubation, lysis, high-throughput fluorescence screening on the lysates, and fluorescent measurements with purified proteins. We have mutated residues at the binding site, for sensitivity to S-Ket. Bacterially expressed iKetSnFR2 responds to S-Ket with EC_{50} of ~ 8 μM, and with maximal fluorescence increases ($\Delta F/F_0$) of ~ 1.7; iKetSnFR3 displays EC_{50} = ~ 13 μM and $\Delta F/F_0$ = 3.8, iKetSnFR4 displays EC_{50} = ~ 7 μM and $\Delta F/F_0$ = 2.8. Various neurotransmitters (glycine, GABA, acetylcholine, serotonin, dopamine, and L-DOPA) are not sensed by iKetSnFRs at concentrations up to 1 mM, thereby displaying specificity.
We will expand the family to sense other KCADs. We will use biosensor constructs with additional sequences that target the sensors either to the plasma membrane (PM) or to the endoplasmic reticulum (ER) [iKetSnFR-PM or -ER, respectively], and we will later extend this strategy to other organelles. We will use fluorescence microscopy to probe localization and interactions of iKetSnFRs.

Disclosures: K. Bera: None. **A. Kamajaya:** None. **A.L. Nichols:** None. **A.V. Shivange:** None. **P.M. Borden:** None. **B.N. Cohen:** None. **J. Jeon:** None. **J.S. Marvin:** None. **L.L. Looger:** None. **H.A. Lester:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.06/QQ16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NCCIHATR010091692

Title: Fatty acids alter cellular antidepressant signature evoked by ketamine in glial cell differential from patient derived neural progenitor cells

Authors: *J.-Z. YU[1], J. WANG[2], R. PERLIS[2], M. M. RASENICK[3]
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Abstract: Major depressive disorder affects nearly 7% of adults in the US in any given year, and is currently the leading cause of disability, worldwide. While effective interventions exist, at least 1/3 of individuals do not achieve symptomatic remission despite treatment. Evidence from epidemiological, laboratory, and randomized placebo-controlled trials suggests supplementation with n-3 PUFAs (alone or in conjunction with antidepressants) may provide a treatment option. The anti-depressant effects of ketamine have piqued interest over the past few years. A recent study in our lab showed that 15 minutes of ketamine treatment translocated Gsα from lipid rafts to augment cAMP signaling. This occurs with most antidepressants, but requires 3 days treatment. In this study, glial cells differentiated from iPSC-derived neural progenitor cells (from depressed subjects and healthy controls) were used to examine the effect of fatty acids on the ketamine-induced cAMP increase. Differentiated glial cells were verified by GFAP staining. Cells were treated with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and saturated fatty acid (steric acid (SA)) for three days, and were infected with baculovirus containing a fluorescent sensor for cAMP. cAMP was detected in living cells with laser fluorescent microscopy at 37^0C with 5% CO_2. The ketamine-induced cAMP response was augmented in cells treated with EPA and DHA. However, in cells treated with SA, the ketamine-induced cAMP signal was dampened. No difference was found in forskolin or isoproterenol-stimulated cAMP between the glial cells from MDD and health subjects, but these subjects were not treated with ketamine. EPA, DHA and SA alone treatment did not change the cAMP accumulation in response to a β adrenergic agonist. We then measured Gsα mobility and subsequent association between Gsα and adenylyl cyclase using Fluorescence recovery after photobleaching (FRAP). This revealed that the mobility of Gsα protein in the cell plasma membrane was increased after treatment with DHA and EPA but decreased after SA treatment. These data suggest that DHA and EPA may augment ketamine's anti-depressive effects using a similar mechanism and could potentially reduce the dose of ketamine required, minimizing its side effects during depression treatment. Saturated fatty acids may exert the opposite effect. Increased membrane mobility of Gαs induced by fatty acids may play a role in antidepressant response. Furthermore, visualization and quantitation of antidepressant actions in stem cells derived from human subjects may prove useful for the development of diagnostic and therapeutic platforms for depression.

Disclosures: J. Yu: None. **J. Wang:** None. **R. Perlis:** None. **M.M. Rasenick:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.07/QQ17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH 8022557

Title: Differential antidepressant actions of ketamine and HNK and its underlying mechanism

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Abstract: Evidence from preclinical and clinical studies shows that ketamine, a noncompetitive NMDA receptor antagonist, exerts rapid and sustained antidepressant responses. However, ketamine's psychotomimetic side effects and abuse liability limit the clinical use of the compound. Elucidating the underlying mechanism of ketamine's fast antidepressant actions is important to design a new safer generation of fast-acting antidepressants. A recent study showed that that ketamine's antidepressant action is mediated by its metabolite 2R, 6R-hydroxynorketamine (2R, 6R-HNK) and in a NMDA receptor-independent manner. However other researchers demonstrated that 2R, 6R-HNK inhibits synaptic NMDA receptor at higher concentration (50 μM) or doesn't exhibit antidepressant actions at same concentration (10 μM) in the same behavioral paradigms. These controversial reports of the antidepressant actions of 2R, 6R-HNK prompted us to compare the fast antidepressant actions of ketamine and HNK. We observed that both ketamine (15 mg/kg) and 2R, 6R HNK (10 mg/kg) exhibit antidepressant actions in forced-swim test and sucrose preference test, compared to saline-treated animals. However 2R, 6R HNK expressed significantly lower antidepressant strength than ketamine. Moreover, 2R, 6R HNK enhanced field EPSPs in hippocampal CA1 to less magnitude than ketamine. We also detected the underlying mechanisms of these differences between ketamine and 2R, 6R HNK.

Disclosures: R. Thapa: None. **S. Yan:** None. **X. Cai:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.08/QQ18

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Does ketamine really modulate glutamate?

Authors: *H. B. JANSSENS, L. YU, H. KOOIJKER, B. CWICK, N. MORISOT, J. ROESER, M. VAN DER HART, A. RASSOULPOUR
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Abstract: The noncompetitive NMDA receptor antagonist ketamine has been shown to elicit psychotic action in humans, exacerbate symptoms in schizophrenic patients, and more recently has been shown to have potential in treating depression. It is hypothesized that these actions may be regulated by ketamine's action on glutamate, as has been previously demonstrated using *in vivo* microdialysis in the prefrontal cortex of rodents. In addition, it has also been demonstrated that ketamine increased dopamine activity. However, we had historically been unable to attain a reproducible ketamine-induced release of glutamate using both in vivo microdialysis and biosensors. Thus, in the current set of experiments we utilized in vivo microdialysis to examine the effects of multiple doses of ketamine on neurotransmitter release in the prefrontal cortex and hippocampus of mice and rats. Consistent with our previous findings, we were unable to see an increase in glutamate levels of either species using 10 and 20 mg/kg of ketamine. Interestingly, we were able to observe a significant increase in dopamine levels, as previously reported as well as an increase in both serotonin and norepinephrine. Some of these monoaminergic changes were more pronounced in the hippocampus as compared to the prefrontal cortex. These results challenge existing reports of the mechanism by which ketamine exerts its actions, and provide additional support for the neuroactive mechanisms of ketamine functioning through monoaminergic pathways.

Disclosures: H.B. Janssens: None. **L. Yu:** None. **H. Kooijker:** None. **B. Cwick:** None. **N. Morisot:** None. **J. Roeser:** None. **M. van der Hart:** None. **A. Rassoulpour:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.09/QQ19

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The role of glutamatergic antagonist activity in the behavioral effects of analogs of the rapid-acting antidepressant RO-25-6981

Authors: L. NGUYEN[1], T. NGUYEN[1], K. LAYMON[1], A. CARAPUCCI[1], W. LEUNG[1], A. TOROSIAN[1], C. CAIN[1], T. ERIVES[1], R. D. KIRSH[2], D. B. RAWLINS[3,1], *J. N. TALBOT[3,1]

[1]Col. of Pharm., [2]Comparative Med. Unit, [3]Res. Ctr. on Substance Abuse and Depression, Roseman Univ. of Hlth. Sci., Henderson, NV

Abstract: Rational design of lead compounds targeting glutamatergic receptors is critical to developing novel therapeutics for treating psychiatric disorders. RO-25-6981, a novel rapid-acting antidepressant compound, was previously identified in a virtual computational screen for monoamine reuptake inhibition. Proposed mechanisms of antidepressant activity of MI-4 include NR2B selective inhibition of the of the NMDA receptor and/or inhibition of monoamine reuptake transporters such as serotonin, norepinephrine, and dopamine. The purpose of the current study is to characterize the in vivo antidepressant-like properties of analogs of RO-25-6981 with varying degrees of glutamatergic antagonistic activity. To assess antidepressant-like behaviors, the tail suspension test (TST) and locomotor activity tests were performed using RO-25-6981 and its analogs and traditional antidepressant drugs, including the serotonin selective reuptake inhibitor fluoxetine and the tricyclic antidepressant desipramine, as positive controls. Four RO-25-6981 analogs (TR-2, TR-4, TR-5, and TR-6) exhibited antidepressant-like activity following administration (30 mg/kg, i.p., 30 min) with maximal reductions in immobility by approximately half compared to vehicle-treated controls. By contrast, RO-25-6981 (10 mg/kg, i.p., 30 min) reduced immobility by approximately 90%, an effect comparable to that exhibited by fluoxetine and desipramine. Interestingly, TR-2, TR-4, TR-5, and TR-6 profoundly limited generalized locomotor activity suggesting increased activity in the tail suspension test were related to psychotropic vs. generalized drug effects. In contrast, other TR analogs tested showed no antidepressant-like activity in the tail suspension test, despite possessing robust NMDA receptor antagonist activity via mid- to low- nanomolar binding affinity at the NR2B subunit. The antidepressant-like activity of the RO-25-6981 analogs tested does not appear to correlate with the degree of NMDA receptor antagonism. These data point to monoamine reuptake inhibition as being a primary contribution to the overall antidepressant-like activity of RO-25-6981 in animal models of mood.

Disclosures: L. Nguyen: None. **T. Nguyen:** None. **K. Laymon:** None. **A. Carapucci:** None. **W. Leung:** None. **A. Torosian:** None. **C. Cain:** None. **T. Erives:** None. **R.D. Kirsh:** None. **D.B. Rawlins:** None. **J.N. Talbot:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.10/QQ20

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: TRPC4/5 as a target for antidepressant with a rapid onset action

Authors: *K. MITSUI, A. KISHI, T. NIWA, S. UENO, T. KITAJIMA, S. KATSUMATA
ONO Pharmaceut. Co., Ltd., Osaka, Japan

Abstract: Transient receptor potential canonical channels (TRPC) are highly expressed in the central nervous system, and regulates intracellular calcium signaling following stimulation of Gq coupled receptors. The TRPC subfamily consists of seven members named TRPC1, TRPC2, TRPC3, TRPC4, TRPC5, TRPC6 and TRPC7. The mice lacking TRPC4 or TRPC5 channel show decreased anxiety-like behaviors in elevated plus maze test, open field and social interaction test, suggesting TRPC4 and TRPC5 may be both involved in the regulation of anxiety and fear responses. We have recently identified novel class of TRPC4/5 inhibitor, ONO-2910640, and found that this compound showed antidepressive-like effects in olfactory bulbectomized mice. To further characterize the antidepressive effects of ONO-2910640 *in vivo*, we investigated effects of ONO-2910640 in a series of mice depression tests, i.e. forced swim test, novelty suppressed feeding test and chronic variable stress model. In addition, effects of ONO-2910640 on mTOR signaling pathways using primary cortical neuron were investigated. ONO-2910640 potently inhibited both mouse and human TRPC4/5 with high selectivity over other receptors, transporters, and ion channels. A single dose of ONO-2910640 significantly decreased the immobility time ($p<0.05$) in forced swim test with an efficacy equivalent to that of paroxetine, given intraperitoneally at 10 mg/kg. In novelty suppressed feeding test, acute treatment of ONO-2910640 significantly decreased the latency to feed ($p<0.05$), and this efficacy was comparable to that of scopolamine (0.03 mg/kg, i.p.). A similar suppressing effect of ONO-2910640 was found in chronic variable stress model. Moreover, we found that ONO-2910640 activated mTOR signaling pathways like ketamine which produces rapid-onset antidepressant effect. These results suggest that TRPC4/5 inhibition results in antidepressive effects, and ONO-2910640 is a promising candidate for the treatment of depression with rapid onset of action.

Disclosures: K. Mitsui: A. Employment/Salary (full or part-time):; ONO Pharmaceutical Co., Ltd. **A. Kishi:** A. Employment/Salary (full or part-time):; ONO Pharmaceutical Co., Ltd. **T. Niwa:** A. Employment/Salary (full or part-time):; ONO Pharmaceutical Co., Ltd. **S. Ueno:** A. Employment/Salary (full or part-time):; ONO Pharmaceutical Co., Ltd. **T. Kitajima:** A. Employment/Salary (full or part-time):; ONO Pharmaceutical Co., Ltd. **S. Katsumata:** A. Employment/Salary (full or part-time):; ONO Pharmaceutical Co., Ltd..

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.11/QQ21

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NSERC

Title: The fast-acting antidepressant effects of reelin require AMPA receptor activation

Authors: *K. BRYMER[1], K. A. BANNOUVONG[2], H. J. CARUNCHO[3], L. E. KALYNCHUK[3]
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Abstract: Reelin is an extracellular matrix protein involved in the regulation of synaptogenesis, learning and memory, dendritic spine plasticity, and hippocampal neurogenesis. We have previously shown that the onset of depression-like behavior in a preclinical animal model of depression is associated with deficient hippocampal neurogenesis and neuronal maturation and a decrease in hippocampal reelin expression. We then discovered that a single intrahippocampal infusion of reelin rapidly reverses the depressive phenotype in this model, normalizes hippocampal neurogenesis, and increases the number of GluA1-ir cells in the proliferative subgranular zone of the dentate gyrus. Here, we examined whether the rapid antidepressant effects of reelin could occur through synaptic activity at AMPA receptors. Rats underwent stereotaxic surgery to implant an indwelling cannula into the dorsal hippocampus, and received either 21 days of daily corticisterone (CORT) injections (40 mg/kg) or vehicle injections. Some rats received a single intrahippocampal infusion of reelin (1μl/μg) on day 21 of the CORT injections, and some of the rats that received reelin also received the AMPA antagonist CNQX to block AMPA receptor activation. The rats were subjected to the forced-swim test (FST) on day 22, and they were sacrificed to permit analyses of hippocampal neurogenesis, and hilar microglia morphology. As expected, the CORT injections significantly increased the time spent immobile in the FST, decreased hippocampal neurogenesis, and produced an active microglia phenotype. A single intrahippocampal reelin infusion normalized behavior in the FST and increased the number but not the dendritic complexity of doublecortin (DCX)-ir cells, and it did not alter the CORT-induced active microglia phenotype. Importantly, CNQX infusion after reelin blocked the antidepressant effects of reelin, such that the CNQX + reelin rats looked much like the CORT rats, with high levels of immobility in the FST and fewer adult-born granule neurons. These novel results demonstrate that CNQX blocks the antidepressant effect of reelin on FST behavior and the rate of cell proliferation without altering microglial morphology. Therefore, AMPA receptors may play an essential role in fast acting antidepressant drug effects.

Disclosures: K. Brymer: None. **K.A. Bannouvong:** None. **H.J. Caruncho:** None. **L.E. Kalynchuk:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.12/QQ22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Assessing ketamine's antidepressant-like effects in lipopolysaccharide (LPS)-induced sickness behavior in male and female mice

Authors: *B. KLOCKE, C. THELEN, N. HALLOY, P. M. PITYCHOUTIS
Biol., Univ. of Dayton, Dayton, OH

Abstract: Challenging the innate immune machinery with the pro-inflammatory agent lipopolysaccharide (LPS) results in the development of a sickness syndrome characterized by numerous depressive-like behavioral and physiological manifestations, most of which overlap with the clinical symptoms of major depressive disorder (MDD). A major discovery in the treatment of MDD was the finding that a single sub-anesthetic dose of ketamine induces both acute and sustained antidepressant effects in treatment-resistant depressed patients. Although women suffer from MDD at roughly twice the rate of men, the vast majority of research on ketamine's antidepressant effects has been mainly focused on the male sex. In the current study, we investigated the putative sex-differentiated antidepressant actions of acute ketamine treatment on LPS-induced sickness behavior. Specifically, male and female C57BL/6J mice were challenged with LPS (0.83 mg/kg; i.p.) and were also administered a single dose of ketamine (10mg/kg; i.p.) or vehicle (0.9% NaCl). Behavioral analysis of locomotor activity (open field test), grooming behavior (splash-test) and food consumption were recorded at 6-24h post LPS and/or drug administration. In our experimental setup a substantial protective effect of ketamine was not observed in either sex. Behavioral analysis of a repeated ketamine treatment regimen (i.e., 3 times per week for two weeks) is currently underway to further characterize the putative sex-differentiated effects of ketamine in LPS-induced sickness behavior.

Disclosures: B. Klocke: None. **C. Thelen:** None. **N. Halloy:** None. **P.M. Pitychoutis:** A. Employment/Salary (full or part-time):; Full-time employee.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.13/QQ23

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Sex differences in the synaptogenic effects of the rapid-acting antidepressant drug ketamine in the mouse hippocampus

Authors: *E. FLAHERTY, C. THELEN, P. M. PITYCHOUTIS
Biol., Univ. of Dayton, Dayton, OH

Abstract: Major depressive disorder (MDD) is a debilitating neuropsychiatric disease and affects more than 350 million individuals worldwide. MDD is often characterized by loss of dendritic spines in plastic brain regions implicated in stress response, such as the hippocampus. Directly combating these neural deficits, the rapid-acting antidepressant drug ketamine has been shown to induce its therapeutic effects by enhancing synaptogenesis in the male rodent brain. Strikingly, research regarding the antidepressant effects of ketamine has focused almost exclusively on the male sex. Published data from our group and others suggest that female rodents are behaviorally more reactive to the antidepressant-like effects of ketamine. However, the underlying mechanisms and potential implications of this sex-differentiated responsiveness to ketamine are still elusive. Herein, a modified Golgi-Cox neurohistological staining technique was used to evaluate the temporal synaptogenic effects of a single dose of ketamine (10mg/kg; previously shown to induce rapid and sustained antidepressant-like effects in mice of both sexes) in the *cornu ammonis 1* (CA1), CA3 and *dentate gyrus* (DG) hippocampal subfields of male and female mice. Overall, we found that ketamine elicits time- and sex-specific synaptogenic effects in the different hippocampal subfields in male and female mice. These findings further support the notion that ketamine induces its antidepressant-like effects in a sex- and brain region-dependent manner.

Disclosures: E. Flaherty: None. **C. Thelen:** None. **P.M. Pitychoutis:** A. Employment/Salary (full or part-time):; Full-time employee.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.14/QQ24

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: University of Dayton graduate student summer fellowship

Title: Sex differences in the neuromolecular effects of the rapid-acting antidepressant drug ketamine in the mouse prefrontal cortex

Authors: *C. THELEN, E. FLAHERTY, J. SAURINE, J. SENS, S. MOHAMED, P. M. PITYCHOUTIS
Biol., Univ. of Dayton Dept. of Biol., Dayton, OH

Abstract: Diagnosis of Major Depressive Disorder (MDD) has steadily been increasing in recent years, and by 2030 this neuropsychiatric disease is projected to be the leading cause of disease burden worldwide. One of the most striking discoveries in the treatment of MDD was the finding that a low dose of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine induces rapid and sustained antidepressant effects by enhancing synaptogenesis in the

medial prefrontal cortex (mPFC). Strikingly, research on ketamine's antidepressant effects has focused almost exclusively on the male sex. Data from our group and others indicate that female rodents are more sensitive to the rapid and the sustained antidepressant effects of ketamine, as they respond to lower doses of the drug in antidepressant-predictive behavioral tasks. It is noteworthy that most studies in the field typically assess only a single end-point following ketamine administration and essentially provide only a "snapshot" of the neurobiological alterations that occur in the brain upon ketamine administration. Thus, it is possible that important sex-dependent neurobiological events that occurred before this time-point or even later could be missed. In the current study we assessed the temporal neurobiological effects of ketamine in order to understand how a single ketamine injection may induce its antidepressant-like effects in the male and the female brain. Specifically, we addressed this matter by assessing the kinetics of prefrontocortical glutamate release and downstream activation of synaptic plasticity processes in behaviorally-naïve mice administered a single dose of ketamine (10mg/kg; i.p.) that we have previously reported to reliably induce both rapid and sustained antidepressant like-effects in both sexes. In our experimental setup ketamine induced a male-specific *"glutamate burst"* in the mPFC. Moreover, ketamine activated the mammalian target of rapamycin complex 1 (mTORC1) pathway, induced rapid and sustained synaptic protein synthesis and enhanced prefrontocortical spine formation in a sex-specific manner. More experiments are underway to characterize this sex-dependent neurobiological responsiveness to ketamine administration.

Disclosures: C. Thelen: None. **E. Flaherty:** None. **J. Saurine:** None. **J. Sens:** None. **S. Mohamed:** None. **P.M. Pitychoutis:** A. Employment/Salary (full or part-time):; Full-time employee.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.15/QQ25

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: FCT PhD Grant: PDE/BDE/113602/2015
FCT project: PTDC/DTP-PIC/6936/2014

Title: Acute effects of antidepressants in the dynamic functional connectome of drug naive patients with major depression

Authors: *J. REIS[1,2], J. CABRAL[3,4,1,2], R. MAGALHÃES[1,2], P. MARQUES[1,2], P. MOREIRA[1,2], C. PORTUGAL-NUNES[1,2], H. SOUSA[1,2], N. DIAS[5,1,2], N. SOUSA[1,2], J. BESSA[1,2]
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Abstract: Major depression is growing in prevalence and is currently ranked as the fourth most urgent health problem worldwide. While antidepressants play an important role in its management, only 60% of patients respond to the first treatment and only 40% achieve total remission of symptoms. Thus, a clinically valuable complementary strategy would be to develop a method able to predict, at the onset of treatment, the probability of therapeutic success with a specific medication. Previous studies have shown that functional brain imaging responses to acute antidepressant treatment may predict the clinical outcome. However, the predictability of treatment responses to a specific antidepressant in different individuals remains to be established. The present study attempts to identify novel imaging biomarkers capable of achieving that goal by analyzing the temporal dynamics of the functional connectome. In the present study, 20 drug-naïve subjects diagnosed with a first episode of Major Depression were recruited in the context of emergency psychiatric evaluations. A total of 5 resting state fMRI were then acquired sequentially: the first prior to administration of the antidepressant (Paroxetine) and the remainder at hourly intervals following. In addition to evaluating the patterns of regional activity and connectivity, we hypothesized that the acute administration of the drug may also modulate the switching behavior of functional connectivity (FC) patterns, which have been shown to be affected in a variety of psychiatric disorders. To evaluate the FC switching behavior, we employed the Leading Eigenvector Dynamic Analysis (LeiDA). This analysis showed that there are demonstrable changes in switching behavior of FC states following the administration of a single dose of antidepressant. The present study suggests that by using the characterization of FC switching behavior it may be possible to develop an imaging biomarker which more accurately predicts an individual therapeutic response to a specific drug. These results provide the first evidence that the temporal dynamics of the functional connectome are modulated by a single dose of an antidepressant drug. Importantly, this observation may pave the way for new predictive approaches in the treatment of Major Depression.

Disclosures: J. Reis: None. **J. Cabral:** None. **R. Magalhães:** None. **P. Marques:** None. **P. Moreira:** None. **C. Portugal-Nunes:** None. **H. Sousa:** None. **N. Dias:** None. **N. Sousa:** None. **J. Bessa:** None.

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.16/QQ26

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Intramural Program of NIH

Title: Differences in neural activity between attempters and non-attempters during emotional attention processing after ketamine and placebo

Authors: *N. GERLUS, E. D. BALLARD, J. L. REED, J. E. SZCZEPANIK, C. A. FARMER, A. C. NUGENT, C. A. ZARATE, JR.
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Abstract: Current literature supports the role of ketamine as a potential rapid acting agent on depression and suicidal ideation, suggesting its use for individuals at high suicide risk. Although past suicidal behavior is the best predictor of prospective suicidal behavior, the link between suicide attempt history and ketamine response remains unclear. We have previously found differential neural activity in people with and without a history of suicide attempts during an emotional dot-probe paradigm using fMRI, specifically in the left precuneus. Using the same paradigm, this project examines the effect of ketamine on emotional attention biases and their neural correlates in a sample of depressed attempters (SA) and non-attempters (NA). 12 medication-free SAs (M = 36.4, 50% f) and 18 medication-free NAs (M = 35.7, 75% f) received one subanesthetic (0.5 mg/kg) ketamine infusion and one placebo infusion in a double-blind placebo-controlled crossover study. Two days after each infusion, participants received fMRI scans at 3T while they performed a dot-probe task using emotional (happy or angry) and neutral face stimuli. Reaction times and attention bias scores were analyzed using a repeated linear mixed model in SAS. fMRI data were analyzed using a linear mixed effects model in AFNI and FWE cluster corrected to $p < 0.05$. Behavioral analysis showed no significant effects of drug or group. We found a significant drug by group interaction in the bilateral fusiform gyri, the right insula, and several other regions throughout the brain. In the fusiform gyri and other regions, SAs showed increased activation while NAs showed decreased activation post-ketamine compared to post-placebo. We found the opposite pattern in the right insula, with SAs showing decreased activation post-ketamine compared to post-placebo and NAs showing increased activation. There was also a significant drug by group by emotion interaction. SAs showed decreased activation in the left precuneus when viewing angry faces post-ketamine compared to post-placebo, and NAs showed increased activation. In the left middle frontal gyrus, SAs showed increased activation when viewing angry faces post-ketamine compared to post-placebo, and NAs showed decreased activation. Results indicate that ketamine differentially affects emotional processing in SAs and NAs. Left precuneus alterations are consistent with our previous findings and current suicide literature. Findings suggest differences in ketamine-related neural functioning between depressed patients with and without a suicide attempt history, highlighting potential targets for therapeutic and research efforts.

Disclosures: N. Gerlus: None. **E.D. Ballard:** None. **J.L. Reed:** None. **J.E. Szczepanik:** None. **C.A. Farmer:** None. **A.C. Nugent:** None. **C.A. Zarate:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Listed as co-inventor on patents for ketamine and metabolites in depression treatment. Patent rights assigned to United States government, but he will share a percentage of any royalties received..

Poster

230. Depression and Bipolar Disorders: Ketamine and Other Rapid Antidepressants I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 230.17/RR1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: IBRO/APRC Exchange Fellowship 2017

Title: Quinolinic acid act as prooxidant in depression evidenced through Nrf2 activity in restrain-stress rat model

Authors: *Y. BANSAL[1], R. SINGH[1], A. KUHAD[1], I. PRAHAR[2], T. SOGA[2]
[1]Panjab Univ., Chandigarh, India; [2]Monash Univ., Selangor, Malaysia

Abstract: *Background:* Quinolinic acid (QA), a neurotoxic metabolite of kynurenine pathway exert neurotoxic effects in depression. It has been found that QA might increases reactive oxygen species through NMDA activation or directly through QA-iron reaction but the exact mechanism is not clear. Enhancing nuclear translocation of endogenous antioxidant transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2) has been found to restore redox homeostasis and decreases vulnerability to depression. *Aim:* With this background present study was designed to investigate the role of QA as pro-oxidant in depression by modulating nuclear translocation of Nrf2. *Materials and Methods:* Restrain-stress model was used to induce depression in male wistar rats (7-8 week old). Animals were restrained for 2 hours daily for 7 days. Animals were divided into three groups: control, restrain-stress group and restrain-stress + UPF-648 (Kynurenine monooxygenase inhibitor, inhibit QA synthesis). Locomotor activity was evaluated in open field test and quantification of Nrf2 mRNA expression in hippocampus was done by qPCR. Serotonin (5-HT) and 5-Hydroxyindole acetic acid (5-HIAA) concentrations were quantified in hippocampus using Liquid Chromatography-Mass Spectroscopy. *Results:* Restrain stress increased Nrf2 mRNA expression in the hippocampus of stressed animals and UPF-648 treatment prevented the activation of Nrf2. Increased serotonin turnover was found in hippocampus of stressed group and UPF-648 microinjection in hippocampus prevented increase in 5-HIAA and decrease in 5-HT levels in restrain-stressed rats. *Conclusion:* QA increases oxidative stress by modulating Nrf2 activity in stressed conditions and hence act as pro-oxidant in depression.

Disclosures: Y. Bansal: None. **R. Singh:** None. **A. Kuhad:** None. **I. Prahar:** None. **T. Soga:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.01/RR2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Janssen Pharmaceutical Research and Development

Title: Dose-dependent effects of the competitive, reversible MGL inhibitor JNJ-42226314 on *in vivo* measures of neural activity in rats

Authors: *R. M. WYATT[1], I. FRASER[1], N. WELTY[1], B. LORD[1], S. YUN[1], B. ZHU[2], C. FLORES[6], M. MACIELAG[2], P. J. CONNOLLY[3], K. CHEVALIER[4], S.-P. ZHANG[5], M. K. AMERIKS[1], C. DUGOVIC[1], T. LOVENBERG[1], P. BONAVENTURE[1]
[1]Neurosci., Janssen Res. and Develop., San Diego, CA; [2]Cardiovasc. and Metabolic Dis., [3]Discovery Sci., [4]Oncology, Janssen Res. and Develop., Spring House, PA; [5]Pharmaceut. Develop. and Manufacturing Sci., Janssen Res. and Develop., Malvern, PA; [6]Johnson and Johnson Consumer Products, Fort Washington, PA

Abstract: Endogenous cannabinoid signaling mediates several neuromodulatory functions in the central and peripheral nervous systems, including regulation of mood and cognition. Human patients with depression and related disorders, for example, exhibit reduced circulating endocannabinoid levels. Enhancement of endocannabinoid signaling is believed to offer a potential therapeutic treatment for depressive disorders. Monoacylglycerol lipase (MGL) is a key enzyme that catalyzes the degradation of the major endocannabinoid, 2-arachidonoylglycerol (2-AG). Thus, augmenting endogenous 2-AG levels via MGL inhibition presents a possible means for achieving this enhancement. Upregulation of endocannabinoid signaling, however, can also produce a number of unwanted side effects, such as deficits in memory and cognition. It is therefore necessary to develop MGL inhibitors that can effectively deliver therapeutic mood benefits while avoiding any of these undesirable impairments. Here we present an in vivo characterization of JNJ-42226314, a novel competitive, non-covalent inhibitor of the MGL enzyme. High doses (30 mg/kg, intraperitoneal dosing) provide full occupancy of the MGL enzyme and robustly increase 2-AG levels in the rat hippocampus, but also induce hippocampal synaptic depression, alter sleep onset and decrease EEG gamma power in both wake and sleep states, indicating potential adverse effects on cognition consistent with increased endocannabinoid signaling. Lower doses (3 mg/kg, i.p dosing) still provide approximately 80% enzyme occupancy and a significant increase in 2-AG levels, but do not induce hippocampal synaptic depression, suggesting a possible therapeutic level of MGL inhibition.

Disclosures: R.M. Wyatt: A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **I. Fraser:** A. Employment/Salary (full or part-time):; Janssen

Pharmaceutical Research and Development. **N. Welty:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **B. Lord:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **S. Yun:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **B. Zhu:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **C. Flores:** A. Employment/Salary (full or part-time):; Johnson and Johnson. **M. Macielag:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **P.J. Connolly:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **K. Chevalier:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **S. Zhang:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **M.K. Ameriks:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **C. Dugovic:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **T. Lovenberg:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development. **P. Bonaventure:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Research and Development.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.02/RR3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Development of an *ex vivo* assay to measure CB1 receptor occupancy after administration of a monoacylglycerol lipase inhibitor

Authors: *B. LORD, M. WENNERHOLM, S. SUTTON, M. AMERIKS, P. BONAVENTURE
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Abstract: Monoacylglycerol lipase (MGL) is the key enzyme responsible for the degradation of the endocannabinoid 2-arachidonoylglycerol (2-AG) into arachidonic acid and glycerol. Inhibition of 2-AG degradation leads to elevation of 2-AG, the most abundant endogenous agonist of cannabinoid receptors (CB1 and CB2). 2-AG levels are decreased in individuals with major depression. In addition, the CB1 receptor inverse agonist/antagonist Rimonabant has been withdrawn from the market due to the high incidence of severe depression and suicidal ideation. Therefore, by selectively potentiating the cannabinoid system, MGL inhibition offers a compelling therapeutic approach for the treatment of mood disorders. Here we developed and validated an ex vivo assay to measure level of MGL occupancy and level CB-1 receptor occupancy in the same animal following administration of an MGL inhibitor. Brain 2-AG content was also measured. Mice were given one of the following compounds intraperitoneally at

30 mg/kg: JZL-184, a literature standard covalent MGL inhibitor, KT182, a covalent ABHD6 inhibitor, rimonabant, a CB1 antagonist, JNJ-42012191, a FAAH inhibitor or vehicle. Brains were collected and frozen at various time points. Hippocampal and striatal tissue sections were prepared for autoradiography. For measurement of MGL occupancy, [^{3}H] SAR127303 was used as a tracer and [^{3}H] CP55940 was used to measure CB1 occupancy. Sections were incubated with the respective tracer for ten minutes followed by washing steps and dried before image acquisition with a β-imager. JZL-184 (30 mg/kg i.p.). exhibited a high level of MGL occupancy (> 90%) and moderate CB1 occupancy (40%) through the entire time course (up to 24 hours). Rimonabant showed a high level of CB1 occupancy (>90%) through the entire time course and no MGL occupancy. No significant levels of MGL or CB1 occupancy were detected with the ABHD6 inhibitor or the FAAH inhibitor. JZL184 was the only compound found to significantly increase brain 2-AG levels correlating with the observed CB1 occupancy. These experiments with various tool compounds demonstrate that CB1 receptor occupancy can be measured after administration of an MGL inhibitor.

Disclosures: M. Wennerholm: None. **S. Sutton:** None. **M. Ameriks:** None. **P. Bonaventure:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.03/RR4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Nellie Ball Trust: Research Grant
Brockman Medical Research Foundation

Title: Protective efficacy of P7C3 compounds in a mouse model of prenatal depression

Authors: *R. SCHROEDER[1], H. E. STEVENS[2], A. A. PIEPER[3]
[1]Neurosci., [2]Univ. of Iowa, Iowa City, IA; [3]Psychiatry, Univ. of Iowa Carver Col. of Med., Iowa City, IA

Abstract: Depression is a prominent mental health issue in the United States that affects nearly twice as many women as men. Maternal depression during pregnancy is difficult to treat, as both the condition and its currently available pharmacologic treatments pose a risk to embryonic neurodevelopment. Furthermore, current treatments are often ineffective; only about half of patients respond to treatment with conventional antidepressants. Therefore, there is a critical need to develop new and more effective treatments for maternal depression. P7C3 compounds have been shown to rescue depressive-like phenotypes in multiple models. Additionally, when administered to dams during gestation and nursing, they have no apparent negative impact on

embryonic or early postnatal development. We hypothesize that (-)-P7C3-S243, one of the most potent members of the P7C3 series of compounds, will rescue maternal depressive-like behavior in an animal model of prenatal stress-induced depression, and also protect offspring from abnormal neurodevelopment and associated neuropsychiatric deficits. To test this, we subjected pregnant CD1 dams to restraint stress in 45-minute sessions three times daily and administered (-)-P7C3-S243 or vehicle via IP injection or oral gavage to dams twice daily. We then assessed outcomes after non-stressed control conditions, stress conditions, and/or P7C3 administration in two protocols: prolonged, starting on embryonic day 5 (E5), and brief, starting on E12. In offspring embryonic brain, we assessed a known neurodevelopmental deficit, GABAergic progenitor migration delay at E13 and E14. By employing a CD1 GAD67GFP+ mouse line, we measured the leading edge of GAD67GFP+ cell distribution in developing cortical plate using fluorescent microscopy in fixed tissue. In an independent cohort of pregnant dams, we assessed depressive-like behaviors at the end of pregnancy, including sucrose preference, forced swim, and tail suspension. Our preliminary data show that (-)-P7C3-S243 administration rescued the embryonic GABAergic migration deficit after prenatal stress. These results support the feasibility of our compound as a treatment for maternal prenatal depression that protects embryonic neurodevelopment.

Disclosures: R. Schroeder: None. **H.E. Stevens:** None. **A.A. Pieper:** F. Consulting Fees (e.g., advisory boards); Proneurotech.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.04/RR5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CAPES/Alexander von Humboldt fellowship award
German Center for Brain Stimulation (GCBS) research consortium (grant 01EE1403E), funded by the Federal Ministry of Education and Research (BMBF)

Title: MRI-based predictors of response to prefrontal transcranial direct current stimulation in major depression: Data from the ELECT study

Authors: *L. BULUBAS[1,3], D. KEESER[1,2], P. V. BUENO[4], F. DURAN[5,6], G. BUSATTO[5,6], E. AMARO, Jr.[7], F. PADBERG[1], A. R. BRUNONI[1,4]
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Psychiatry, Univ. of Sao Paulo, Sao Paulo, Brazil; [7]Inst. of Radiology, Clinics Hosp., Univ. of Sao Paulo Med. Sch., Sao Paulo, Brazil

Abstract: Transcranial direct current stimulation (tDCS) is a promising novel intervention for major depression (MD). Yet neurobiological determinants of tDCS response are still to be investigated. In The Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-TDCS), a trial with patients randomly assigned to receive escitalopram (ESC), tDCS, or placebo (PLA), Brunoni et al. (2017) have shown antidepressant effect of tDCS superior to PLA, yet not noninferior to ESC. In our exploratory study, we investigated structural data from a sub-sample of ELECT-TDCS to identify MRI-based predictors of tDCS response, such as volume of the left dorsolateral prefrontal cortex (DLPFC) or adjacent areas. We enrolled 52 patients with MD from ELECT-TDCS (22 to 67 yrs, 15 men, n[tDCS] = 15, 37 controls: n[ESC] = 16, n[PLA] = 21) with baseline structural MRI scans (MPRAGE T1, 3T Phillips Scanner, TFE, FOV 240x240x180 mm3, res. 1x1x1 mm, TR 7 ms, TE 3.2 ms, FA 8°, 180 slices). TDCS was delivered at 2 mA over 10 weeks in 22 sessions à 30 min with anode over the left and cathode over the right DLPFC. After quality check and brain extraction, a region of interest (ROI)-based approach was used to calculate grey matter volumes of underlying regions using FSL, AFNI and in-house scripts. As the DLPFC cannot be located within classical anatomical boundaries, we used a parcellation of the dorsal frontal cortex (Sallet et al. 2013) to define the ROIs (10/10 left/right hemisphere). General linear models were run to explore ROIs that may predict the primary outcome (difference in Hamilton Depression Rating Scale [HDRS] score from baseline to week 10) using group, ROI volume and their interaction as dependent variables. The intervention groups did not differ considering primary outcome, sex, and age. Specifically in the tDCS group, compared to ESC and PLA, we saw a direct correlation of ROI volumes and HDRS for a small right-sided region medial to DLPFC (cluster 3; tDCS vs. PLA slope [β] = 33.29, 95% CI [4.86; 61.71], p = 0.023; tDCS vs. ESC β = 29.55, CI [-1.18; 57.93], p = 0.042), and at the level of a statistical trend for the whole left dorsal prefrontal cortex (cluster 3-8, 10; tDCS vs. PLA β = 3.54, CI [-0.010; 7.10], p = 0.051; tDCS vs. ESC β = 3.19, CI [-0.45; 6.84], p = 0.085) and a larger region containing the DLPFC and medial areas (cluster 3, 4, 5; tDCS vs. PLA, β = 5.67, CI [-0.16; 11.49]; p = 0.056; tDCS vs. ESC β = 5.05, CI [-0.87; 10.96], p = 0.093). Hence, based on MRI data from ELECT-TDCS, we hypothesize that the clinical response to tDCS is determined by volumetric information from prefrontal cortex regions. This hypothesis should be confirmed in further trials applying multiparametric MRI approaches.

Disclosures: L. Bulubas: None. **D. Keeser:** None. **P.V. Bueno:** None. **F. Duran:** None. **G. Busatto:** None. **E. Amaro:** None. **F. Padberg:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); neuroConn GmbH, Mag&More GmbH, Brainsway Inc.. F. Consulting Fees (e.g., advisory boards); Mag&More GmbH, neuroCare Group, European Advisory Board. **A.R. Brunoni:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.05/RR6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R41MH113398
NIH Grant R01 AT009169
NIH Grant T32 MH067631
VA Grant BX001149-06

Title: Antidepressant-like effect of polyunsaturated fatty acids in lymphoblasts from depressed human subjects

Authors: *P. CHUKAEW, J. SCHAPPI, A. KOUTSOURIS, M. RASENICK
Dept. of Physiol. and Biophysics, Univ. of Illinois at Chicogo, Chicago, IL

Abstract: Depression is one of the most common and costliest mental disorders. While several drugs are available as antidepressants, most require several weeks before achieving efficacy and about one third of those treated with antidepressants do not find remission from their symptoms. In addition, most antidepressants have a variety of side effects ranging from annoying to life-altering. Therefore, additional compounds that act as antidepressants or serve as “adjuvants” for conventional antidepressants should be sought out. Omega-3 polyunsaturated fatty acids (n-3 PUFA) have been reported to mitigate both inflammation and depression, although this topic remains controversial. We have established a simple cellular biosensor for both depression and antidepressant action, and thought to apply this to ascertain whether n-3 PUFA possessed or facilitated the actions of antidepressants. This biosensor is based on the translocation of the G protein, Gαs, from lipid raft to non-raft membrane fractions, where it engages in a more facile coupling with adenylyl cyclase, generating increased cAMP. Thus, we sought to determine whether n-3 PUFA modified Gαs localization or increased cAMP. Human lymphoblast cell lines were obtained from NIMH from depressive patients responding to initial selective serotonin reuptake inhibitor (SSRI) therapy and ones that did not (STAR*D subjects). Cells were treated with n-3 PUFA alone or in combination with (SSRIs) antidepressant. Then biochemical fractionation of membrane components, and mass spectrometry (MS) analysis were used to determine the modification of Gαs and its localization in cell membrane. cAMP measurements were also performed. Results revealed that n-3 PUFA, alone or in concert with SSRI effects the antidepressant biosignature in cells from antidepressant responders and some non-responders.

Disclosures: P. Chukaew: None. **J. Schappi:** None. **A. Koutsouris:** None. **M. Rasenick:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support);

Lundbeck S.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.06/RR7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Research Grant Council, Hong Kong [GRF 14101714]

Title: Dorsolateral prefrontal-subgenual cingulate connectivity as biomarker for repetitive transcranial magnetic stimulation antidepressant response trajectories

Authors: *H. J. HOPMAN[1], S. S. M. CHAN[2], C. W. W. CHU[3], H. LU[2], L. C. W. LAM[2], A. D. P. MAK[2], R. S. KAHN[5], C.-Y. TSE[4], S. F. W. NEGGERS[5]
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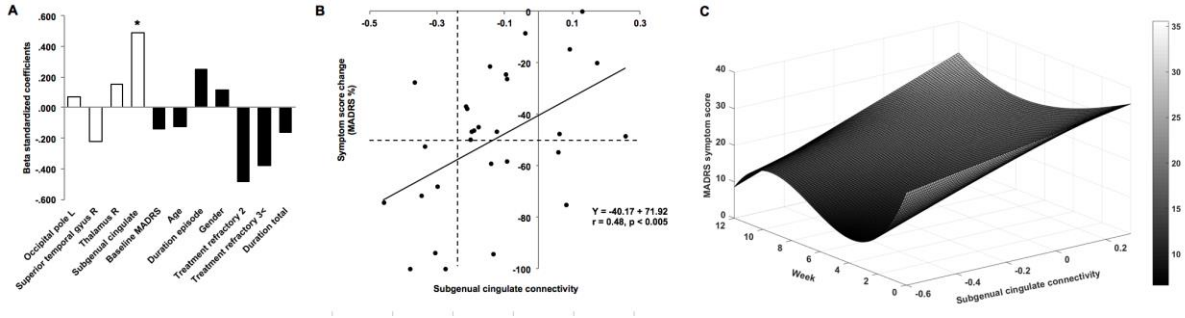
Abstract: Background: Previous studies suggest that functional connectivity between left dorsolateral prefrontal cortex (DLPFC) and subgenual anterior cingulate cortex (sgACC) might serve as predictive biomarker for repetitive transcranial magnetic stimulation (rTMS) antidepressant treatment response, but direct evidence is lacking as connectivity measures were based on normative connectome data from healthy subjects and a controversial preprocessing method was applied. Furthermore, crucial information might have been overlooked as TMS-related symptomatic change over time to explain inter-individual differences has been largely ignored.
Aim: Investigate the predictive value of DLPFC-sgACC functional connectivity on rTMS treatment response trajectories in medication-resistant depression.
Method: Resting-state functional magnetic resonance imaging data was collected from 30 medication-resistant depressed patients before undergoing 20 sessions of 10 Hz left DLPFC neuronavigated rTMS over 4 weeks. Primary outcome measure was the Montgomery-Åsberg Depression Rating Scale. Multiple regression with backward elimination was used to investigate predictors of treatment response at week 12, including several control connections to test the specificity of DLPFC-sgACC connectivity. Symptom score trajectories over 12 weeks were analyzed using growth curve analysis.**Results:** Regardless preprocessing method, DLPFC-sgACC connectivity was the only variable that could predict rTMS treatment response at week 12 (adjusted R^2=0.20, $p<0.01$; figure A and B), and explain inter-subject variability in rTMS response trajectories (global effect size=0.55, $p<0.01$; figure C); stronger anticorrelation was associated with faster and better treatment response.
Conclusions: DLPFC-sgACC functional connectivity can contribute to rTMS treatment

response prediction. Future studies should use more sophisticated techniques considering other connections to further examine the prognostic value of network mechanisms as biomarker of treatment response.



Disclosures: H.J. Hopman: None. **S.S.M. Chan:** None. **C.W.W. Chu:** None. **H. Lu:** None. **L.C.W. Lam:** None. **A.D.P. Mak:** None. **R.S. Kahn:** None. **C. Tse:** None. **S.F.W. Neggers:** Other; minority share in Brain Science Tools BV, a company manufacturing stereotactic navigation technology for TMS. This did not influence the design, analysis or reporting.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.07/RR8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Saudi Arabian Cultural Mission

Title: Effects of alpha-7 nicotinic allosteric modulator PNU 120596 on lipopolysaccharide-induced anhedonia, anxiety, and cognition-like behaviors in mice

Authors: *S. ALZAREA, S. RAHMAN
Col. of Pharm. Dept. of Pharmaceut. Sci., South Dakota State Univ., Brookings, SD

Abstract: Evidence indicates that α7 nicotinic acetylcholine receptor (nAChR) plays a critical role in regulating neuroinflammation implicated in depression, anxiety, and cognitive disorders. The present study examined the effects of PNU 120596, an α7 nAChR positive allosteric modulator (PAM), on lipopolysaccharide (LPS)-induced anhedonia, anxiety, and cognition-like behaviors. PNU 120596 (1 or 4 mg/kg, i.p.) was administered 0.5 h before LPS (1 mg/kg, i.p.) injection in male C57BL/6J mice. Behavioral measures for anhedonia, anxiety, and cognition were performed using sucrose preference test, elevated plus maze, and Y-maze, respectively 24 h after LPS injection. Acute administration of PNU 120596 prevented the development of LPS-

induced anhedonia, anxiety, and cognition-like behaviors. Pretreatment of methyllycaconitine (MLA, 3 mg/kg, i.p.), an α7 nAChR antagonist, significantly reversed the effects of PNU 120596 (4 mg/kg). We also examined the effects of PNU 120596 on LPS-induced microglial activation and proinflammatory cytokines in the hippocampus, an important brain region associated with mood disorders. The PNU 120596 prevented LPS-induced mRNA expressions of CD11b, a microglial activation marker, interleukin-1β, and tumor necrosis factor-α. Similarly, pretreatment of MLA significantly reversed the effects of PNU on the mRNA expressions. Furthermore, the effects of PNU 120596 on noradrenergic transmission in the hippocampus were assessed during LPS-induced anhedonia, anxiety, and cognition-like behaviors. The PNU 120596 enhanced norepinephrine level in the hippocampus after LPS administration. Overall, these results suggest that PNU 120596 produces anti-inflammatory effects by reducing LPS-induced anhedonia, anxiety, and cognition-like behaviors. Therefore, PNU 120596 or α7 nAChR PAMs could be promising new drug candidates for the treatment mood disorders in humans.

Disclosures: S. Alzarea: None. **S. Rahman:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.08/RR9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Ministerio de Economía y Competitividad (SAF2015-67457-R)

Title: Involvement of the mTOR pathway in the antidepressant-like effect of cannabidiol infralimbic administration in rat

Authors: E. FLORENSA-ZANUY[1,2], D. VASTURZO[1], A. ARCHITRAVO[1], E. CASTRO[1,3,2], Á. DÍAZ[1,3,2], *F. PILAR-CUELLAR[1,3,2], A. PAZOS[1,2,3]
[1]IBBTEC, Santander, Spain; [2]Univ. de Cantabria, Santander, Spain; [3]Ctr. de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Santander, Spain

Abstract: Nowadays major depression presents a high prevalence in the world population, and it is predicted to increase in the following years. One of the main problems in major depression treatment is that current pharmacological drugs are highly ineffective and present a delayed response, so the finding of new antidepressants is considered of paramount importance. In order to take a step forward in this search, we have focused our study in cannabidiol (CBD), the main non-psychotomimetic component of *Cannabis sativa*. CBD has a potential therapeutic efficacy for diverse non-psychiatric and psychiatric diseases, although its mechanism of action is still unknown. Therefore, the aim of this work is to determine the molecular mechanism by which CBD exerts its antidepressant properties and the brain areas involved.

In this study, we have infused 60 nmols of CBD in two relevant brain areas for the antidepressant effect, which are the infra-limbic (IL) cortex (bilateral administration) and the dorsal raphe nucleus (DRN) of 2-month-old male Sprague Dawley rats. The acute behavioral effect was evaluated in an open field (OF) test and a forced swimming test (FST) 30 minutes after the infusion. Then, protein expression of different signaling pathways associated to neuronal plasticity (i.e.: mTOR, BDNF, GSK-3β) was evaluated by western blot in prefrontal cortex samples.
The bilateral CBD-IL infusion induced an antidepressant-like effect evidenced by a reduction in immobility in the FST ($p<0.05$), and an increase in swimming ($p<0.05$) compared to the vehicle group. Conversely, the intra-DRN administration of CBD presented no changes in the FST immobility, although an increase in swimming ($p<0.05$) and a decrease in climbing ($p<0.05$) behaviors was detected in these animals. No significant changes were observed in the anxious behavior and locomotion assessed in the OF test after either IL or DRN CBD administration. Interestingly, the CBD-IL infusion induced an increase of synaptic plasticity markers as BDNF ($p<0.01$) and mTOR pathway activation ($p<0.05$) in the prefrontal cortex (PFC). The CBD infusion in DRN also induced an increase in BDNF ($p<0.05$) in PFC, with no changes in the activation of the mTOR pathway.
In summary, our data indicate that the local administration of CBD in the infralimbic prefrontal cortex induces an antidepressant-like response that may be mediated by the activation of synaptic plasticity pathways as mTOR in the prefrontal cortex. Additional experiments are necessary to fully understand the CBD behavioral and molecular effects.

Disclosures: E. Florensa-Zanuy: None. **D. Vasturzo:** None. **A. Architravo:** None. **E. Castro:** None. **Á. Díaz:** None. **F. Pilar-Cuellar:** None. **A. Pazos:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.09/RR10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant GM61394
NHMRC APP1051931
SAHMRI Institutional Funding
Flinders Foundation

Title: Rare genetic variants and antidepressant remission

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Abstract: About 30-40% of functional variability in genes related to drug action can be contribute by rare variants. Around 12% of Americans take antidepressants currently; thus, the capability to predict antidepressant could have an impact in public health. We investigate the role of rare functional genetic variants in antidepressant response in a cohort of Mexican-American individuals who met DSM-VI criteria for major depressive disorder and participated in a prospective randomized pharmacogenetics study of 8 weeks of double-blind treatment with desipramine or fluoxetine. Our primary outcome was measured by the Hamilton Depression Rating Scale; we obtained whole exome genotyping data in 36 remitters and 29 non-responders and performed regression- and permutation-based kernel-based adaptive cluster (KBAC) analysis. We identified several genes significantly associated with treatment remission (FDR<0.05), and their network and pathway analysis revealed the involvement of the following processes: sensory transduction, regulation of response to cytokine stimulus, and meiotic cell cycle process. Our results substantiate the involvement of rare variants in antidepressant drug response in major depressive disorders. <!--EndFragment-->

Disclosures: M. Wong: None. **M. Arcos-Burgos:** None. **J. Licinio:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.10/RR11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: iCUREUS awarded to J.M.
Canadian Funds for Innovation
Ontario Small Infrastructure Funds
Canadian Institute of Health Research Canada Research Chair award to N.S.

Title: Fibroblast growth factor 2 (fgf2) is necessary for the antidepressant effects of fluoxetine in chronically stressed mice

Authors: *P. SHAIL[1], S. SIMARD[2], J. MACGREGOR[1], M. ELSAYED[3], R. S. DUMAN[4], F. M. VACCARINO[5], N. SALMASO[2]
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Abstract: The neurotrophic hypothesis of depression states that changes in neurotrophic factor expression and function can alter structures of the brain's limbic system, particularly in the hippocampus and prefrontal cortex. Previous research has shown that the neurotrophic factor, fibroblast growth factor 2 protein (FGF2) can act as an anxiolytic and anti-depressive agent in rodents. Levels of hippocampal *FGF2* and *FGF2* receptors are decreased in post-mortem brains of individuals with mood disorders. Furthermore, no changes in *FGF2* were noted in the post-mortem brains of individuals with mood disorders that were successfully treated with anti-depressant medication prior to death. Even mutations in the *FGF2* gene in humans have been shown to predict non-responsiveness to the therapeutic effects of selective serotonin reuptake inhibitors (SSRIs). These findings suggest that *FGF2* may potentially be required for the therapeutic effects of antidepressant medications. We sought to assess the effects of *FGF2* gene deletion on the ability of fluoxetine to decrease depressive behaviour in wild-type (WT) and FGF2 knock-out (FGF2KO) mice. To achieve this, we used a rodent model of depressive behaviour, chronic variable stress (CVS), to induce a depressive behavioural phenotype in these mice. WT and FGF2KO mice were treated with either vehicle or fluoxetine intraperitoneal injections. Results showed that fluoxetine reversed the effects of CVS on both depressive and anxiety behaviours in wild-type mice only, suggesting that the *FGF2* gene is indeed necessary for the therapeutic effects of fluoxetine. We have previously shown that FGF2 is involved in HPA regulation, more specifically, loss of the *FGF2* gene reduces glucocorticoid receptor (GR) expression in the hippocampus through the effects of FGF2 on the transcription factor, egr-1. Moreover, administration of a GR antagonist blocks the anxiolytic effects of FGF2 protein administration. Using qPCR we examined hippocampal GR levels in the current study and found that although GR was decreased in FGF2KO mice, no changes were seen in GR with fluoxetine administration in either WT or FGF2KO mice, suggesting that the therapeutic effects of fluoxetine are not mediated through FGF2's effects on GR. The current study reaffirms a role for FGF2 in both the etiology and the treatment of depression and anxiety disorders. Future studies will be needed, however, to delineate the mechanisms by which FGF2 mediates the therapeutic effects of fluoxetine.

Disclosures: P. Shail: None. **S. Simard:** None. **J. MacGregor:** None. **M. Elsayed:** None. **R.S. Duman:** None. **F.M. Vaccarino:** None. **N. Salmaso:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.11/RR12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: This work was supported by a grant of £11.5M awarded to Professor Tony Bjourson from European Union Regional Development Fund (ERDF) EU Sustainable

Competitiveness Programme for N. Ireland; Northern Ireland Public Health Agency (HSC R&D) & Ulster Uni

Title: Towards proteomic differentiation of mental health disorders

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Abstract: Alterations in the inflammatory response have been studied extensively in connection with psychiatric disorders including depression. A small number of pro-inflammatory cytokines have been consistently reported, however the immune response is complex, involving both innate (inflammatory) and adaptive processes. The aim of this study was to conduct proteomic analyses to examine a broad spectrum of immune-related proteins in plasma samples from individuals with depression (n=15), schizophrenic patients (n=21) and healthy controls (n=16). Proteins were characterised with the O-Link proximity extension assay using the cardiovascular II and III, immune response and the inflammation panels to determine difference in protein concentrations between cohorts. The comparison of depression and healthy cases revealed significant differential abundance in the relative expression of 22 proteins between the depression and healthy groups, 7 downregulated and 15 upregulated across the four panels. Those upregulated proteins were enriched for inflammatory processes, and have been previously linked to chronic inflammatory conditions. Between schizophrenia and healthy controls, there were 143 proteins differently expressed, and similar to depression the upregulated proteins showed significant enrichment for inflammation. Finally, 99 proteins were found to be differentially expressed between depression and schizophrenia cases. A combined score of a selection of the top ranked differentially expressed proteins showed robust sensitivity and specificity to distinguish between the healthy and depression cases. These results indicate that a panel of inflammatory proteins could have clinical utility in screening for depression, and in differentiating between psychiatric disorders.

Disclosures: C.R. Lapsley: None. **S. Watterson:** None. **J. Brady:** None. **A.J. Bjourson:** None. **E.K. Murray:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.12/RR13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01 MH093320
NIH Grant R01 MH106978

Title: Investigating organic cation transporter 3 (OCT3) and plasma membrane monoamine transporter (PMAT) as targets for development of new antidepressant treatments for juveniles and adolescents

Authors: *M. A. BOWMAN[1], N. C. MITCHELL[1], R. FRASER-SPEARS[2], G. G. GOULD[1], L. C. DAWS[1]
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Abstract: Depression is a psychiatric illness that affects individuals of all ages, yet only two antidepressants are approved to treat depression in children and adolescents. Both belong to the selective serotonin reuptake inhibitor (SSRI) class. Moreover, children and adolescents are less effectively treated by SSRIs than adults. SSRIs block reuptake of serotonin via the high-affinity, low-capacity serotonin transporter (SERT). The resulting increase in extracellular serotonin is thought to initiate a cascade of downstream effects, which underlie the therapeutic utility of SSRIs. However, other transporters also clear serotonin from extracellular fluid, including the low-affinity, high-capacity organic cation transporters (OCTs) and plasma membrane monoamine transporter (PMAT). Our lab has shown that, in adults, decynium-22 (D22), an inhibitor of OCT1-3 and PMAT, produces antidepressant-like effects when SERT function is either genetically or pharmacologically impaired. However, whether OCTs or PMAT may be useful targets for therapeutic intervention in juveniles and adolescents remains unknown. In contrast to adults, our preliminary studies show that D22 has antidepressant-like effects in juvenile (postnatal day 21 (P21)) SERT+/+ mice, suggesting that OCTs and/or PMAT may be functionally upregulated in juvenile mice. Using both homogenate binding and autoradiography to quantify expression of D22-sensitive transporters, we found expression of D22-sensitive transporters to be increased in both P21 and adolescent (P28) mice, relative to adults (P90). Ongoing studies are utilizing genetic (i.e. OCT3, PMAT knockout mice) and pharmacological tools in efforts to parse out which D22-sensitive transporter(s) is/are driving the increase in [^{3}H]D22 binding in juveniles and adolescents. In addition, we are using *in vivo* high-speed chronoamperometry to determine the effect of D22 on serotonin clearance kinetics as a function of extracellular serotonin concentration. These studies will expand our understanding of differences in serotonin signaling among the juvenile, adolescent, and adult brain, and will aid in discovery of novel targets for the development of antidepressants with improved therapeutic efficacy for children and adolescents suffering from depression.

Disclosures: M.A. Bowman: None. **N.C. Mitchell:** None. **R. Fraser-Spears:** None. **G.G. Gould:** None. **L.C. Daws:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.13/RR14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH RO1 MH098554

Title: Innate immunity in the postmortem brain of depressed and suicide subjects: Role of toll-like receptors

Authors: *H. ZHANG[1], H. S. RIZAVI[4], X. REN[2], G. N. PANDEY[3]
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Abstract: Abnormalities of Toll-like receptors (TLRs) have been implicated in the pathophysiology of depression and suicide. Interactions of TLRs with pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) initiate signaling through myeloid differentiation primary response-88 (MyD88) and produce cytokines through the activation of the transcription factor nuclear factor kappa beta (NF-kB). We have earlier shown an increase in the mRNA expression of TLR3 and TLR4 in the prefrontal cortex (PFC) of depressed suicide (DS), depressed non-suicide (DNS) patients compared with normal control (NC) subjects. To examine if other TLRs are altered in postmortem brain, we have now determined the protein and mRNA expression of other TLRs (TLR1, TLR2, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10) in the PFC of DS, DNS, non-depressed suicide (NDS) and NC subjects. We determined the protein expression by Western blot and mRNA expression levels by real-time PCR (qPCR) in the PFC of 24 NC, 24 DS, 12 DNS and 11 NDS subjects. Combined with the previous study of TLR3 and TLR4, we found that the protein expression of TLR2, TLR3, TLR4, TLR6 and TLR10, and mRNA expression of TLR2, TLR3 was significantly increased in DS group compared with NC group. This study demonstrated that specific TLRs are altered in DS subjects, and hence some specific TLRs may be appropriate targets for the development of therapeutic agents for the treatment of suicidal behavior.

Disclosures: H.S. Rizavi: None. **X. Ren:** None. **G.N. Pandey:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.14/SS1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH RO1 MH098554

Title: Proinflammatory cytokines expression in the teenage suicide brain

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Abstract: Abnormalities of the immune function in depression and suicide are based in part on the observation of increased levels of proinflammatory cytokines in the serum and in postmortem brain of depressed and suicidal patients. Several studies suggest dysregulation of the immune system in suicide as increased microgliosis has been reported in postmortem brain of suicide subjects and increased levels of proinflammatory cytokines in the cerebrospinal fluid (CSF) of suicidal patients. In the previous studies we reported a significant increase in the protein and mRNA levels of cytokines such as TNF-α, IL-1 and IL-6. To further examine the role of proinflammatory cytokines in suicide we have now studied the protein expression of IL-8, IL-10, TNF-beta and IL-1ra in teenage suicide subjects. We determined the protein expression of IL-8, IL-10, TNF-beta and IL-1ra in the PFC of 17 teenage suicide victim and 17 normal control subjects. The postmortem brain tissues were obtained from the Maryland Brain Collection and the psychological autopsies were performed for the diagnosis of the subjects using DSM-IV-SCID. TNF-beta and IL-1ra protein expression was determined using Western blot technique and IL-8 and IL-10 protein expressions by ELISA, respectively. When we compared the protein expression of IL-8, we found that the IL-8 protein levels were significantly increased and IL-10 significantly decreased in teenage suicide victims compared with normal control subjects, while there was no difference in the protein expression of TNF-beta and IL-1ra in teenage suicide victims compared with normal control subjects. These results suggest that increased protein levels of IL-8 and decreased levels of IL-10 may be in part related to abnormalities of proinflammatory cytokines in the brain of suicide victims and that abnormalities of inflammatory markers are associated with suicide.

Disclosures: X. Ren: None. **H.S. Rizavi:** None. **H. Zhang:** None. **G.N. Pandey:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.15/SS2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01AT009169
VA BX001149

Title: Molecular mechanisms of antidepressant withdrawal

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Abstract: $G\alpha_s$ expression has been detected at high levels in membrane microdomains known as lipid rafts. Lipid rafts are characterized by their high cholesterol content, expression of caveolin-1 protein, and relative insolubility in weak ionic detergents. $G\alpha_s$ signaling is attenuated in lipid rafts due to impaired coupling to effectors, such as adenylyl cyclase. Consequently, cAMP levels decrease as $G\alpha_s$ lipid raft localization increases. Furthermore, $G\alpha_s$ lateral membrane mobility is reduced in non-raft regions due to association with the large, relatively immobile, adenylyl cyclase. These effects have been observed in post-mortem cortical tissue from depressed subjects, as well as animal models. Various drugs with known clinical antidepressant activity, including escitalopram, desipramine and ketamine, promote the translocation of $G\alpha_s$ out of lipid raft domains following chronic treatment. This translocation event produced by antidepressants with distinct primary targets may represent a common mechanism of action shared by antidepressant drugs.
Recent studies have highlighted the prevalence and severity of an antidepressant withdrawal syndrome following cessation of antidepressant drug use. This syndrome is highly dependent on the drug used, dosage, and duration of treatment. In this study, we probe the molecular mechanisms underlying these effects by observing changes related to $G\alpha_s$ localization following removal of the antidepressant drug from our model systems. Differences in the persistence of antidepressant induced signaling changes between these drugs may provide insight into the molecular basis of their associated symptoms following treatment cessation.
We investigate these effects using a live-cell cAMP accumulation assay, analysis of $G\alpha_s$ lateral membrane mobility with fluorescence recovery after photobleaching (FRAP), quantification of $G\alpha_s$ expression in lipid raft vs. non-raft regions, and detection of antidepressant drug accumulation in lipid rafts via mass spectrometry. These techniques are employed following extended treatment with an antidepressant drug, and again at various time points following drug removal. We then compare reversal of the antidepressant biosignature with known

pharmacokinetic parameters (such as lipid solubility and half-life) to determine whether a predictive profile of drug disposition can be obtained.

Disclosures: N. Senese: None. **J. Schappi:** None. **M.M. Rasenick:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.16/SS3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CIHR Doctoral Foreign Study Award

Title: Identifying glucocorticoid receptor mediated mechanisms of polygene-environment interactions involved in stress sensitivity

Authors: *S. PENNER-GOEKE[1], J. MARTINS[1], J. ARLOTH[1], S. RÖH[1], E. BINDER[1,2]
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Abstract: Despite the significant social and economic costs of stress related psychiatric disorders, the molecular mechanisms underlying these diseases remain poorly understood. Using an eQTL approach, previous research from our group successfully identified common functional genetic variants mediating stress sensitivity by altering the transcriptional response of stress-related genes (Arloth, 2015, Neuron). These variants are enriched in long-range enhancer regions in genes targeted by the glucocorticoid receptor (GR), a key transcription factor in the stress response system. Using the variants, a genetic profile score (PRS) was calculated describing transcriptional sensitivity to glucocorticoids (GR-PRS). Importantly, a derivative of this score could predict risk for major depressive disorder (MDD) and changes in neural circuit activity related to emotion-processing, highlighting the clinical importance of understanding the molecular mechanisms by which these variants alter transcriptional activity at GR target genes. We speculate that under stress conditions, these variants alter a number of different molecular mechanisms, namely GR binding, GR induced demethylation at GR binding sites, and chromatin interactions between transcriptional start sites and GR-driven enhancer regions, resulting in transcriptional changes in stress relevant networks.
MDD patient-derived LCLs harboring high and low GR-PRSes were selected. RNA-sequencing was performed to assess whether there were transcriptional differences in stress relevant networks in LCLs with high vs. low GR-PRSes upon treatment with the GR agonist, dexamethasone. Clustering of samples into high and low polygenic risk was observed when stress relevant genes were analyzed, but not when all differentially expressed genes were included. Next, the mechanisms by which these variants cause this altered transcriptional response upon activation of the stress response system will be identified, using GR-ChIP, a

methylation capture assay, and Capture-C. The relevance of the identified mechanisms will be validated in a neuronal context. Identification of specific mechanisms mediating stress sensitivity may represent new therapeutic targets for stress-related disease, such as MDD.

Disclosures: S. Penner-Goeke: None. **J. Martins:** None. **J. Arloth:** None. **S. Röh:** None. **E. Binder:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.17/SS4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: 1R01MH102238
UH3NS103550

Title: Neurophysiological biomarkers of the acute effect of subcallosal cingulate stimulation in treatment resistant depression

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Abstract: **Introduction**: Recent studies show that high frequency stimulation of the subcallosal cingulate (SCC) region using deep brain stimulation (DBS) has therapeutic effects in Treatment Resistant Depression (TRD). In this study, we utilize machine learning approach to investigate the acute effect of SCC DBS on local field potentials (LFPs). We investigated the spectral features of the LFP before and after initial exposure to high frequency stimulation. **Methods:** Bi-lateral LFPs were recorded intra-operatively from the SCC in five TRD patients. For analysis, we selected (1) 60 seconds of baseline recordings (prior to any stimulation), (2) 60s recordings after cessation of consecutive 130Hz- 2 min stimulation trials at each of the 4 contacts in the L and R hemisphere (post contact sweep, POST-CS) and (3) 60s recordings following cessation of 2 rounds of L, R and bilateral stimulation at the optimized contacts (post on-target stimulation POST-OT). We averaged the signal from the four left and right contacts separately and estimated the spectral power of each averaged signal in pre-defined frequency bands: θ(4-9Hz), α (9-12Hz), β (12-20Hz and 20-30 Hz) and γ (30-60Hz, divided into 10Hz frequency bins). These spectral features were used to train a logistic regression classifier with elastic net regularization to discriminate the baseline from post-stimulation states. **Results:** The classification accuracy was 0.7012± 0.0622 using left recordings and 0.7101 ±0.0481 on the right for the POST-CS and 0.7439± 0.0301 using left and 0.6929 ±0.0485 on the right for the POST-OT. In addition,

classifying between baseline and post-stimulation (POST-OT) state using spectral power features identified DECREASES in Left and Right beta band power (in the range of 20-30 Hz) and Right alpha INCREASES (9-12 Hz) by repeated on-target stimulation (N=5, $p<0.001$). These changes were not observed after consecutive stimulation of all single contacts (POST-CS). **Conclusion:** These findings demonstrate that initial stimulation of the SCC during implantation surgery evokes changes in neural dynamics. Significant decreases in Left and Right beta and increase in Right alpha were seen only after repeated stimulation at tractography-optimized contacts (POST-OT). These results define a putative biomarker of effective target engagement with SCC DBS in TRD with implications for tracking DBS effects using chronic LFP recordings.

Disclosures: M.S.E. Sendi: None. **V. Tiruvadi:** None. **A.C. Waters:** None. **H.S. Mayberg:** None. **B. Mahmoudi:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.18/SS5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Intra-individual alteration of plasma metabolites for bipolar disorder, a pilot study

Authors: *Y. KAGEYAMA[1], Y. DEGUCHI[2], T. KASAHARA[3], M. TANI[4], K. KURODA[5], K. INOUE[6], T. KATO[7]
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Abstract: There is an urgent need for biomarkers of bipolar disorder (BD) to optimize its treatment. Although various candidate biomarkers were reported, no one has been established. The purpose of the present study was to search for novel biomarkers using human plasma samples. We measured plasma metabolites, by capillary electrophoresis time-of-flight mass spectrometry, in the human participants with depressive state (dBD) and remitted state (rBD) of the same BD patients (10 pairs) and 10 healthy controls. The human study was approved by the ethics committees of Hannan Hospital, Osaka City University, RIKEN and conducted in accordance with the Declaration of Helsinki. From 110 metabolites with determined absolute concentrations, a nominal significant difference was found for two metabolites: sarcosine (mean (μM) ± SD; rBD, 3.4 ± 0.9; dBD, 2.5 ± 0.7, $P = 0.030$) and threonine (rBD, 116.3 ± 28.9; dBD, 150.4 ± 40.1, $P = 0.029$). To investigate the relationship between dBD patient's HAM-D suicide score and 110 metabolites, betaine concentration negatively correlated with the HAM-D suicide

score in dBD patients (ρ = -0.88, P = 0.001). Creatinine concentration positively correlated with the HAM-D suicide score in dBD patients (ρ = 0.64, P = 0.048). Sarcosine, betaine and creatine are included in glycine, serine and threonine metabolism pathway. Sarcosine is an intermediate and byproduct in glycine synthesis and degradation, and acts as N-methyl-D-aspartic acid (NMDA) receptor co-agonist. Based on its role on NMDA receptors, sarcosine has been studied in patients with schizophrenia and depression. We need further investigation in a larger number of samples to draw a conclusion whether sarcosine and other metabolites related to depressive episode and suicide symptom.

Disclosures: Y. Kageyama: None. **Y. Deguchi:** None. **T. Kasahara:** None. **M. Tani:** None. **K. Kuroda:** None. **K. Inoue:** None. **T. Kato:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.19/SS6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CAPES

Title: CB1 receptor antagonism prevents hyperlocomotion induced by the dopamine transporter inhibitor GBR12909

Authors: *J. D. BASTOS[1], N. FONT[1], A. L. TEIXEIRA[2], F. S. MACHADO[1], A. S. MIRANDA[1], F. D. MOREIRA[1]
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Abstract: INTRODUTION: Bipolar disorder is featured by occurrence of mania and depression episodes and the neurobiological mechanisms remain poorly understood. The inhibition of dopamine transporter by GBR12909 was recently proposed as animal model of mania. The endocannabinoid system modulates dopaminergic neurotransmission. AIMS: We tested the hypothesis that CB1 receptor antagonism prevents hyperlocomotion induced by GBR12909. METHODS: C57Bl6 male mice (25–30 g; 10/group) were pretreated with vehicle, lithium carbonate (50 mg/Kg) or the CB1 receptor antagonist AM251 (0,1; 0,3; 1 and 3 mg/Kg) and 20 min later they received injections of saline or GBR12909 (15 mg/Kg). Locomotion was analyzed immediately after the second injection by Any-maze Software. The data were analyzed by ANOVA followed by the Bonferroni test and p-value was set at 0.05. RESULTS: GBR12909 administration increased locomotion and positive control Lithium and the highest dose of AM251 inhibited this effect. CONCLUSION: GBR12909 administration seems to be a useful model of mania-like behavior, since it mimics some changes observed in patients undergoing a

mania state, moreover, CB1 antagonist can inhibit the effect of GBR12909.
Financial support: CAPES. CEUA nº 78/2014.

Disclosures: J.D. Bastos: None. **N. Font:** None. **A.L. Teixeira:** None. **F.S. Machado:** None. **A.S. Miranda:** None. **F.D. Moreira:** None.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.20/SS7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01MH083643
NIH Grant R34MH101365

Title: Combining transcranial magnetic stimulation and machine learning to predict treatment outcome in late-life depression

Authors: *J. I. LISSEMORE[1,4], R. ZOMORRODI[4], A. BHANDARI[4], Y. ZHANG[2], S. WANG[2], H.-Y. LO[2], W. CAO[2], A. J. BONNER[3], T. K. RAJJI[1,4], B. H. MULSANT[1,4], Z. J. DASKALAKIS[1,4], D. M. BLUMBERGER[1,4]
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Abstract: Background. Subjective reports continue to guide treatment decisions in psychiatry, and objective biomarkers capable of predicting individual treatment outcomes are needed. Most research on clinical biomarkers of depression has focused on patients under the age of 60, yet late-life depression (LLD) is prevalent and often treatment-resistant. Neurophysiological processes including cortical inhibition and plasticity, which can be assessed in humans non-invasively using transcranial magnetic stimulation (TMS), have been implicated in the neuropathology of depression. However, the neurophysiological correlates and predictors of treatment response in LLD remain unknown.
Objectives & Hypotheses. We investigated (i) within-subject changes in TMS measures of cortical inhibition and plasticity with pharmacotherapy, and (ii) the ability of pre-treatment cortical excitability and plasticity, together with clinical data, to predict treatment response in LLD. We hypothesized that cortical inhibition and plasticity would change significantly pre-post treatment in treatment responders, and that including pre-treatment TMS measures would improve the predictive accuracy of machine learning algorithms vs clinical data alone.
Methods. We used single- and paired-pulse TMS, combined with electromyography, to measure cortical excitability and plasticity before and after 12 weeks of open-label venlafaxine XR treatment in 76 LLD patients (49F/27M, 67 ± 6.5 years of age). First, a machine learning model

(e.g. logistic regression, random forest, k-NN or SVM) was chosen to assess neurophysiological biomarkers of treatment response, then a genetic algorithm was used to select the most predictive features for the chosen model.
Results. No significant pre-post treatment changes in cortical inhibition or plasticity were observed in treatment responders. Based on a genetic algorithm, the features most predictive of treatment response were TMS measures of neuroplasticity and cortical excitability, and clinical measures of symptom severity, treatment resistance and duration of depressive episode. When applied together, this feature set achieved >75% predictive accuracy in k-NN and SVM models.
Conclusions. Our findings indicate that machine learning models that combine clinical data with baseline TMS measures may help predict the response of LLD patients to antidepressant treatment. Going forward, additional objective brain-based features may improve prediction accuracy, and thus treatment outcomes and efficiency, as we transition towards a precision medicine approach in psychiatry.

Disclosures: J.I. Lissemore: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Brainsway Ltd., Magventure Inc., Indivior. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen Inc.. F. Consulting Fees (e.g., advisory boards); Sunovion Inc.. **R. Zomorrodi:** None. **A. Bhandari:** None. **Y. Zhang:** None. **S. Wang:** None. **H. Lo:** None. **W. Cao:** None. **A.J. Bonner:** None. **T.K. Rajji:** None. **B.H. Mulsant:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Bristol-Myers Squibb, Eli-Lilly, Pfizer. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); General Electric. **Z.J. Daskalakis:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Brainsway Ltd., Magventure Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen Inc.. F. Consulting Fees (e.g., advisory boards); Sunovion Inc. **D.M. Blumberger:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Brainsway Ltd., Magventure Inc., Indivior.

Poster

231. Depression and Bipolar Disorders: Treatment and Drug Discovery

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 231.21/SS8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R41MH113398
NIH Grant RO1 AT009169
NIH Grant T32 MH067631
VA Grant BX001149-06

Title: Membrane localized tubulin shows decreased alpha-tubulin acetylation in postmortem brain tissue from depressed suicides: Cytoskeletal dynamics and depression

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Abstract: Recent studies suggest that post-translational modifications of tubulin, such as acetylation, result in altered microtubule dynamics. Furthermore, tubulin interacts closely with $G\alpha_s$, the G-protein responsible for activation of adenylyl cyclase. $G\alpha_s$, when ensconced in lipid-rafts, couples less effectively with adenylyl cyclase to produce cAMP, and postmortem human brain tissue from depressed suicide subjects showed increased localization of $G\alpha_s$ in lipid-raft domains. Conversely, all antidepressants tested thus far translocate $G\alpha_s$ from lipid rafts to a non-raft fraction of the membrane where they enjoy a more facile coupling to adenylyl cyclase. A recent study revealed that tubulin anchors $G\alpha_s$ to lipid-rafts and that treatment of cells with histone deacetylase-6 (HDAC6) inhibitors, as well as conventional antidepressants, decreased the proportion of $G\alpha_s$ complexed with tubulin within lipid-rafts. Therefore, we suggested that deacetylated-tubulin might be more prevalent in depression, as it would provide more binding sites for Gαs in lipid rafts. In this study, we examined α-tubulin acetylation in brain homogenate, plasma-membrane and lipid-raft/non-raft membrane domains from prefrontal cortex of control subjects and suicide cases with confirmed major depression. Lipid-rafts were isolated by differential-detergent-extraction, and tubulin (both acetylated and non-acetylated) was determined by immunodetection. While there was no change in total α-tubulin acetylation between control vs depression, plasma-membrane associated structures showed significant decreases in acetyl-α-tubulin in depression vs. controls. These data suggest that during depression, membrane-localized tubulin maintains a lower acetylation state, sequestering more $G\alpha_s$ in lipid-raft domains, where it is less likely to activate adenylyl cyclase. These data reveal a molecular mechanism for lipid-raft sequestration of $G\alpha_s$ that might be exploited for purposes of diagnosis and treatment of mood disorders

Disclosures: H. Singh: None. **J. Chmura:** None. **R. Bhaumik:** None. **G.N. Pandey:** None. **M.M. Rasenick:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PAX Neuroscience.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.01/SS9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Ministry of Science and Technology of China Grant 2015CB559200
National Natural Science Foundation of China Grant 81371432
Beijing Natural Science Foundation Grant 7182087

Title: Epigenetic regulation of stress-induced depressive behaviors

Authors: *L. Y. QING, L. M. HUA, H. ZHUO
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Abstract: Major depressive disorder (MDD) is a prevalent and life-threatening illness in modern society. The susceptibility to MDD is profoundly influenced by environmental factors, such as stressful lifestyle or traumatic events, which could impose maladaptive transcriptional program through epigenetic regulation. However, the underlying molecular mechanisms remain elusive. Here we report that stress-susceptible rodents exhibit lower levels of histone crotonylation in the medial prefrontal cortex (mPFC), which is concurrent with upregulation of chromodomain Y-like (CDYL), a crotonyl-CoA hydratase and histone methyllysine reader. Overexpression of CDYL in the prelimbic cortex (PL), a sub-region of mPFC, increases microdefeat-induced social avoidance and anhedonia in mice. Conversely, knockdown of CDYL in PL prevents chronic social defeat stress-induced depressive-like behaviors. Mechanistically, we show that CDYL inhibits structural synaptic plasticity mainly by transcriptional repression of neuropeptide VGF, and this activity is dependent on its dual effect on regional histone crotonylation and H3K27 tri-methylation on the VGF promoter. Together, our data indicate CDYL plays a critical role in regulating stress-induced depressive-like behaviors, providing a potential therapeutic target for MDD.

Disclosures: L.Y. Qing: None. **L.M. Hua:** None. **H. Zhuo:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.02/SS10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: FWF grants P25912-B23 and W1241-B18
EU grant 613979 (MyNewGut)

Title: Antibiotics block depression-like behavior induced by high fat diet in mice

Authors: *A. M. HASSAN, A. FARZI, G. ZENZ, P. HOLZER
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Abstract: Objective and rationale: Unfavorable nutrition and obesity are risk factors for developing depression. In rodents, obesity induced by high fat diet (HFD) is associated with depression-like behavior (DLB). The intestinal microbiome (IM) is required for the development of obesity and associated metabolic and endocrine changes in response to HFD, but the role of the IM in HFD-induced DLB remains uncertain. In this work, we used a cocktail of non-absorbable antibiotics (Abs) to deplete the IM and evaluated the effect of this intervention on the behavioral and endocrine changes induced by HFD.
Methods: 40 male C57Bl/6J mice were allocated to 4 groups: (1) control diet (12 kJ% from fat) + water, (2) control diet + Abs, (3) HFD (60 kJ% from fat) + water, (4) HFD + Abs. The Abs included meropenem (1 mg/ml), neomycin (5 mg/ml) and vancomycin (0.3 mg/ml) in the drinking water. The administration of Abs started 5 days before feeding with HFD began, both interventions being continued for 4 weeks. Subsequently a battery of behavioral tests was used to assess anxiety- and depression-like behaviors, after which the mice were sacrificed and heart blood was collected. Insulin, glucagon-like peptide (GLP-1), and leptin were measured in blood plasma with a multiplex immunoassay. Statistical analysis was performed with two-way analysis of variance using diet and Abs as the two variables.
Results: Mice receiving HFD + Abs gained less weight compared to mice receiving HFD + water but still gained more weight compared to control diet + Abs. In the absence of Abs, HFD induced a DLB as revealed by anhedonia in the sucrose preference test and reduced motivational behavior in the splash test along with an increase in plasm leptin. In contrast, in the presence of Abs, HFD did not affect DLB and plasma leptin. HFD reduced locomotion in the open field and increased plasma insulin independently of Abs, while Abs leaded to an anxiolytic effect in the elevated plus maze test and increased plasma GLP-1 independently of the type of diet.
Conclusion: Abs prevent the DLB and the increase in plasma leptin induced by HFD. This attributes the IM an essential role in HFD-induced DLB. In addition, IM depletion by Abs has an anxiolytic effect and increases plasma GLP-1 independently of the diet.

Disclosures: A.M. Hassan: None. **A. Farzi:** None. **G. Zenz:** None. **P. Holzer:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.03/SS11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CONACYT 485970

Title: Participation of the monoaminergic systems in the antidepressant-like effect of a histamine H_3 receptor inverse agonist in adolescent male mice

Authors: *H. MANCHA GUTIÉRREZ, C. LOPEZ-RUBALCAVA
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Abstract: Nowadays, the pharmacological application of histamine related agents may bring forth new prospects for the therapy of several central nervous system (CNS) disorders, such as depression. Previous works have shown that histamine H_3 receptor (H_3R) inverse agonists have an antidepressant-like effect in adult rodents. However, there is no evidence of its effect on adolescent rodents, and its mechanism of action is not entirely clear. The H_3R is a $G_{i/0}$ protein coupled receptor with a high degree of constitutive activity; it is the most abundant histamine receptor in the CNS and is mainly expressed in the hypothalamus, cerebral cortex, striatum and hippocampus. The H_3R is found like a presynaptic receptor on terminal axons of histaminergic neurons (autoreceptors), as well as on terminal axons of serotonergic, noradrenergic and dopaminergic neurons (heteroreceptors). Our aim is to analyze the antidepressant-like effect of clobenpropit (H_3R inverse agonist) and study the possible mechanisms that underlay this effect, in adolescent male mice of the Swiss Webster (SW) strain. To achieve it, we used the forced swim test (FST) to evaluate the effect of clobenpropit in adolescent intact mice and in adolescent mice that previously were treated with the serotonergic (5,7-DHT) or noradrenergic (DSP4) or dopaminergic (6-OHDA) neurotoxins. Also, we analyzed the effect of clobenpropit and the neurotoxins on the tissue content of monoamines in the prefrontal cortex (PFC) by high performance liquid chromatography (HPLC). We found that clobenpropit (5 mg/kg; i.p) had an antidepressant-like effect characterized by a decrease in immobility behavior and an increase in both swimming and climbing behaviors. Also, clobenpropit increases the tissue content of serotonin (5-HT), noradrenaline (NA) and dopamine (DA) in the PFC. The pre-treatment with each of the neurotoxins blocked the antidepressant-like effect of clobenpropit in the FST and decreased the tissue content of each monoamine in the PFC. Together, our results show that clobenpropit has an antidepressant-like effect in adolescent male mice, and suggest the participation of serotonergic, noradrenergic and dopaminergic systems in its mechanism of action.

Disclosures: H. Mancha Gutiérrez: None. **C. Lopez-Rubalcava:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.04/SS12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01 MH105675

Title: Loss of forebrain 5-HT_{1A} heteroreceptors results in increased stress-reactivity and decreased motivation

Authors: A. GARCIA[1], I. ALY[2], A. DRANOVSKY[3], *E. D. LEONARDO[4]
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Abstract: 5-HT_{1A} receptors in particular, and the serotonin (5-HT) system in general, have been implicated in the etiology and treatment of anxiety and depressive disorders. The 5-HT_{1A} receptor exists in two major forms: as an autoreceptor in 5-HT neurons in the raphe nuclei, where it regulates 5-HT tone, and as heteroreceptor in non-5-HT neurons where it mediates hyperpolarizing responses to released 5-HT. Previous work from our lab demonstrated that mice lacking all 5-HT_{1A} receptors or only raphe autoreceptors display prominent conflict-based anxiety. More recently, we have shown that mice lacking forebrain 5-HT_{1A} heteroreceptors (Hetero-KO) fail to develop sucrose preference and demonstrate increased behavioral despair in the forced-swim test. Remarkably, selective loss of 5-HT_{1A} heteroreceptors in the medial prefrontal cortex (mPFC) is sufficient to recapitulate this phenotype. However, whether and how forebrain 5-HT_{1A} heteroreceptors might regulate other depression-related phenotypes, like motivation, stress reactivity or cognition remains unanswered. Having seen a failure to develop sucrose preference, we asked whether Hetero-KO mice show additional evidence of either anhedonia or motivational deficits by using a progressive ratio reinforcement paradigm. We find that male Hetero-KO mice have fewer lever presses and earn fewer rewards in a PR+2 and PR+5 reinforcement schedule. In contrast, when given a choice to press a lever for milk, versus consume freely available chow, the control mice pressed more for milk and eat less chow, while Hetero-KO mice pressed the lever less and eat more chow. We next tested Hetero-KO mice in an inescapable shock paradigm, followed by an avoidance task and found that Hetero-KO male mice have a longer latency to escape and have significantly more escape failures, suggesting that they are more susceptible to developing learned helplessness. Finally, as mPFC function is affected in the Hetero-KO animals, we tested working memory in a delayed match to sample T-maze paradigm. Using a short delay, we find no significant differences between groups. We are currently testing a longer delay. Taken together our data suggest that Hetero-KO mice are less willing to work for a preferred reward, suggesting that loss of forebrain 5-HT_{1A} heteroreceptors results in a specific motivational deficit. Further, decreased 5-HT signaling through forebrain 5-HT_{1A} heteroreceptors make male mice more susceptible to a stressor as they adopt a passive coping style. Finally, we are currently determining whether selective loss of mPFC 5-HT_{1A} heteroreceptors recapitulates these phenotypes.

Disclosures: A. Garcia: None. **I. Aly:** None. **A. Dranovsky:** None. **E.D. Leonardo:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.05/SS13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CNPq 428815/2016-2
CAPES
AFIP

Title: Social defeat stress: Impacts on ethanol reward, corticosterone secretion and brain monoamines

Authors: *I. M. QUADROS[1], C. A. FAVORETTO[2], Y. C. NUNES[2], G. C. MACEDO[2]
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Abstract: Introduction: Chronic exposure to stress may dysregulate the hypothalamic-pituitary-adrenal axis and brain monoamines, contributing to the development of stress-related disorders, including drug and alcohol dependence. The present study assessed ethanol-induced corticosterone responses and brain monoamine levels in mice previously submitted to continuous social defeat stress.
Methodology: Male Swiss mice were exposed to a 10-day continuous social defeat protocol, with daily confrontations with an aggressive male resident. Ten days after the final defeat, mice were tested for locomotor response to an ethanol injection (2.2g/kg; i.p.) or saline. Thirty minutes after the locomotor test, blood was collected for determination of plasmatic corticosterone, and brains were dissected for determination of tissue monoamines.
Results: Socially stressed mice failed to show a stimulating locomotor response to ethanol, while controls displayed ethanol-induced stimulation ($p<0.05$). Ethanol administration induced increases in plasma corticosterone ($p<0.05$), but to a lesser extent in defeated mice ($p<0.05$). Monoamine levels were affected by defeat stress exposure, and also by ethanol, in different brain regions. In the hypothalamus, social stress promoted reduced levels of dopamine, noradrenaline and serotonin ($p<0.05$). In the frontal cortex, defeated mice presented reduced serotonin and dopamine levels ($p<0.05$). In the striatum, ethanol treatment increased dopamine levels in control mice ($p<0.05$), but failed to do so in defeated mice.
Conclusion: Our results suggest that chronic exposure to continuous defeat stress blunted ethanol-induced locomotor stimulation, and also reduced ethanol-induced corticosterone secretion. Social stress promoted differential reductions in brain monoamine contents in the hypothalamus, frontal cortex and striatum.
Acknowledgments: Funded with grants from CNPq (#428815/2016-2), CAPES, FAPESP (#2014/14623-2) and AFIP.

Disclosures: C.A. Favoretto: None. **Y.C. Nunes:** None. **G.C. Macedo:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.06/SS14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Effects of depression-like behavior in alpha CGRP transgenic mice over-expressing mice

Authors: *N. HASHIKAWA-HOBARA[1], A. OTSUKA[2], R. YAMAMOTO[2], T. FUKUNAGA[2], N. HASHIKAWA[2]
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Abstract: Calcitonin gene-related peptide (CGRP) plays an important role in several physiological processes such as vasodilation, cardiovascular homeostasis and transmission of pain. We have been reported CGRP administration into the mice brain before the beginning of stress exposure, normalized the behavioral dysfunctions. In the present study, the role of highly expressing an *αCgrp* gene steadily was investigated using transgenic (Tg) mice over expressing αCGRP. These Tg mice display hypotension, increase in thermal reaction and downregulation of the cardiovascular system, presumably due in increased levels of αCGRP. The locomotor and rearing activity in the open field test were significantly decreased in 8-week-old Tg mice when compared to wild-type mice. αCGRP Tg mice also display depression-like behavior in forced swim test and tail suspension test but not sucrose preference test. Furthermore, Tg mice revealed anxiety-like response rather than wild-type mice in the elevated plus maze test.These results indicate that we establish αCGRP overexpression mice, which are genetic model mice of anxiety but not depressive-like behavior.

Disclosures: N. Hashikawa-Hobara: None. **A. Otsuka:** None. **R. Yamamoto:** None. **T. Fukunaga:** None. **N. Hashikawa:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.07/TT1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH IRP Grant Z01 MH001090

Title: Adaptive immune signaling at the meningeal barrier: Neuroimmune interactions underlying stress-induced mood disruption

Authors: *S. L. KIGAR[1], S. J. LISTWAK[1], D. KIM[1], V. H. SUN[2], A. ELKAHLOUN[3], M. L. LEHMANN[1], M. HERKENHAM[1]
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Abstract: Major depressive disorder (MDD) is strongly correlated with increased peripheral inflammation, but basic mechanisms by which the immune system influences the brain under these conditions remain largely unknown. The blood brain barrier (BBB) in particular prevents free exchange of peripheral immune signals with the central nervous system (CNS); however, relatively high numbers of $CD4^+$ T (Th) cell lymphocytes extravasate across the BBB under homeostatic conditions to gain direct access to the CNS via cerebrospinal fluid (CSF). Whereas Th cells have access to the CNS from within this space, there is no evidence to suggest they reside in healthy brain parenchyma, and they must therefore transmit information to the brain indirectly. Greater understanding of this process is critical to exploit peripheral immunity for MDD treatment.
I focus on the meninges—which envelop the brain, contain the BBB, and confine the CSF—as a key interface between the CNS and peripheral immune system. My hypothesis, supported by flow cytometric, bioinformatic, and IHC analyses, is that Th cells are recruited to the meninges to facilitate the repair of neurovascular damage accumulated during stress. Once inside, they release signaling factors that alter neurobiology. To test this idea, I use chronic social defeat (CSD) stress in mice, which reliably induces depressive- and anxious-like behavior and leads to elevated levels of peripheral inflammation, consistent with a subset of patients exhibiting symptoms of MDD. CSD triggered increased infiltration of T cells into the meninges, accompanied by the robust peripheral skewing of T cells towards a pro-inflammatory phenotype. Multicolor flow cytometry and single-cell RNA sequencing analysis are being used to determine the Th cell variants most closely associated with CSD stress, what resident meningeal cells are responsible for their recruitment, and what CNS-mediated events precipitate an immune reaction. Candidates generated will be further studied for their role in inducing or alleviating the depressive effects of CSD stress.

Disclosures: S.L. Kigar: None. **S.J. Listwak:** None. **D. Kim:** None. **V.H. Sun:** None. **A. Elkahloun:** None. **M.L. Lehmann:** None. **M. Herkenham:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.08/TT2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NRF-2011-0019227
NRF-2013M3C7A1056732
NRF-2012M3A9B6055378
NRF-2011-0019229
NRF-2013R1A1A2060527

Title: Mice show depression-like behaviors after inescapable electric foot shock regardless to active avoidance results

Authors: *J. KIM, S. YANG, H. LEE, H. KIM
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Abstract: Among the many depressive animal models, the learned helplessness paradigm has long been used in studies involving depressive symptoms. Especially in mice, an unpredictable and inescapable electrical foot shock is used to induce learned helplessness. In general, the learned helplessness of the animal is assessed by whether they show defect in the active avoidance test (learned helplessness, LH) or not (non-learned helplessness, NLH). Here we investigated whether mice with LH or NLH exhibited depressive symptoms including anhedonia, anxiety and despair. We showed that both LH and NLH mice who received uncontrollable foot shock showed anhedonia and anxiety when compared to control mice, but not despair. Notably, the mice who underwent inescapable foot shock showed similar behavior regardless of whether they showed LH or NLH. Since both LH and NLH mice showed only anhedonia and anxiety but not despair, it may be generally inappropriate for assessment of classic depression behavioral symptoms. In conclusion, an uncontrollable shock can lead to depression-like behavior regardless of state of helplessness.

Disclosures: J. Kim: None. **S. Yang:** None. **H. Lee:** None. **H. Kim:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.09/TT3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MH099580-01

Title: Glucocorticoids regulation of norepinephrine turnover in limbic brain regions

Authors: *D. F. BARNARD, K. M. GABELLA, A. KULP, P. DUGAN, J. D. JOHNSON
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Abstract: Catecholamines, principally norepinephrine, released in response to stress are known to mediate brain IL-1β production via beta-adrenergic receptors (β-AR). Increases in brain cytokines, particularly IL-1β, as a result of stress exposure, can precipitate depression. Thus, understanding how norepinephrine is regulated is critical to better understand the mechanisms of stress and the role they play in mediating neuro-inflammatory disorders such as depression. Research by our lab has shown that blocking glucocorticoid synthesis by metyrapone results in a significant increase in IL-1β production in the hippocampus, amygdala, and hypothalamus. Interestingly, treatment with propranolol, a β-adrenergic receptor antagonist, inhibits this increase suggesting glucocorticoids may be playing a role in modulating noradrenergic neurons. Here we examine the role glucocorticoids have on norepinephrine turnover in limbic brain regions including the medial prefrontal cortex, amygdala, hypothalamus, and hippocampus. Male Fisher 344 rats were given subcutaneous injections of either 100mg/kg of metyrapone or saline. Two hours following drug administration, norepinephrine turnover was measured in limbic brain areas. Metyrapone treatment resulted in a significant increase in norepinephrine turnover in the mPFC and trended towards significance in the hypothalamus. While metyrapone treatment resulted in higher norepinephrine turnover in both the amygdala and hippocampus it did not reach significance. Future studies will add additional animals to see if trends reach significance and uncover the role glucocorticoids have on modulating stressed-induced norepinephrine turnover. Results indicate that glucocorticoids have a strong inhibitory effect on norepinephrine levels in the mPFC and may be responsible for the modulation of brain cytokines following stress exposure.

Disclosures: D.F. Barnard: None. **K.M. Gabella:** None. **A. Kulp:** None. **P. Dugan:** None. **J.D. Johnson:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.10/TT4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: This work was supported in part by the Natural Science Foundation of Beijing (no. 7162101)

Title: Gender specific effects of environmental stress on depression - like behaviors and endocrinology in adolescent rats

Authors: *S.-X. LI[1], M. YUAN[2], L.-J. LIU[3], C.-Y. WANG[2]
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Abstract: Healthy lifestyle habits, especially at younger ages, are important both for current health and also for prevention of diseases. Over the past 3 decades, children's and adolescents' lifestyles have changed, with dramatic increases in screen based media use, sedentary behaviorw, which are often acompanied by irregular sleep and eating time, and the associated adverse health outcomes. In the present study, we investigated the effects of environmental stress (ES) on the depression - like behaviors and the plasma concentration of corticosterone (CORT), cholecystokinin (CCK), leptin and neuropeptide Y (NPY) in male and female adolescent rats. We found that ES led to depression - like behaviors in female but not in male adolescent rats. ES induced a significant difference of plasma CORT in female rats ($F2, 20 = 6.19$, $p = 0.01$) and in male rats ($F2, 20 = 5.10$, $p = 0.019$). Plasma CORT in both LF and HF group significantly increased in female rats and decreased in male rats compared with CON group (p values < 0.05), respectively. A significant difference in plasma leptin in both gender, respectively, was found ($F2, 19 = 4.57$, $p = 0.026$ for female rats; $F2, 20 = 4.85$, $p = 0.021$ for male rats). Plasma leptin in both LF and HF group significantly increased compared with CON group for both genders (p values < 0.05). A significant difference in plasma CCK and NPY in female but not in male rats was found ($F2, 19 = 5.16$, $p = 0.018$ for CCK, $F2, 19 = 6.8$, $p = 0.007$ for NPY, in female rats; $F2, 20 = 0.14$, $p = 0.89$ for CCK, $F2, 20 = 2.05$, $p = 0.157$ for NPY, in male rats). ES induced a significantly increased in plasma CCK and decreased in plasma NPY in both LF and HF group in female rats compared with CON group, respectively (p values < 0.05). Our findings indicated that increased CORT and decreased NPY may be involved in the depression - like behaviors in female rats induced by ES.

Disclosures: S. Li: None. **M. Yuan:** None. **L. Liu:** None. **C. Wang:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.11/TT5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant MH112861

Title: Effects of chronic stress paradigms on instrumental behaviors in mice

Authors: *A. DIETERICH[1], M. L. PHAN[3], B. A. SAMUELS[2]
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Abstract: Exposure of rodents to chronic stress may provide behavioral phenotypes that are relevant experimental systems for mood disorders such as major depressive disorder. One such paradigm involves chronic corticosterone (CORT) administration, which impairs the acquisition

of instrumental response for food pellets and lowers the breakpoint ratio in the progressive ratio test, a measure indicative of motivation. Social defeat stress (SDS) is another frequently used paradigm. SDS reduces the sensitivity to a devalued outcome in satiety-specific outcome devaluation and contingency degradation procedures. To further clarify the behavioral effects of these chronic stress paradigms in mice, we assessed the behavioral effects of both CORT and SDS in separate groups of adult male C57BL/6J mice. We used outcome devaluation and progressive ratio tests to assess the effects of these chronic stress paradigms on instrumental behavior. For instrumental acquisition, mice were trained to lever press for a food pellet reward on a fixed ratio 1 schedule. In outcome devaluation, mice were trained on a random ratio 20 schedule, before undergoing satiety-based outcome devaluation as well as contingency degradation. In progressive ratio, mice were trained to stably respond on a variable ratio 3 schedule, before undergoing the progressive ratio test, where the response requirement to obtain a reinforcer increased linearly (1, 5, 9, X+4) until the mice ceased to respond for 5 minutes, or 4 hours. The CORT group showed impaired lever press acquisition across the 8 days of training compared to the Vehicle group. In the outcome devaluation test, CORT mice failed to show sensitivity to the devalued condition relative to the valued condition. However, Vehicle mice displayed a trend toward reduced responding for the devalued condition in the test. In the progressive ratio test, both CORT and SDS reduced breakpoint ratio and active lever presses. These results suggest that CORT and SDS have a similar effect on instrumental behavior learning and performance in mice.

Disclosures: A. Dieterich: None. **M.L. Phan:** None. **B.A. Samuels:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.12/TT6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CNRS UPR3212
Neurotime Erasmus Mundus
University of Strasbourg
NARSAD Young Investigator Grants (18893 and 24736) from the Brain & Behavior Research Foundation
EUR Euridol (ANR)

Title: Role of the anterior cingulate cortex in the comorbidity of chronic pain and mood disorders: Electrophysiological and molecular bases

Authors: *I. YALCIN-CHRISTMANN[1,2], M. HUMO[2], J. SELLMEIJER[2], F. BARTHAS[2], C. FILLINGER[2], S. HUGEL[2], E. WALTISPERGER[2], V. MATHIS[2], R. GILSBACH[4], L. HEIN[4], C.

BELZUNG[5], A. AERTSEN[6], P. VEINANTE[3], M. BARROT[2]
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Abstract: Pain associates both sensory and emotional aversive components, and often leads to mood disorders when it becomes chronic. We characterized, in a mouse model, the long-term development of these sensory and aversive components as well as anxiodepressive-like consequences of neuropathic pain and determined their electrophysiological impact on the anterior cingulate cortex (ACC, cortical areas 24a/24b). We showed that these symptoms of neuropathic pain evolve in different time courses following nerve injury. *In vivo* electrophysiological recording evidence increased firing rate and bursting activity within the ACC when anxiodepressive-like consequences developed and this hyperactivity persists beyond the period of mechanical hypersensitivity. Optogenetic inhibition of the ACC hyperactivity alleviated the aversive and anxiodepressive-like consequences of neuropathic pain while the activation of the ACC was sufficient to induce depressive-like behaviors, indicating that these behaviors are underpinned by ACC hyperactivity. In parallel, we also aimed at identifying key ACC molecular factors subserving anxiodepressive behaviors. Global gene expression changes in the ACC highlighted the overexpression of a critical regulator of the mitogen-activated protein kinase (MAPK) pathway, the MAPK Phosphatase-1 (MKP-1). This upregulation is associated with the presence of transcriptionally active chromatin marks (acetylation) at its proximal promoter region, as well as an increased cAMP response element (CRE)-mediated transcriptional activity, and phosphorylation of CREB and ATF. MKP-1 overexpression is also observed with the UCMS and repeated ACC optogenetic stimulation, and is reversed by chronic fluoxetine treatment. Moreover, a knock-out, an antagonist or a local silencing of MKP-1 attenuates depressive-like behaviors, pointing to a causal role of this phosphatase in depression. Altogether, these data shows that the ACC is one of the critical hub of the comorbidity of chronic pain and depression.

Disclosures: I. Yalcin-Christmann: None. **M. Humo:** None. **J. Sellmeijer:** None. **F. Barthas:** None. **C. Fillinger:** None. **S. Hugel:** None. **E. Waltisperger:** None. **V. Mathis:** None. **R. Gilsbach:** None. **L. Hein:** None. **C. Belzung:** None. **A. Aertsen:** None. **P. Veinante:** None. **M. Barrot:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.13/TT7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: SATT AxLR /Maturation grant (Montpellier, France)

Title: Training in an enriched and complex environment, the Hamlet test, alleviates chronic corticosterone-induced depressive status in mice

Authors: *L. CROUZIER[1], D. GILABERT[1], I. MENDEZ-DAVID[2], A. M. GARDIER[2], D. J. DAVID[2], T. MAURICE[1]
[1]INSERM UMR-S1198, Montpellier, France; [2]CESP/UMR-S1178, Univ. Paris-Sud, Fac Pharmacie, Inserm, Univ. Paris-Saclay, Châtenay-Malabry, France

Abstract: Anxiety/depressive status can be induced in C57Bl/6j mice by a chronic corticosterone treatment (CORT; 35 µg/ml in drinking bottle for 4 weeks; David et al., Neuron 2009; 62:479-93). Chronic antidepressant treatment reversed the behavioral alterations and inhibition of hippocampal neurogenesis induced by CORT. Moreover, CORT-induced anxio-depressive phenotype is associated with cognitive deficits affecting several memory processes, assessed using behavioral tests measuring episodic, associative and visuo-spatial memory (Darcet et al., Front Behav Neurosci 2014;8:136). As enriched environment (EE) stimulates brain plasticity, hippocampal neurogenesis and memory processes, we analyzed the impact of CORT in mice trained in a complex enriched environment, the Hamlet test (Crouzier et al., Neurobiol Learn Mem 2018;149:118-34). The test is a novel behavioral analysis appliance, fully automatized (ViewPoint, Lissieu, France), that provides a complex environment for testing topographical memory in mice. The apparatus mimics a small village with a central agora and streets expanding from it, leading to functionalized houses (Drink, Eat, Hide, Run, Interact). EE is induced by training animals in the Hamlet, in groups of 6/8 individuals, during 4 h per day, for several weeks. Memory can be tested by depriving mice from water and testing their ability to locate the Drink house. Four groups were analyzed (Veh- or CORT-treated and non-trained or trained). Behavioral outcomes during training, general activity in open-field, recognition and topographic memories and hippocampal neurogenesis were analyzed. CORT treatment did not impact general exploration of the houses during training but prevented correct topographical representation of the Hamlet since probe test was altered: mice failed to retrieve the Drink house location when tested in water-deprived condition. However, hypolocomotion, increased anxiety/depression-like phenotype and recognition memory deficits induced by CORT were alleviated in trained mice. Analysis of adult hippocampal neurogenesis, demonstrated no consequence in newborn cell proliferation (total KI67 labeled cells) in trained animals but a

preserved effect of training in CORT-treated mice on dendritic length and intersections of newborn neurons using Scholl analyses. These data show that training mice in an enriched and complex environment represented by the Hamlet alleviated several locomotor, anxiety/depression and memory alterations induced in the depressive model and suggest that Hamlet training may help to address biological differences in environment-impoverished *vs* environment unrelated depressions.

Disclosures: L. Crouzier: None. **D. Gilabert:** None. **I. Mendez-David:** None. **A.M. Gardier:** None. **D.J. David:** None. **T. Maurice:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TM is inventor of the Hamlet test patent.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.14/TT8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Development of a novel rodent model of epilepsy and depression comorbidity

Authors: *B. S. REIVE, K. ROSIN, T. FRANCIS, A. KALININA, N. M. FOURNIER
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Abstract: Depression represents one of the most frequent and disabling comorbidities associated with epilepsy. Seizure disorders occur with a ~5-fold greater frequency among individuals with a history of depression (or even a family history of depression) than the general population. However, despite the frequent association of depression and epilepsy, the neurobiological mechanisms underlying the co-occurrence of these conditions remain poorly understood. Research using animals models offer a unique opportunity to begin exploring shared pathophysiological mechanisms responsible for the association between epilepsy and depression. In the present study, we demonstrate that rapid amygdala kindling can produce robust changes in depressive-like behaviour. In our study, rats underwent two cycles of rapid kindling (40 stimulations administered over two days, i.e. 20 stimulations per day) carried out 1-week apart resulting in each subject receiving a total of 80 electrical stimulations. A few days after the final stimulation, rats were examined on a series of behavioural tests that measure anhedonia, exploration, anxiety, and depressive behaviours. We found that rapid kindling induced hyperactivity during exploration of an unfamiliar environment along with disruptions in open arm entries in the elevated plus maze. In addition, rapid kindling reduced sucrose consumption and produced greater immobility over the last 5 minutes of a 15-minute forced swim test suggesting that repeated limbic seizures increase vulnerability to develop depressive-like behaviours. Future research will examine the impact of stress on the emergence of depression

after kindling as well as explore potential molecular mechanisms. Together, these findings demonstrate that rapid kindling can provide an effective method for exploring the neurobiological substrates underlying epilepsy and depression comorbidity raising the hope to discover novel therapeutic agents for the treatment of these conditions.

Disclosures: B.S. Reive: None. **K. Rosin:** None. **T. Francis:** None. **A. Kalinina:** None. **N.M. Fournier:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.15/TT9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: The Canadian Biomarker Integration Network in Depression (CAN-BIND) under the umbrella of the Ontario Brain Institute.

Title: The combination of escitalopram and aripiprazole: Focus on the 5-HT_{1a} receptor

Authors: *F. LERI[1], T. D. LAPOINTE[2], R. M. HUDSON[4], S. DANIELS[3], B. MELANSON[2], Y. ZHOU[5]
[1]Psychology, Univ. Guelph, Guelph, ON, Canada; [3]Psychology and Neurosci., [2]Univ. of Guelph, Guelph, ON, Canada; [4]Neurosci., Univ. of Western Ontario, London, ON, Canada; [5]Rockefeller Univ., New York, NY

Abstract: The antidepressant efficacy of the selective serotonin reuptake inhibitor escitalopram (ESC) can be augmented by co-administration of the partialdopamine and serotonin 5-HT_{1a}agonist aripiprazole (ARI). The current research was designed to explore the specific role of the 5-HT_{1a}receptor in mediating the behavioral effects relevant to mood disorders caused by ESC+ARI. Hence, males Sprague-Dawley rats received ESC (s.c., acute injections: 0.33 mg/kg/day; or mini-pump maintenance: 10 mg/kg/day) alone or in combination with ARI (s.c., acute injections: 0.33 or 2 mg/kg/day) and were tested in activity chambers to assess psychomotor functions and in forced-swim to assess reactivity to unescapable stress. To explore the role of the HT_{1a}receptors, ESC+ARI treated rats also received the 5-HT_{1a}antagonist WAY-100635 (WAY; 0.01 or 1 mg/kg) or agonist 8-OH-DPAT (DPAT; 0.3 or 1 mg/kg), and mRNA of the 5-HT_{1a}receptor was quantified in two key brain regions implicated in treatment response: the dorsal raphe nucleus (DRN) and hippocampus (H). In locomotion, it was found that DPAT blocked, while WAY enhanced, the effects of ESC+ARI. In the forced-swim test, however, the pre-treatment effects of DPAT and WAY were reversed. Finally, DPAT blocked the elevation of 5-HT_{1a}mRNA that was observed in the DRN of animals treated with ARI+ESC, while WAY had no effect. These data in rats indicate that the effect of ESC+ARI in the forced swim are not

influenced by motor side effects and suggest that the 5-HT_{1A}receptor is central to the augmentation of antidepressant efficacy of ESC by ARI.

Disclosures: F. Leri: None. **T.D. Lapointe:** None. **R.M. Hudson:** None. **S. Daniels:** None. **B. Melanson:** None. **Y. Zhou:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.16/TT10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Assessment of intracranial self-stimulation as a preclinical model to predict rimonabant- and eticlopride-induced anhedonia at clinically-relevant receptor occupancies

Authors: *C. TYSZKIEWICZ[1], J. B. KUZMISKI[2], D. HORTON[1,3], V. M. JACKSON[2], M. G. GOODY[1]
[1]Global Safety Pharmacol., Pfizer Global Res. and Develop., Groton, CT; [2]Intrnl. Med. Res. Unit, Pfizer Global Res. and Develop., Cambridge, MA; [3]Medpace, Cincinnati, OH

Abstract: Identification of a translatable preclinical model that identifies risk factors associated with suicidal ideation and behaviors, such as anhedonia or depression, has the potential to offer significant value for earlier detection of drugs that cause serious neuropsychiatric events in humans. Intracranial self-stimulation (ICSS) is a model that quantifies changes in reward sensitivity. In this model, rodents are chronically implanted with electrodes in areas of the brain that mediate reward and are trained to respond on a manipulandum to receive a reinforcing electrical stimulation. When reward states are enhanced in animals (eg, with drugs of abuse), ICSS reward thresholds are lowered. Conversely, when reward states are suppressed (eg, during anhedonic states following withdrawal from drugs of abuse), reward thresholds are increased, reflecting a diminished sensitivity to rewarding stimuli. Data in the ICSS model with drugs that have been been associated with treatment-emergent neuropsychiatric events in humans are either lacking or inconsistent in the literature. Rimonabant is a cannabinoid 1 receptor (CB1R) antagonist/inverse agonist that was previously approved as an anti-obesity drug in 2006, but was subsequently removed from the market because increased incidence of severe psychiatric adverse events at clinically approved doses. Here, rimonabant (oral gavage at 1, 3, and 10 mg/kg, 30 min pretreatment) was evaluated in ICSS in male rats previously trained to respond in a discrete-trial ICSS procedure. Food intake was also evaluated at these doses to determine the anorectic efficacy of rimonabant. Furthermore, eticlopride, a dopamine 2 receptor (D2R) antagonist associated with anhedonia in humans, was evaluated in the ICSS model for comparison. Although efficacy was achieved at all doses of rimonabant (ie, >30% decrease in food intake) and plasma concentrations reached clincially-relevant exposures, there were no

effects of rimonabant on ICSS thresholds. By constrast, eticlopride (SC injection at 3, 10 and 30 μg/kg, 30 min pretreatment) significantly increased ICSS thresholds at 10 and 30 μg/kg, which was consistent with suppression of reward processing and anhedonic-like states. Receptor occupancy estimates at the CB1R and D2R in these rat experiments are similar to those achieved in the clinic for rimonabant and D2R antagonists, respectively, at doses that induce neuropsychiatric events. These findings reveal that the predictive value of the rat ICSS model for assessing anhedonic risk may be dependent on the drug's mechanism of action and/or may require optimization of dosing paradigms that more closely resemble clinical treatments.

Disclosures: C. Tyszkiewicz: A. Employment/Salary (full or part-time):; Pfizer. **J.B. Kuzmiski:** None. **D. Horton:** None. **V.M. Jackson:** None. **M.G. Goody:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.17/TT11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The impact of acute uncontrollable tail shock stress on the development of depression- and anxiety-like behavior using a mouse model

Authors: *C. REED, E. BAUER, P. J. CLARK
Iowa State Univ., Ames, IA

Abstract: Rats exposed to acute uncontrollable tail shocks display a sequelae of anxiety- and depression-like behaviors, that includes exaggerated fear, impaired punishment avoidance, less social interaction, reduced interest in rewarding stimuli, and increased preferences for environments associated with drugs of abuse. Anxiety- and depression-like behaviors in rats have been shown to persist for approximately 72h post exposure to uncontrollable stress. While decades of research into this model have yielded several exciting discoveries concerning the development of anxiety- and depression-like behavior following uncontrollable stress, to the best of our knowledge not a single published study has characterized these behaviors in mice using the same paradigm. Therefore, we explored the impact of acute uncontrollable tail shock on the development of anxiety- and depression-like behavior in adult C57BL/6J mice using 1) shuttle box escape, 2) shock-elicited freezing behavior, 3) social exploration, 4) sucrose preference, and 5) alcohol consumption. Separate cohorts of mice were tested on these behavioral tasks 1 and 5 days following exposure to tail shock (uncontrollable stress) or being undisturbed in home cages (non-stressed controls). Data collection is currently underway. Since mice offer a greater degree of genetic control (e.g. knockout, transgenic, and selective breeding models) than rats, mice may offer a useful tool for further exploration of the mechanisms behind uncontrollable stress-generated anxiety and depression behavior.

Disclosures: C. Reed: None. **E. Bauer:** None. **P.J. Clark:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.18/TT12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The impact of running on the expression of brain adenosine receptors

Authors: *E. BAUER, C. H. REED, B. A. BAUSTIAN, A. SHOEMAN, A. BELL, M. R. CARLSON, P. J. CLARK
Iowa State Univ., Ames, IA

Abstract: Regular participation in physical activity is associated with a reported decrease in central-mediated fatigue, however, the precise mechanisms are not well understood. Adenosine is a product of cellular adenosine triphosphate (ATP) consumption and can act as a neuromodulator during metabolic demand. Adenosine signaling in the brain is known to play a significant role in the modulation of fatigue. Previous work from our group found that 6 weeks of wheel running potently reduces the adenosine 1 (A_{R1}) & 2a (A_{R2A}) receptor mRNA throughout the rat striatum. The purpose of this study was to determine if wheel running also reduces the expression of adenosine receptor protein in the striatum, as well as other brain areas where adenosine modulates fatigue behavior including the hippocampus, prefrontal cortex, and hypothalamus. Therefore, adult male C57BL/6J mice were individually housed with access to running wheels or in standard cages for 8 weeks. Following 8 weeks, mice were transcardially perfused with saline and paraformaldehyde. Immunohistochemistry was performed on thin brain sections to detect A_{R1} and A_{R2A}. Brain sections were imaged and densitometry was performed to semi-quantitatively measure the density of adenosine receptors in brain regions. Data collection is underway. Preliminary data shows a trending decrease in A_{R1} and A_{R2A} expression in the striatum. We hypothesize A_{R1} and A_{R2A} expression will decrease across the all brain regions, as a result of peripheral increases of adenosine entering the brain during running. A widespread reduction in brain adenosine receptors may contribute to reduced sensations of fatigue in individuals that regularly exercise and may have implications for the pro-cognitive and anti-depressant effects of exercise.

Disclosures: E. Bauer: None. **C.H. Reed:** None. **B.A. Baustian:** None. **A. Shoeman:** None. **A. Bell:** None. **M.R. Carlson:** None. **P.J. Clark:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.19/DP13/TT13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: State of Connecticut
Mears Endownment to Ronald Duman

Title: Cell -specific ablation of microglial pattern recognition receptors RAGE and TLR4 alters susceptibility to depressive-like behaviors after chronic unpredictable stress

Authors: *T. C. FRANKLIN[1], R. S. DUMAN[2]
[1]Yale Univ. Sch. of Med., New Haven, CT; [2]Yale Univ. Sch. Med., New Haven, CT

Abstract: Chronic stress promotes dysregulation of the innate immune system leading to enhanced inflammatory signaling often associated with depressive symptomology. Growing evidence suggests that innate immune cells such as microglia, promote neuroinflammation in response to stress by releasing danger associated molecular pattern (DAMP) molecules leading to increased inflammatory signaling through their ligation to pattern recognition receptors (PRR) such as toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE). Our previous studies show that microglial RAGE is upregulated in response to chronic unpredictable stress (CUS) and enhanced microglial RAGE expression coincides with the onset and recurrence of stress-induced depressive-like behaviors. Most importantly, constitutive RAGE KO mice show *partial* attenuation of stress-induced behavioral effects. These novel findings suggest that stress-induced depressive like behaviors is at least partially mediated by enhanced microglial DAMP signaling due to increased receptor availability. We therefore hypothesize that microglial RAGE or TLR4 deletion will attenuate depressive-like behaviors following stress due to suppressed DAMP signaling. Moreover, we hypothesize that the combined deletion of both microglial RAGE and TLR4 in RAGE/TLR4 double knockout mice (RGTR-DKO) will enhance resilience against stress-induced depressive-like behaviors. We will present data from ongoing studies that examine the role of RAGE and TLR4 signaling in the development of depressive-like behaviors following chronic stress. To test this hypothesis, we have generated $RAGE^{fl/fl}$:$CX3CR1^{CreERT}$, $TLR4^{fl/fl}$:$CX3CR1^{CreERT}$ and $RAGE^{fl/fl}$:$TLR4^{fl/fl}$:$CX3CR1^{CreERT}$ mice and utilized tamoxifen-induced Cre recombinase system for cell-specific knockout of microglial RAGE, TLR4 or both, respectively. Cre negative animals are used as controls. Tamoxifen-induced conditional knockout (KO) mice will be tested for cognitive, anxiety and depressive-like behaviors at baseline and after CUS exposure using novel object recognition (NOR), forced swim test (FST), open field test (OFT) and sucrose consumption test (SCT). Microglial morphology will be assessed immediately following CUS

exposure to determine if microglial PRR deficient mice display reduced microglial reactivity following chronic stress exposure compared to littermate controls. Together, these data will provide novel insights into the role of microglial RAGE and TLR4 signaling in stress-induced microglial reactivity and the development of depressive-like behaviors.

Disclosures: T.C. Franklin: None. **R.S. Duman:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.20/TT14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The effects of a bipolar disorder associated SNP on ADCY2 protein function and mouse behavior

Authors: *P. SEN[1,2], O. ORTIZ[1], W. WURST[1], J. M. DEUSSING[2]
[1]IDG, Helmholtz Zentrum München, Oberschleissheim, Germany; [2]Max Planck Inst. of Psychiatry, Munich, Germany

Abstract: Bipolar Disorder (BD) is a multifactorial disease with both genetic and environmental factors contributing to it. The single nucleotide polymorphism (SNP): rs13166360 located at 5p15.31 was identified to be one of the polymorphisms that associated with genome- wide significance with BD. This SNP is a deviation from the major allele G to T (minor allele) that encodes a Valine to Leucine missense codon in adenylate cyclase 2 (ADCY2). This polymorphism is speculated to cause functional variation in the protein that may affect BD susceptibility. However, the precise effect of this polymorphism on protein function and its influence on BD susceptibility is still not known. In order to study the differences in function of the major and the minor allele of ADCY2, we cloned the two variants of ADCY2 into expression vectors and will transfect cell lines with low level of endogenous ADCY2. Time-course assay and an end-point assay cAMP assays will be used to compare the differences in activity of the transiently overexpressed ADCY2 variants.To address the function of ADCY2 in vivo we generated a V151L mouse line mimicking this desired polymorphism in mice using the CRISPR/Cas9 system. In order to investigate the influence of this polymorphism on BD susceptibility, we screened for differences in anxiety, locomotion and stress coping behavior under basal housing conditions and under chronic social stress. Taken together, these approaches will help to validate the functional significance of the disease-associated SNP in ADCY2.

Disclosures: P. Sen: None. **O. Ortiz:** None. **W. Wurst:** None. **J.M. Deussing:** None.

Poster

232. Depression and Bipolar Disorders: Animal Models: Behavioral Mechanism I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 232.21/TT15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: USPHS R01 MH92412
USPHS R01 MH105623

Title: Sex differences in the alteration of mouse nesting behavior observed following administration of the kappa opioid receptor ligands, U50,488 and CERC-501

Authors: *M. L. JACOBSON, H. A. WULF, C. A. BROWNE, I. LUCKI
Pharmacol. & Mol. Therapeut., Uniformed Services Univ., Bethesda, MD

Abstract: Background: Selective kappa opioid receptor (KOR) antagonists, including CERC-501 (formally LY2456302), are currently under clinical investigation for the treatment of stress-related psychiatric disorders, such as depression. Evidence suggests that females are less sensitive than males to the effects of KOR ligands. Establishing whether this extends to CERC-501 is of significant importance. As women are twice as likely to be diagnosed with depression as men, this information could directly inform sex-specific dosing in humans. Therefore, we investigated sex differences in response to the KOR agonist U50,488 (U50) and the KOR antagonist CERC-501 in mice, using an ethologically relevant indicator of overall well-being, nesting. Nesting is an innate spontaneously performed behavior in the mouse. Impaired nesting produced by stress may be indicative of negative affect, a common symptom in depression.
Objective: We examined the following hypotheses; 1) U50 would suppress nesting and CERC-501 would block U50-induced suppression of nesting and 2) females would require higher doses of these KOR ligands to affect nesting behavior.
Methods: Nest building behavior was assessed in adult male and female C57BL/6J mice by providing individual mice with compressed square cotton nestlet material. Nesting was scored using a scale of 1 to 5 every half hour for five hours. The primary measures included the time it took to reach a criterion score of 3, in addition to the final additive score of the last two hours, when scores typically plateaued in value. First, intraperitoneal injections of U50 (5 or 10 mg/kg) were administered immediately prior to testing. Second, CERC-501 (1, 3, or 10 mg/kg) was administered 24 hours prior to vehicle or U50 (10 mg/kg), and nesting was again assessed.
Results: U50 dose-dependently suppressed nesting at both doses in males. U50 suppression of nesting was reduced by CERC-501 at 3 and 10 mg/kg. In females, nesting was suppressed only at the highest dose of U50, and the effects of U50 were blocked by CERC-501 only at 10 mg/kg.
Conclusions: Nesting is a behavioral measure that is sensitive to alteration by KOR signaling manipulations. Activation of KORs by U50 reduced nest building in males, an effect that was

blocked by the KOR antagonist CERC-501. Activation of KORs also affected nesting in females, but required higher doses of both U50 and CERC-501. Overall, these findings agree with earlier preclinical investigations that demonstrated sex-differences in response to KOR ligands. Going forward, studies will address the role of KOR receptor availability, KOR signaling, and drug metabolism in mediating these sex-differences in response to KOR ligands.

Disclosures: M.L. Jacobson: None. **H.A. Wulf:** None. **C.A. Browne:** None. **I. Lucki:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.01/TT16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01MH104261
ONR N00014-12-1-0366
Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Consortium
NIDA U01DA043098

Title: The hippocampal glycome contributes to behavioural phenotype in a novel rodent model of mood disorders

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Abstract: Introduction: bred High-Responder (bHR) and bred Low-Responder (bLR) rats present a novel rodent model of mood disorders. bHR animals emulate externalising mood disorders, and bLR animals emulate internalising mood disorders. bLRs have lower Fibroblast Growth Factor 2 (FGF2) expression within the hippocampus than bHRs. Early-life administration of FGF2 reverses this deficit, and also alters the bLR behavioural phenotype. Membrane-bound Heparan Sulfate Proteoglycans (HSPGs) mediate FGF2 binding with FGF Receptor-1 (FGFR1), particularly Syndecan-4 (Sdc4) and Glypican-1 (Gpc1). This study investigates the hippocampal HSPG profiles of bHR and bLR animals and the behavioural impact of altering the hippocampal glycome. **Materials and Methods:** Hippocampi were collected from male animals of the bHR and bLR colonies, homogenised and processed using RNA sequencing. Whole brain tissue was collected from adult male animals, and P14 male and female animals at baseline and with vehicle/FGF2 administered on postnatal day 1. Tissue was sectioned at 10μm, and in situ hybridisation for Gpc1 and Sdc4 performed using radioisotope

labelling. Immunohistochemistry was performed on perfused brain tissue against Sdc4, Gpc1, GFAP and NeuN. **Results:** RNA Sequencing data revealed that Sdc4 and Gpc1 are differentially expressed within the bHR and bLR hippocampus. In situ hybridisation was used to confirm these results, revealing that bLR animals express greater levels of Gpc1 than bHR animals throughout all hippocampal regions and the basolateral amygdala at all ages assessed, and that Sdc4 was more highly expressed in juvenile bLR and adult bHR hippocampus. P1 FGF2 administration altered the expression patterns at P14 of both Gpc1 and Sdc4 in the bLR line and Sdc4 in the bHR line. Immunohistochemistry revealed that Gpc1 is expressed in neurons within the rodent hippocampus. **Discussion:** bHR and bLR animals demonstrate differential HSPG profiles within the hippocampus, which are modulated by early-life FGF2 administration. These results suggest that not only do bLR animals express less FGF2 within the hippocampus than their bHR counterparts, but that the signalling activity of FGF2-FGF Receptor-1 within this brain region is potentially altered. Studies are currently underway to alter the hippocampal glycome and determine the impact on emotional behaviours of bLR and bHR animals.

Disclosures: A.M. O'Connor: None. **T. Pardo:** None. **I. Birt:** None. **M. Hagenauer:** None. **P.M. Maras:** None. **K.E. Prater:** None. **P. Blandino:** None. **E.K. Hebda-Bauer:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.02/TT17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: GluA2-lacking AMPA receptor expression in dopamine D1 or D2 receptor neurons affects behavior differently

Authors: *J. SHOU[1], A. TRAN[1], N. SNYDER[1], E. BLEEM[1], S. KIM[1,2,3]
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Abstract: Dopaminergic signaling in the central nervous system regulates several aspects of animal behavior. There are two classes of dopamine receptors in medium spiny neurons (MSNs) in the striatum, which can be differentiated by their output connectivity and their expression of dopamine receptors, D1 or D2 receptors (D1R or D2R). Notably, Ca^{2+}-permeable, GluA2-lacking glutamate AMPA receptors (CP-AMPARs) are important for gating synaptic plasticity and gene expression in MSNs. Moreover, CP-AMPAR expression in the nucleus accumbens (NAc) of the striatum affects several animal behaviors. However, differential roles of GluA2-lacking AMPARs in D1R or D2R neurons have not been understood. Here, we employed the Cre-Lox recombination system to remove GluA2 selectively in D1R or D2R neurons to express

CP-AMPARs and carried out multiple behavior assays. First, the open field assay revealed that D1R mutant animals showed increased locomotor activity, while D2R animals had the opposite behavior. The three-chamber test identified that D2R mice exhibited impaired sociability, but D1R animals showed normal social behavior. Moreover, deletion of GluA2 in D1R neurons induced fearless behavior in the elevated-plus maze and antidepressant effects during the tail-suspension test. Conversely, D2R animals showed normal behaviors in these tests except D2R males exhibited depression-like behavior. Importantly, D1R animals exhibited an increase in body weight although they consumed less food than wild-type animals, while food intake and body weights were not affected by GluA2 knockout in D2R neurons. Finally, an accelerated rotarod test revealed that motor learning was significantly disrupted only in D2R animals. Taken together, GluA2 deletion in D1R and D2R pathway regulates behavior differently.

Disclosures: J. Shou: None. **A. Tran:** None. **N. Snyder:** None. **E. Bleem:** None. **S. Kim:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.03/TT18

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NRF-2011-0019227
NRF-2013M3C7A1056732
NRF-2012M3A9B6055378
NRF-2011-0019229
NRF-2013R1A1A2060527

Title: Reduction of CHAT in medial habenula induces depression-like behavior

Authors: *S.-H. YANG[1], J. KIM[1], S. MO[1], E. YANG[1], K. SONG[1], B.-J. HAM[2], N. MECHAWAR[3], G. TURECKI[3], H. LEE[1], H. KIM[1]
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Abstract: The dysfunction of cholinergic signaling in the brain has long been known to be associated with depressive disorders. However, the functional effects of habenular cholinergic signals on specific depressive behaviors are not well known. We demonstrated that the expression levels of cholinergic signaling genes (CHAT, VACHT, CHT, CHRNA3, CHRNB3 and CHRNB4) were down-regulated in a chronic restraint stress (CRS) rat model of depression, in which rats display depression-like behaviors such as anhedonia and mood despair. Moreover,

knockdown of CHAT in rat habenula was enough to evoke anhedonia-like behavior. Anhedonia-like behavior induced by CHAT knockdown was not reversed by the chronic administration of the selective serotonin reuptake inhibitor fluoxetine. To determine whether habenular cholinergic signaling regulates dopaminergic neurons in the ventral tegmental area (VTA) and serotonergic neurons in the dorsal raphe nucleus (DRN), we used CHAT::cre transgenic mice to express the Designer Receptors Exclusively Activated by Designer Drugs (DREADD). Pharmacological activation of habenular cholinergic neurons induces dopaminergic neuron excitation in VTA and reduces the immunereactivity of 5-hydroxytryptamine (5-HT) in DRN. Down-regulation of the Habenular cholinergic genes was recapitulated in postmortem habenula of suicide victims diagnosed with major depressive disorder (MDD).

Disclosures: S. Yang: None. **J. Kim:** None. **S. Mo:** None. **E. Yang:** None. **K. Song:** None. **B. Ham:** None. **N. Mechawar:** None. **G. Turecki:** None. **H. Lee:** None. **H. Kim:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.04/TT19

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01MH104261
NIDA U01DA043098
Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Consortium

Title: Mechanisms of hippocampal development: Molecular and cellular phenotypes in the selectively bred high-responder/low-responder model of affective disorders

Authors: *K. L. HILDE[1], M. H. HAGENAUER[2], A. V. STEFANOV[2], I. BIRT[2], E. K. HEBDA-BAUER[1], S. J. WATSON, Jr.[2], H. AKIL[2]
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Abstract: Mood disorders have complex etiologies that originate from an interplay between genetic and environmental factors. Although numerous gene expression changes have been described in adults with depression, anxiety, and other mood disorders, the underlying developmental mechanisms that predispose individuals for psychiatric disorders in adulthood are less well understood. In this study, we utilize a selectively bred rat model of high responder (HR) and low responder (LR) animals that represent extreme ends of the behavioral spectrum in their baseline propensity for anxiety- and depressive-like behavior, as well as their response to environmental factors such as stress.
We identify molecules that are differentially expressed in HR and LR animals during

developmental stages that are critical for establishing proper molecular and cellular composition of the postnatal hippocampus. Using gene expression analyses, cell fate studies, pharmacological manipulation, and behavioral testing we study the mechanisms that contribute to the proper development of the hippocampus, the response of these molecules to stress, and test their role in the emergence of anxiety- and depressive-like behaviors in adulthood.

Disclosures: K.L. Hilde: None. **M.H. Hagenauer:** None. **A.V. Stefanov:** None. **I. Birt:** None. **E.K. Hebda-Bauer:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.05/TT20

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: R01MH090264
F30MH100835

Title: Depression and social defeat stress commonly impair inhibition in the nucleus accumbens

Authors: *M. HESHMATI[1], K. LECLAIR[1], C. MENARD[1], D. J. CHRISTOFFEL[2], S. A. GOLDEN[3], M. FLANIGAN[1], H. ALEYASIN[4], A. K. FRIEDMAN[5], M.-H. HAN[1], S. J. RUSSO[1]
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Abstract: Background: We recently reported that chronic stress induces a down regulation of neuroligin-2, a key inhibitory postsynaptic protein, in the nucleus accumbens (NAc) that modifies behavioral responses to stress. Here we extend this observation by examining the role of two other inhibitory synapse constituents, vesicular GABA transporter (vGAT) and gephyrin, in the NAc of mice that underwent chronic social defeat stress (CSDS) and postmortem NAc from patients with major depressive disorder (MDD).
Methods: In Exp. 1, we first performed whole cell electrophysiology recordings in the NAc of stress susceptible and resilient mice following 10 days of CSDS. In Exp. 2, we performed immunohistochemistry for vGAT and gephyrin proteint in the NAc from both populations. In Exp. 3, we performed transcriptional profiling of vGAT and gephyrin in postmortem NAc from a cohort of healthy control subjects, medicated and non-medicated MDD patients.
Results: In Exp. 1, we observed that stress susceptible, but not resilient, mice exhibit decreased NAc medium spiny neuron mini inhibitory postsynaptic (mIPSC) frequency relative to control mice that do not undergo stress. Conversely, resilient mice exhibit increased mIPSC amplitude

relative to controls. mIPSC frequency, but not amplitude, was correlated with social avoidance behavior. In Exp. 2, vGAT protein expression was decreased in susceptible mice. Both vGAT and gephyrin expression were significantly correlated with changes in social avoidance behavior. In Exp. 3, vGAT and gephyrin mRNA expression were decreased in the postmortem NAc of non-medicated depressed patients.
Conclusions: Our results extend previous findings on the critical role of impaired inhibitory tone in the NAc following stress, and provide new neuropathological evidence for reduced levels of vGAT and gephyrin mRNA in human NAc from non-medicated MDD patients. This finding is corroborated in stress susceptible mice that have undergone CSDS at both the level of synaptic function and protein expression. These data support the hypothesis that regulation of inhibitory tone within the NAc plays a critical role the stress response.

Disclosures: M. Heshmati: None. **K. LeClair:** None. **C. Menard:** None. **D.J. Christoffel:** None. **S.A. Golden:** None. **M. Flanigan:** None. **H. Aleyasin:** None. **A.K. Friedman:** None. **M. Han:** None. **S.J. Russo:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.06/TT21

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Otx2 as a possible mediator for depressive-like behavior

Authors: *A. MUNDORF, N. FREUND
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Abstract: Child maltreatment (CM) is complex and difficult to study as there are many different subtypes, one of it being early life stress (ELS), and most cases are not being reported. According to the World Health Organization, more than a quarter of all adults state being physically maltreated, whereas the numbers for sexual abuse are even higher. CM can have lifelong consequences for mental and physical health, accompanied by molecular changes, like epigenetic changes as well as changes in the transcription of specific genes which can influence the brain development until adolescence and even adulthood. A gene that recently has been identified to increase the susceptibility to stress and depressive-like behavior in mice after induced ELS is the transcription factor *Orthodenticle homeobox 2* (*Otx2*). It is mainly expressed in dopaminergic neurons of the ventral tegmental area (VTA) where it regulates the proliferation and differentiation of dopaminergic neurons. The study showed that stress at a specific postnatal period increased the susceptibility to adult social defeat stress due to long-lasting transcriptional alterations mediated by *Otx2* which set the VTA to a depression-like state. An overexpression of *Otx2* reversed the effects of ELS. In another study, mouse mutants overexpressing *Otx2* in the

hindbrain showed fluctuations in mania- and depressive-like behavior. We examined the behavior of adult rats that experienced maternal separation, as a model of induced ELS, in their early childhood (P2- P21) and with a second stressor in late childhood (P22-P40) compared to control animals. At adult age (P>60), all animals were examined in two different anxiety tests, followed by real-time PCR analysis of *Otx2* mRNA levels in the VTA. No significant difference in *Otx2* mRNA levels between sexes nor group was observed, even though a significant difference in anxiety-like behavior between male and female rats was shown, with male rats showing more anxiety-like behavior than females. However, a significant correlation was found between anxiety-like behavior and *Otx2* mRNA levels in the control group (n=14) but not in the stress-exposed group (n=15), including both sexes. It seems that low levels of *Otx2* mRNA correlate with high anxiety but that this correlation is disturbed after ELS. The found correlation is in line with previous findings that low levels of *Otx2* mRNA are associated with depressive-like behavior and underlines the new but relevant role of *Otx2* in influencing the mood behavior.

Disclosures: A. Mundorf: None. **N. Freund:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.07/TT22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH F32MH116574
NIH R01MH106500
One Mind/ Janssen Rising Star Translational Research Award

Title: Chronic stress causes cell-type specific dendritic remodeling of nucleus accumbens medium spiny neurons

Authors: *M. E. FOX[1], R. CHANDRA[1], M. S. MENKEN[1], E. J. LARKIN[2], H. NAM[1], M. ENGELN[1], T. C. FRANCIS[1], M. LOBO[1]
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Abstract: Chronic stress alters the structure and function of brain reward circuitry and can precipitate the development of depression. Previous work suggests that medium spiny neurons (MSNs) in the nucleus accumbens (NAc) undergo structural plasticity after stress, however the molecular mechanisms and behavioral significance are poorly understood. Here we show diverse morphologic adaptations in D1 and D2 receptor expressing MSNs in mice susceptible to social defeat stress. D1-MSNs undergo dendritic atrophy that is caused by upregulation of GTPase RhoA and its effector Rho-kinase. Reduction of activated RhoA in D1-MSNs prevents

depressive outcomes to stress by preventing loss of dendritic arbor, while promotion of activated RhoA in D1-MSNs enhances depressive outcomes by reducing dendritic arbor. Activated RhoA in D1-MSNs is sufficient to promote depressive-like behaviors in stress-naïve mice, and Rho-kinase can be targeted pharmacologically to reverse depression-like behavior after stress. In D2-MSNs, dendritic complexity and RhoA are unaltered. Instead, we find increased D2-MSN spine density in susceptible mice. Together, our data demonstrate a role for cell-type specific dendritic remodeling in depression-like behavior. Our future experiments will address the molecular mechanisms underlying spine changes specifically in D2-MSN and their contributions to stress-susceptibility.

Disclosures: M.E. Fox: None. **R. Chandra:** None. **M.S. Menken:** None. **E.J. Larkin:** None. **H. Nam:** None. **M. Engeln:** None. **T.C. Francis:** None. **M. Lobo:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.08/TT23

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: 5 SC2 GM122646 NIGMS
NSF GRFP Fellowship

Title: The role of estrogen in the stress response in the ventral tegmental area

Authors: *M. SHANLEY, C. GUEVARA, A. SEIDENBERG, E. HERNANDEZ, A. ONOICHENCO, P. GOLUBOWSKI, R. KARIM, A. K. FRIEDMAN
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Abstract: Although major depressive disorder (MDD) is more than twice as likely to be diagnosed in women compared to men, there are limited ethological animal models to explore the possible neurophysiological mechanisms underlying this disparity. Therefore, it is imperative to utilize non sex-reliant animal models to reveal possible sex-specific differences in the response to chronic psychosocial stress. These differences may contribute to the development of depressive or resilient behaviors in females and reveal new mechanistic insight for the development of sex-specific therapeutics. Recent work has demonstrated the importance of maintaining healthy activity of the dopamine (DA) neurons of the ventral tegmental area (VTA) in regulating mood. Further, the β isoform of the estrogen receptor (ER) is expressed in a population of dopaminergic neurons in the VTA. Since estrogen level fluctuations across the menstrual cycle are closely associated with changes in mood, we are investigating the role of estrogen in disturbances in the mesolimbic pathway found in depressive disorders. We utilize a preclinical mouse model of depression, called repeated variable social stress (RVSS), which,

over ten days, uses a series of psychosocial stressors applicable to both sexes to induce a long-lasting reduction in social preference in a subset of male and female C57BL/6J mice. Importantly, a subset of mice of both sexes are resilient to RVSS and show no change in social preference. Further, DA neurons in the VTA of susceptible mice exhibited hyperactivity, while firing activity remained similar to controls in the resilient subset. Potassium (K+) channel function was also selectively increased in DA neurons in both the male and female resilient mice. Using vaginal cytology to determine the estrous cycle and corresponding high- or low-estrogen state (diestrus and proestrus = high estrogen; estrus and metestrus = low estrogen) we found differences in K^+ channel function at differing estrogen levels in non-stressed female mice. Therefore, to directly evaluate the contribution of estrogen to the behavioral response to psychosocial stress we utilized a modified one-day version of RVSS, called acute variable social stress (AVSS). 24 hours post AVSS, we found no changes in male social behaviors. Interestingly, female mice with high estrogen levels on the day of stress demonstrated increased social preference 24 hours post AVSS, as compared to females with low estrogen levels and non-stressed females. Thus, we hypothesize that fluctuations in estrogen during chronic stress increases susceptibility, whereas high levels of estrogen acts to buffer the behavioral effects of acute stress.

Disclosures: M. Shanley: None. **C. Guevara:** None. **A. Seidenberg:** None. **E. Hernandez:** None. **A. Onoichenco:** None. **P. Golubowski:** None. **R. Karim:** None. **A.K. Friedman:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.09/TT24

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NARSAD Grant 570769

Title: Targeted neuroepigenetic editing of Cdk5 regulates chronic stress

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Abstract: Major depressive and posttraumatic stress disorders share stress as an etiological contributor and are more common in women than in men. Over the past several decades it has become clear that gene expression changes conferred by molecular alterations to the genome,

known as epigenetic modifications, underlie mood regulation and resilience to environmental stressors. The vast majority of preclinical studies to elucidate gene regulatory underpinnings of mood disorders are limited to male rodents, yet the human epidemiological and neurobiological literatures report female-specific stress responsivity. Cyclin-dependent kinase (Cdk5) is a neuronally expressed gene implicated in a number of neurological disorders and neurodegenerative diseases including major depressive disorder, Alzheimer's disease, amyotrophic lateral sclerosis, and ischemia. While epigenetic modifications driving gene expression related to stress are widely documented, identification of the precise molecular mechanisms by which they regulate specific gene expression remains elusive. Cdk5 is known to regulate stress related behaviors and magnitude of these behaviors. Although there is much evidence on the function of Cdk5 protein, very little is known about the regulation of *Cdk5* gene expression particularly in chronic stress. We hypothesize that (1) chronic stress sex-specifically regulates epigenetic activation of *Cdk5* expression (2) histone modification(s) of *Cdk5* is sufficient to regulate its expression, and influence sexually-dimporphic behavioral responses to chronic stress. We determined the spatiotemporal regulation of Cdk5 expression following chronic unpredictable stress (CUS) in male and female mice. We find that male, but not female, mice activate Cdk5 expression in response to 28-days of CUS, and that this activation is specific to the nucleus accumbens (NAc). We also found sex-specific behavioralal responses to 14 days or 28 days CUS. We then utilized targeted epigenetic editing to examine the behavioral and biochemical consequences of *Cdk5* histone modifications in CUS. This work will provide a model of stress evoked chromatin remodeling at C*dk5*, and reveal the causal relevance of *Cdk5* transcriptional regulation to stress induced behavior. The identification of such precise mechanisms in stress-mediated gene expression is necessary for the development of targeted therapeutic treatments.

Disclosures: A. Sase: None. **B. Santhumayor:** None. **S. Lombroso:** None. **R. Wood:** None. **E.A. Heller:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.10/UU1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant K22MH099164
NIH Grant R01MH110681

Title: Cortical gaba reduction mediates effort-based dopamine release deficits in anterior cingulate cortex

Authors: *K. NAKAO[1], S. M. KOLATA[3], E. L. FARMER-ALROTH[1], R. E. SORGE[2], K. NAKAZAWA[1,4,3]
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Abstract: Whereas cortical GAD67 reduction and subsequent GABA level decrease are consistently observed in schizophrenia and depression, it remains unclear how these GABAergic abnormalities contribute to specific symptoms. We modeled cortical GAD67 reduction in mice, in which the Gad1 gene is genetically ablated from ~50% of cortical and hippocampal interneurons and characterizes them with in vivo microdialysis and behavioral assays. Mutant mice exhibited a cluster of effort-based behavior deficits including decreased home-cage wheel running (genotype × time interaction: $F(1,120)=2.68$, $p<0.001$) and increased immobility in both tail suspension ($t(17)=4.51$, $p=0.0003$) and forced swim tests ($t(14)=-2.77$, $p=0.015$). Since saccharine preference, progressive ratio responding to food, and learned helplessness task were normal, such avolition-like behavior could not be explained by anhedonia or behavioral despair. In line with the prevailing view that dopamine in anterior cingulate cortex (ACC) plays a role in evaluating effort cost for engaging in actions, we found that tail-suspension triggered dopamine release in ACC of controls, which was severely attenuated in the mutant mice (repeated measures ANOVA, $F(1,45)=2.44$, $p=0.07$, post-hoc test $F(1,15)=22.1$, $p=0.00028$). Conversely, ACC dopamine release by progressive ratio responding to reward, during which animals were allowed to effortlessly perform the nose-poking, was not affected in mutants (repeated measures ANOVA, $F(1,36)=0.181$, $p=0.91$). These results suggest that cortical GABA reduction preferentially impairs the effort-based behavior which requires much effort with little benefit, through a deficit of ACC dopamine release triggered by high-effort cost behavior, but not by reward-seeking behavior. Collectively, a subset of negative symptoms with a reduced willingness to expend costly effort, often observed in patients with schizophrenia and depression, may be attributed to cortical GABA level reduction.

Disclosures: S.M. Kolata: None. **E.L. Farmer-Alroth:** None. **R.E. Sorge:** None. **K. nakazawa:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.11/UU2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Ministry of Economy and Competitiveness Grant (SAF2011-25020)
Ministry of Economy and Competitiveness Grant (SAF2015-67457-R)

Title: Hippocampal β-catenin in GLAST^{+} cells: A key-mediator between proliferation and the serotonergic system

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Abstract: Several hypotheses have been postulated in order to elucidate the pathophysiology of depression. Among them, the implication of serotonergic system and neurogenesis in the adult brain are widely accepted. It is well established the regulatory role of the serotonergic system over hippocampal proliferation. However, little is known regarding the implication of proliferation in the modulation of different neurotransmitter systems. Here we study the effect of β-catenin ablation or stabilization in GLAST-expressing cells on the serotonergic system functionality *in vivo*. These transgenic mice present changes in hippocampal proliferation and in the anxious/depressive-like behavior (Vidal et al., 2018).

Male mice with β-catenin deletion (*Ctnnb1*$^{fl/fl}$, cKO) or stabilization (*Ctnnb1*$^{(ex3)\ fl/fl}$, cST) were crossed with a mouse line expressing CreERT under the control of the astrocyte-specific glutamate transporter (GLAST) promoter, inducible by tamoxifen (1 mg/day, 5 days; i.p.). After 4 weeks, we evaluated the serotonergic system functionality: 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors functional autoradiography, 5-HT$_{1A}$ and 5-HT$_{1B}$ agonist induced hypothermia and microdialysis studies.

5-HT$_{1A}$-receptor functionality: the [^{35}S]GTPγS binding induced by 8-OH-DPAT agonist was reduced in some brain areas as the medial prefrontal cortex ($p<0.001$), CA1, CA2-3 and dentate gyrus of the hippocampus ($p<0.05$), and the hypothalamus ($p<0.05$) in β-catenin cKO mice. In contrast, the [^{35}S]GTPγS binding was reduced in the dorsal raphe nucleus in cST animals ($p<0.05$). The cKO animals displayed a higher (+)8-OH-DPAT-induced hypothermic response compared to their controls ($p<0.001$), while in cST animals the hypothermic response was lower (t=15-45 min, $p<0.001$; t=60 min, $p<0.01$). *5-HT$_{1B}$-receptor functionality:* the 5-HT$_{1B}$-induced [^{35}S]GTPγS binding was lower in the caudate-putamen ($p<0.05$) and the hypothalamus ($p<0.05$) in the β-catenin cKO mice, while binding values were higher in the CA1 area of the hippocampus ($p<0.05$) in the cST animals. CP 94,253-induced hypothermia was lower in the cKO group ($p<0.01$), while no changes were observed in cST mice. *In vivo* microdialysis studies showed lower serotonin release after a pulse of veratridine and a reduction in the transient increase of 5-HT efflux ($p<0.01$) in the cKO mice ($p<0.01$).

Our findings demonstrate that the deletion or stabilization of β-catenin levels in GLAST^{+} cells, modulate the serotonergic system functionality resembling either depressive- or antidepressant-like behavior, respectively. This suggests a link between the main canonical Wnt/β-catenin signaling effector and the classical hypothesis of depression.

Disclosures: A. Adell: None. **F. Pilar-Cuéllar:** None. **E. Garro-Martínez:** None. **R. Vidal:** None. **Á. Pazos:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.12/UU3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Medial prefrontal cortex inhibition attenuates symptoms of depression in long evans rats

Authors: *J. J. CORTRIGHT, A. MILLER, B. PODGORSEK, A. WILLARD, S. ACKERMAN, M. BAUMGARDNER
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Abstract: Self-focus (i.e. the process by which one engages in self-referential processing) is a core issue in the psychopathology of major depression, which affects 350 million people worldwide. Previous studies have used functional neuroimaging to identify that the cortical midline structures, including the medial prefrontal cortex (mPFC), play a key role in self-referential processing in depressed subjects. The current study investigates the hypothesized link between the mPFC and depression using an animal model of learned helplessness to measure self-referential processing. It is hypothesized that a decrease in symptoms of depression will be seen in animals that have undergone inhibition of the mPFC. This research holds significance in that it builds on previous studies, with conflicting results, that have aimed to link specific patterns of activity to the PFC as mediating symptoms of depression. Further examination of the mPFC is therefore warranted not only as a possible precursor to the implication of its involvement in mediating depression, but also in order to provide support for a theory of dominant pattern of brain activity (inhibition) which interacts with symptoms of depression. The current study utilized female Long Evans rats in order to more accurately generalize findings to the population of women, which make up the majority of depressed individuals in humans. Subjects were exposed to 28 days of randomized stressors during adulthood including forced swim, cage tilt, wet bedding, mild restraint and restriction of food and water. Control animals were housed in pairs, while animals exposed to randomized stress were housed in isolation. Following surgical placement of guide cannula animals were either infused with an inhibitory cocktail (0.3 nmol/0.5µl/side baclofen/0.3 nmol/0.5µl/side muscimol) or sham (artificial cerebrospinal fluid) before being tested for resiliency against learned helplessness. Subjects were tested for latency in a forced swim test and hot plate test, for motivation in a radial arm maze, for lethargy in an open field test, and for anhedonia using sugar pellets. To date, attenuation of learned helplessness symptoms have been found in stress-exposed animals which had undergone inhibition of the mPFC (having also had their self-referential processes inhibited) compared to

controls. Collectively, these findings hold significance in that they build on recent research that has aimed to link areas of the PFC to symptoms of depression.

Disclosures: J.J. Cortright: None. **A. Miller:** None. **B. Podgorsek:** None. **A. Willard:** None. **S. Ackerman:** None. **M. Baumgardner:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.13/UU4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Epigenetic regulation of bdnf gene transcription in two animal models of depression

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Abstract: Chronic social defeat and chronic unpredictable stress are widely used to induce depression-like phenotypes. Expression levels of brain derived neurotrophic factor (BDNF) in the hippocampus have been implicated in depression and the therapeutic action of antidepressant treatment. In this study, we compared chronic stress-induced changes in Bdnf expression in mice exposed to chronic social defeat stress (CSDS) or chronic unpredictable stress (CUS) and separated into stress susceptible and resilient subgroups. We found that 10-day CSDS decreased the levels of total Bdnf mRNA and exon-specific Bdnf transcripts (I, III, IV and VI) in the hippocampus. Based upon their social interaction ratio, socially defeated mice were divided into susceptible and resilient groups. Downregulation of total Bdnf mRNA and exon-specific transcripts in the hippocampus was observed in both stress-susceptible and resilient mice. In the CUS model, mice were subjected to a variety of stressors for 10 days. Susceptible and resilient mice were segregated based upon the female urine sniffing duration ratio. Contrary to CSDS, CUS decreased total Bdnf mRNA and exon-specific transcripts (I, II, IV and VI) in the hippocampus of susceptible mice but not resilient mice. CSDS and CUS resulted in distinct patterns of histone acetylation and methylation at Bdnf promoters. Moreover, total Bdnf mRNA expression was negatively correlated with depressive behavior in the CUS model but not in the CSDS model. Our results suggest that regulation of hippocampal Bdnf exon-specific mRNA expression may underlie stress susceptibility and the development of depressive behaviors.

Disclosures: C. Li: None. **F. Meng:** None. **J. Liu:** None. **X. Liu:** None. **M. Guo:** None. **X. Lu:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.14/UU5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01MH106500

Title: Reduced enkephalins in the nucleus accumbens regulate depression-like phenotype to social defeat stress

Authors: *H. NAM, R. CHANDRA, T. FRANCIS, M. LOBO
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Abstract: Enkephalins are primary endogenous ligands for delta opioid receptors (DORs) and are highly enriched in D2-medium spiny neurons (MSNs) in the striatum. Enkephalins are highly implicated in depression, as preproenkephalin knockout and DOR knockout mice display anxiety- and depression-like phenotypes. Furthermore, enkephalinase inhibitors can act as antidepressants. However, the specific the role of enkephalins, especially in the nucleus accumbens (NAc), a critical brain region for motivational behavior, in depression is not fully investigated. To provide insight into enkephalin function in this region we used mice that underwent chronic social defeat stress, after which the animals were either categorized as susceptible (displaying depression-like behavior) or resilient to social stress based on their performance in a social interaction test. First, we directly measured Met- and Leu-enkephalin levels within the NAc using radioimmunoassays after social defeat stress. Compared to non-stressed control and resilient animals, the susceptible animals showed reduction in NAc enkephalin levels. Then we sought to investigate the mechanisms that reduce levels of enkephalins in the depression-like conditions by analyzing levels of different enzymes that can degrade or produce enkephalins. Our results indicate that the decrease in enkephalin levels observed in susceptible animals may be due to increased mRNA levels of enkephalinases and reduced proprotein convertase 1. To determine if the reduced enkephalin levels cause depression-like behavior through disrupted enkephalin-DOR signaling, we infused DOR agonist SNC80 into the NAc of the animals that experienced chronic social defeat stress. Our data shows that SNC80 can reverse the depression-like behavior in susceptible animals. Overall, results from our studies implicate that depression-like behavior induced by social defeat stress is caused by reduced DOR signaling resulting from lowered levels of enkephalins in the NAc, which may be mediated through elevated expression of enkephalinases and decreased proprotein convertases.

Disclosures: H. Nam: None. **R. Chandra:** None. **T. Francis:** None. **M. Lobo:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.15/UU6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: PhRMA Foundation Starter Grant (V.D.)

Title: Chronic pain evokes limbic dysregulation of MAPK phosphatases

Authors: D. NERLAND, *L. SEMKE, V. DURIC
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Abstract: Clinical studies have shown a high co-morbidity between different chronic pain conditions and major depressive disorder. The exact brain mechanisms that connect these two neurological illnesses are still largely unknown; however, it is thought that chronic pain may produce negative effects on different limbic brain regions similar to chronic stress. Our previous studies have shown that expression of mitogen-activated protein kinase phosphatase-1 (MKP-1 or DUSP-1) is both necessary and sufficient for the development of depressive-like behaviors in rodents. In the current study, we investigated the role of MKP-1 and other DUSP genes in affective pain processing within specific limbic brain areas. In male rats exposed to 21 days of peripheral inflammatory pain (i.e., hindpaw injections of Complete Freund's Adjuvant; CFA) a robust increase in expression of MKP-1 gene was observed within the contralateral hippocampus, prefrontal cortex (PFC) and anterior cingulate cortex (ACC). Similar upregulation of hippocampal MKP-1 was also observed in female animals exposed to 21 days of CFA. However, the overall pattern of MKP-1 expression across various limbic areas differed in females exposed to chronic pain, as significant downregulation of MKP-1 was observed in the ACC, and no changes were detected within the PFC. Furthermore, similar region-specific variances in pain-related dysregulation were also observed for other DUSP genes (i.e., MKP-2 and MKP-3). Overall, the results of this study suggest that chronic pain activates specific MAPK phosphatases within different limbic brain regions, which may underlie previously reported pain-related decreases in MAPK signaling. Thus, dysregulation of MKP-1 and other DUSP genes may play an important role in the development of mood disorders associated with chronic pain state.

Disclosures: D. Nerland: None. **L. Semke:** None. **V. Duric:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.16/UU7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: The Pritzker Neuropsychiatric Disorder Research Consortium

Title: Analysis of gaba-ergic interneuron markers in the anterior and posterior cingulate cortex of subjects diagnosed with bipolar disorder and schizophrenia

Authors: *D. M. KROLEWSKI[1], V. KUMAR[1], M. WASELUS[1], R. M. MYERS[2], F. S. LEE[3], J. D. BARCHAS[3], A. SCHATZBERG[4], W. E. BUNNEY JR[5], H. AKIL[1], S. J. WATSON, Jr.[1]
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Abstract: Bipolar disorder (BP) and Schizophrenia (SZ) represent clinically distinct psychiatric illnesses yet are thought to display overlapping features such as alterations in mood and information processing by cortical gamma-aminobutyric acid (GABA)-ergic interneurons. For example, BP and SZ postmortem analyses reveal deficits in classic interneuron-related molecular markers including glutamic acid decarboxylase 67 (GAD67), calcium-binding proteins, and neuropeptide expression in several cortical regions. It should be noted that similar investigation of the anterior cingulate (ACg) and posterior cingulate (PCg) cortices have largely focused on the ACg of SZ subjects with effects highlighting diminished GAD67, parvalbumin (PV) and somatostatin (SST) mRNA. In contrast, potential abnormalities regarding the orchestration of GABA-ergic interneuronal networks are less understood in the ACg and PCg of BP subjects. Considering the ACg and PCg differentially contribute to behaviors linked to control of emotion and memory-based evaluative process, respectively, prospective gene expression changes may also generate new anatomical correlates. Therefore, the aim of the present study is to quantify and compare the relative distribution of GAD67 mRNA transcripts as well as those demarcating distinct GABA-ergic interneuron subpopulations that utilize differential synaptic contacts with pyramidal neurons. More specifically, we chose to examine PV (cell body, axon initial segment), SST (dendrites), and vasoactive intestinal peptide ((VIP); other interneurons)) in the ACg and PCg of both BP and SZ subjects. To achieve this, we performed *in situ* hybridization (ISH) using radiolabeled cRNA probes applied to 10 ɥm fresh-frozen ACg and PCg sections from control (n=16), SZ (n=19), and BP (n=19) subjects. With quantitation currently ongoing, preliminary results indicate similar SST and VIP mRNA layer-expression patterns within the ACg and PCg of controls while PV intensity level seems to depend on ACg subregion (BA24a vs. BA24b and

BA24c). To better characterize distinct cingulate-localized interneuron subpopulations, we have developed complementary cDNA probes suitable for fluorescent ISH (FISH) to visualize the degree of specific mRNA colocalization. Moreover, we also look to illuminate the 3-dimensional neuroanatomical relationships between interneurons using CLARITY and iDISCO brain transparency methods. The results of these experiments will serve to further elucidate the underpinnings of GABA-ergic interneuron function in the ACg and PCg of patients diagnosed with BP and SZ. Support: The Pritzker Neuropsychiatric Disorder Research Consortium

Disclosures: D.M. Krolewski: None. **V. Kumar:** None. **M. Waselus:** None. **R.M. Myers:** None. **F.S. Lee:** None. **J.D. Barchas:** None. **A. Schatzberg:** None. **W.E. Bunney Jr:** None. **H. Akil:** None. **S.J. Watson:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.17/UU8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MH049698
MH107487

Title: A bioinformatics analysis of enrichment loss in rats: Molecular mechanisms underlying depression-like behaviors

Authors: *M. A. SMAIL[1], B. L. SMITH[1], A. FUNK[2], E. DEPASQUALE[1], C. R. SULLIVAN[1], E. BENTEA[1], S. M. O'DONOVAN[2], R. MORANO[1], O. HOSKINS[1], E. M. COTELLA[1], P. MAHBOD[1], J. P. HERMAN[1], R. E. MCCULLUMSMITH[2]
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Abstract: Significant loss, whether it is psychosocial, physical, or financial, is a devastating event that can precipitate the onset of depression symptoms. While loss is a commonly experienced phenomenon, little is known about the underlying mechanisms. Here we combine an animal model of loss with bioinformatics analyses to gain a deeper understanding of loss-induced depression.
We first simulated loss by exposing rats to, and then removing, environmental enrichment. This model consists of 3 experimental groups: environmentally enriched (EE), enrichment removed (ER), and control (CON). In the EE and ER groups, male and female rats are housed in groups of 10 in large, multi-level cages that are filled with various toys that provide cognitive, physical, and social stimulation. CON animals are kept in standard pair-housing while EE animals remain in enriched housing throughout the protocol. To simulate loss in the ER group, animals are

removed from enriched housing after 4 weeks and placed into standard pair-housing. The ER group exhibits an unusual depression phenotype compared to the EE and CON groups. These animals show increased immobility in the forced swim test, hypoactive HPA axis responses to restraint stress, and increased food consumption, all of which are rescued by antidepressants. In the present study, two weeks after enrichment removal male and female rats were sacrificed and brains were collected. Bilateral micropunches were taken to precisely dissect brain regions implicated in loss, including the infralimbic prefrontal cortex, basolateral amygdala, and medial amygdala. These regions were simultaneously analyzed using RNAseq, shotgun proteomics, and kinomics (n=5). This method allowed us to identify parallel changes in genes, proteins, and activity, yielding a more compelling argument for involvement in loss than one line of evidence alone.
To investigate the molecular mechanisms underlying the observed behavioral changes, we will use a novel bioinformatic approach based on the combination of transcript expression, protein level, and kinase activity data to identify dysregulated pathways. Initial analyses suggest that ER altered synaptic function, apoptotic processes, and neuroendocrine activity. Bioinformatics analyses will continue to generate region- and sex-specific expression signatures for ER, relative to EE and CON. These signatures will offer a deeper understanding of the molecular mechanisms underlying the unique depression phenotype generated by this model. They will also suggest potential therapeutic targets that could prove useful in the development of novel antidepressants to help patients cope following loss.

Disclosures: B.L. Smith: None. **A. Funk:** None. **E. Depasquale:** None. **C.R. Sullivan:** None. **E. Bentea:** None. **S.M. O'Donovan:** None. **R. Morano:** None. **O. Hoskins:** None. **E.M. Cotella:** None. **P. Mahbod:** None. **J.P. Herman:** None. **R.E. McCullumsmith:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.18/UU9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH (F32MH115565-01A1) to JB
JJPVAMC-CSR&D (1I01CX001395-01) to FH
NIH (P50MH096890, subproject 2) to SA

Title: The role of NSUN2-mediated tRNA methylation in the adult mouse cortex on depressive- and anxiety-like behavior

Authors: *J. BLAZE[1], S. ESPESO-GIL[2], B. JAVIDFAR[3], F. G. HAGHIGHI[2], S. AKBARIAN[4]
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Abstract: The RNA methylome, in contrast to the DNA methylome, has barely been explored in the context of normal and diseased brain development and function. RNA cytosine methylation (m^5C), characterized by the addition of a methyl group on the 5' position of a cytosine in RNA, is a novel modification only recently characterized in mammalian tissue and most abundant in tRNAs. NSUN2, a tRNA methyltransferase that methylates the variable loop of tRNA, is expressed at high levels in the central nervous system and has been linked to neurodevelopmental defects in humans and mice. Humans with a mutation in the NSUN2 gene exhibit intellectual disability accompanied by other neurological abnormalities, including microcephaly, speech delays, and other cognitive impairments. Likewise, adult NSUN2 knockout mice exhibit deficits in cognitive and emotional behavior, a phenotype which may be related to altered methylation at distinct tRNA cytosines during embryonic stages of brain development leading to impaired neuronal survival and synaptic puncta in the cortex. However, it is still unknown whether tRNA methylation patterns regulate brain function or behavioral outcomes outside the realm of development. The current study focused on the regulation of RNA cytosine methylation in the mouse brain and its role in anxiety and depressive-like behavior. Here, we used viral overexpression of NSUN2 in the male and female adult mouse PFC to elucidate the effect of altered NSUN2 expression on 1) tRNA methylation and abundance of tRNA fragments in the PFC and 2) anxiety and depressive-like behavior. We used next-generation RNA bisulfite sequencing and tRNA fragment sequencing to assess tRNA methylation and tRNA fragment abundance, respectively. We also performed various behavioral tests on NSUN2-overexpressing and control mice to test anxiety and depressive-like behaviors. Results indicate that overexpressing NSUN2 in the adult PFC alters emotional behavior in male and female mice in a sex-specific manner, which may be related to alterations in tRNA methylation and abundance of 5' tRNA halves. Overall, understanding the role of tRNA methylation in the adult brain may elucidate mechanisms underlying aberrant brain function during adulthood.
Funded by:
NIMH (F32MH115565-01A1) to JB
JJPVAMC-CSR&D (1I01CX001395-01) to FH
NIH (P50MH096890, subproject 2) to SA

Disclosures: J. Blaze: None. **S. Espeso-Gil:** None. **B. Javidfar:** None. **F.G. Haghighi:** None. **S. Akbarian:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.19/UU10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NRF-2017R1A2B3011098
NRF-2017M3C7A1023471
IBS-R026-D1

Title: Synaptic modifications of the hippocampus for depression by learned helplessness in mice

Authors: *S. KIM, G.-E. CHANG, H. LEE, D. LEE, G. KIM, G. HA, E. CHEONG
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Abstract: Major Depressive Disorder (MDD) is among the most devastating mental disorders characterized by disturbed symptoms in emotional states. MDD is a heterogeneous and multi-factorial etiology, but the mechanisms underlying its pathologies remain to be elucidated. Here, we used the learned helplessness procedure in mice to examine the role of hippocampus, a brain region highly shown the structural and functional deficits in MDD patients. During the learned helplessness procedure, mice are subjected to an unpredictable and inescapable electrical foot shock, and subsequently develop coping deficits for aversive but escapable situations. These learned helplessness mice showed depressive-like behaviors. By using whole cell patch clamp and immunohistochemistry, we observed changes of GABAergic synaptic inputs and neuronal activity within hippocampus in learned helplessness mice. These finding provide direct evidence that GABAergic synaptic dysfunction of hippocampus is strongly linked to depressive-like behavior by learned helplessness.

Disclosures: S. Kim: None. **G. Chang:** None. **H. Lee:** None. **D. Lee:** None. **G. Kim:** None. **G. Ha:** None. **E. Cheong:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.20/UU11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH
HDRF

Title: Brain extracellular matrix genes are dysregulated in major depressive disorder

Authors: *E. M. PARISE[1], L. F. PARISE[2], Z. S. LORSCH[1], P. J. HAMILTON[1], B. LABONTÉ[3], C. A. BOLANOS-GUZMAN[2], E. J. NESTLER[1]
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Abstract: As one of the leading causes of disease burden and disability in the world, Major Depressive Disorder (MDD) is a major public health concern. Mounting evidence suggests that structural brain abnormalities may contribute to MDD pathology, although this remains a largely unexplored area of research. The extracellular matrix (ECM) plays a crucial role both in providing structural support to the brain and facilitating synaptic plasticity. We hypothesized that alterations to this complex network of proteins surrounding neurons and glial cells could regulate morphological processes that may be involved in MDD. Therefore, to understand the role of the brain ECM in MDD, we analyzed transcriptional profiles from the nucleus accumbens (NAc) and prefrontal cortex (PFC) in postmortem brain tissue of humans with MDD and matched controls. In order to develop a translational approach to study any identified ECM-specific gene targets from MDD patients, we also assessed transcriptional profiles of mice exposed to chronic variable stress (CVS). Numerous ECM-specific genes were identified as being differentially expressed in our datasets. For the greatest translational value, only genes identified as being similarly differentially regulated across species were selected for further investigation. Of such genes, relatively few were regulated similarly in the two brain regions studied and in both sexes. For example, *Cyr61* and *Htra1* were identified as being dysregulated only in males and specifically in the PFC or NAc, respectively. Interestingly, *Cyr61* and *Htra1* are both highly enriched in astrocytes. We are currently developing the viral and transgenic tools necessary to manipulate these genes selectively within astrocytes of the PFC or NAc in order to study their functional role in stress responses at the behavioral and molecular levels. Our findings thus far support the hypothesis that the ECM of the brain is a potentially important mediator of stress responding that is influenced in both a sex- and region-specific manner.

Disclosures: E.M. Parise: None. **L.F. Parise:** None. **Z.S. Lorsch:** None. **P.J. Hamilton:** None. **B. Labonté:** None. **C.A. Bolanos-Guzman:** None. **E.J. Nestler:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.21/UU12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Hope for Depression Research Foundation
NIDA
NIMH

Title: Endogenous and CRISPR-mediated CREB-Zfp189 interactions regulate a resilient-specific transcriptional network in mouse models of depression

Authors: Z. S. LORSCH[1], *P. J. HAMILTON[3], A. RAMAKRISHNAN[2], A. LEPAK[2], P. MEWS[2], E. PARISE[2], O. ISSLER[2], L. ALCANTARA[2], S. PIRPINIAS[2], I. ORTIZ TORRES[2],

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Abstract: Only a subset of people exposed to stress develop depression. Accordingly, some animals exposed to chronic social defeat stress (CSDS) are resilient to this stress and do not develop depression-like behaviors. However, the broad transcriptional adaptations observed in resilience are not well understood. To explore this, we evaluated coexpression networks from resilient mice following CSDS. We identified a resilient-specific network in which *Zfp189*, which encodes a previously uncharacterized zinc finger transcription factor, is the top key driver and most connected gene in the network. Its expression is also decreased in PFC of human depression. We interrogated known binding motifs within this network and identified CREB as a predicted upstream regulator of the gene module. Previously published ChIP-chip data from our laboratory showed that endogenous CREB binds to *Zfp189;* this interaction is decreased following CSDS, and reversed by treatment with the antidepressant imipramine. In prefrontal cortex (PFC), viral overexpression of *Zfp198* activated our identified resilient network, which was sufficient to reverse depression-like behavior in mice. Knockdown of CREB increased susceptibility, an effect mitigated by concomitant *Zfp189* overexpression. However, it was unclear whether CREB's regulation of depression-like behaviors was acting through its interaction with *Zfp189*. To explore this mechanism, we employed a novel CRISPR-mediated, locus-specific transcriptional reprogramming method to direct CREB selectively to the *Zfp189* promoter in mouse PFC. CRISPR-mediated targeted recruitment of CREB to *Zfp189* was behaviorally pro-resilient and significantly activated our resilient network. These findings establish a causal role for CREB-*Zfp189* interactions in regulating a resilient-specific transcriptional network and illustrate how the regulatory structure of coexpression networks can be targeted to affect both broad transcriptional patterns and behavior. Given the success of these CRISPR approaches, we have broadened our research to investigate targeted CREB binding to *Zfp189* and other genes of interest in their causal contribution to the pathogenesis of addiction.

Disclosures: Z.S. Lorsch: None. **P.J. Hamilton:** None. **A. Ramakrishnan:** None. **A. Lepak:** None. **P. Mews:** None. **E. Parise:** None. **O. Issler:** None. **L. Alcantara:** None. **S. Pirpinias:** None. **I. Ortiz Torres:** None. **A. Conkey:** None. **A. McKenzie:** None. **S. Montgomery:** None. **E. Loh:** None. **A.E. Symonds:** None. **R.L. Neve:** None. **B. Zhang:** None. **I.S. Maze:** None. **L. Shen:** None. **R.C. Bagot:** None. **E.J. Nestler:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.22/UU13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NRF-2017M3C7A1048448
NRF-2016R1D1A1B03935615
ICT grant 18-BR-04-03
ICT grant 18-BD-0402
USAMRMC Grant W81XWH-16-1-0681
NARSAD Grant 20695
JPB grand 475

Title: Hippocampal mossy cell involvement in behavioral and neurogenic responses to chronic antidepressant treatment

Authors: *S. OH[1], J. CHENG[2], Y.-S. OH[4], P. GREENGARD[3], M. JUNG[5], C. SHIN[5], J. PARK[5]
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Abstract: Most antidepressants, including selective serotonin reuptake inhibitors (SSRIs), initiate their drug actions by rapid elevation of serotonin, but they take several weeks to achieve therapeutic onset. This therapeutic delay suggests slow adaptive changes in multiple neuronal subtypes and their neural circuits over prolonged periods of drug treatment. Mossy cells are excitatory neurons in the dentate hilus that regulate dentate gyrus activity and function. Here we show that tonic firing of hippocampal mossy cells is enhanced by chronic, but not acute, SSRI administration. Behavioral and neurogenic effects of chronic treatment with the SSRI, fluoxetine, are abolished by mossy cell-specific knockout of *p11* or *Smarca3* or by inhibition of the p11/AnxA2/SMARCA3 heterohexamer, an SSRI-inducible protein complex. Furthermore, acute chemogenetic inhibition of mossy cells, using Gi-DREADD activation, impairs behavioral and neurogenic responses to chronic administration of SSRI. The present data establish that mossy cells play a crucial role in mediating the effects of chronic antidepressant medication. Our results indicate that compounds which target mossy cell activity would be attractive candidates for the development of new antidepressant medications.

Disclosures: S. Oh: None. **J. Cheng:** None. **Y. Oh:** None. **P. Greengard:** None. **M. Jung:** None. **C. Shin:** None. **J. Park:** None.

Poster

233. Depression and Bipolar Disorders: Animal Models: Neural Mechanisms

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 233.23/UU14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: grant #2015/25308-3, São Paulo Research Foundation (FAPESP)

Title: DeltaFosB transcription factor is differentially regulated in brain areas related to fear processing in resilient and susceptible rats to social defeat stress

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Abstract: Although stress is known as a risk factor for psychiatric disorders, not every exposed individual develop diseases. This difference may be related to individual's ability to adapt to adversity, i.e. their resilience or susceptibility to stress. After exposure of rodents to Social Defeat Stress (SDS), two phenotypes are observed: one susceptible (SUS), that shows decreased social interaction (SI) and behavioral changes related to depression, and a resilient (RES), that does not show these alterations. An important molecule related to neuroplasticity and stress response is DeltaFosB. Its accumulation in mesocorticolimbic neurons is different between RES and SUS animals and it is related to depressive-like behaviors. However, little is known about the changes in DeltaFosB expression in brain areas related to the fear processing in these phenotypes. Thus, the aim of this study was to evaluate the DeltaFosB expression in brain areas related to defensive behaviors in RES and SUS rats to SDS. Male Wistar rats (n = 32) were exposed to 7 days of SDS (4 aggressive encounters with a male Long Evans rat, every other day). Control (CON) animals were not exposed to SDS. During this period the coat state was evaluated. After SDS animals were evaluated in the SI test to the segregation in RES and SUS by *k-means* cluster analyses using the interaction ratio (IR). Animals were perfused 24 hours later and brains processed for immunofluorescence staining of DeltaFosB in the amygdala (AMY), ventromedial hypothalamus (VMH) and periaqueductal gray (PAG). Data showed that SUS rats (stressed animals that developed social avoidance) presented increased coat state deterioration, a depression-like sign. RES rats showed an increase in DeltaFosB+ neurons in both hemispheres of the basolateral AMY (BLA), in the right hemisphere of the dorsolateral nucleus of the PAG (DLPAG) and a decrease in the right hemisphere of the central nucleus of the AMY (CeA). SUS rats showed increased DeltaFosB+ neurons in the right hemisphere of the medial nucleus of the AMY (MeA) and in the dorsomedial PAG (DMPAG). There were no alterations in the dorsal and ventrolateral parts of the VMH and in the lateral and ventrolateral PAG. Our results suggest differential molecular adaptations in RES and SUS rats to SDS in fear circuitry. RES rats showed altered DeltaFosB expression in the amygdaloid circuitry related to the fear processing of painful

stimuli (BLA and CeA), whereas SUS rats showed altered expression in circuitry related to fear processing to aggressive conspecifics (MeA and DMPAG). Thereby, coping strategies to stress seems to be related to brain processing of painful stimuli and aggression from a conspecific animal.

Disclosures: G. Morais-Silva: None. **I.B. Rossanesi:** None. **J.C. Pavan:** None. **M.T. Marin:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.01/UU15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH grant DA037426
NIH grant DA039895
R25NS090989 (NINDS)

Title: Characterizing inflammatory status of the ventral tegmental area in mouse models of depression

Authors: *V. BALI[1], B. ABOLIBDEH[2], A. R. STARK[2], M. S. MAZEI-ROBISON[1]
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Abstract: Major depressive disorder (MDD) is a devastating disease with increasing social and financial costs. Current treatments are ineffective in a substantial proportion of patients due to incomplete understanding of underlying molecular mechanisms. Rodent models suggest that dysfunction of the brain reward system, and particularly changes in activity and output of dopamine (DA) neurons in the ventral tegmental area (VTA), are necessary and sufficient for depressive-like phenotypes. Brain inflammation is a contributing factor in the development of MDD and microglia are key players in inflammatory processes of the central nervous system. Microglia undergo a phenotypic change upon activation including alterations in cellular morphology and upregulation of a number of genes. The aim of this study is to characterize the inflammatory status of the VTA in two well-established mouse models of depression, physical (PS) and emotional chronic social defeat stress (ES) that utilize experiencing (PS) or witnessing (ES) social subordination induced by short interactions with a dominant animal to cause long-term changes in neuronal function and behavior. We use ionized calcium-binding adapter molecule 1 (Iba1) stain to study number, localization, morphology and activation of microglia. Tyrosine hydroxylase, a rate-limiting enzyme in catecholamine synthesis, will be used to visualize VTA DA neurons. Next, to assess microglial reactivity we will measure mRNA levels of genes known to be deregulated by inflammation such as innate immune receptor toll-like

receptor 4, proinflammatory cytokines interleukin 1 beta, interleukin 6, and tumor necrosis factor, and anti-inflammatory cytokine interleukin 10. Changes in inflammatory signaling in neighboring dopamine-rich brain region, substantia nigra, will also be analyzed as a control. Preliminary data indicate a differential regulation of VTA inflammatory processes by PS and ES. This study seeks to identify the role of chronic stress in inflammation of the VTA, a key region of the reward circuit. Our findings have the potential to improve the understanding of fundamental cellular changes involved in development of MDD.

Disclosures: V. Bali: None. **B. Abolibdeh:** None. **A.R. Stark:** None. **M.S. Mazei-Robison:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.02/UU16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Augusta University/University of Georgia Seed Grant

Title: Does galanin mediate the effects of chronic inflammation on the mesolimbic dopamine system?

Authors: *J. SMITH[1], S. M. MOHANKUMAR[2], P. S. MOHANKUMAR[3], L. L. MILLER[5], P. V. HOLMES[4]
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Abstract: Chronic pain increases risk for anxiety and depressive disorders, which may be mediated in part by alterations in the mesolimbic dopamine system. Regulation of this system involves projections to the ventral tegmental area from noradrenergic/galaninergic neurons of the locus coeruleus. Inflammatory pain induced by intraplantar injection of complete Freunds adjuvant (CFA) decreases monoamine function in this pathway. Whether this effect is mediated by galanin was examined in rats. Guide cannula were implanted in the nucleus accumbens core and lateral ventricle. 1-week later rats received hind-paw injections of CFA (50 ul) or vehicle followed by daily injections of a galanin receptor antagonist, M40, (12 ug/day, ICV) or aCSF for 10 days. Following injections on Day 10, microdialysis probes were inserted into nucleus accumbens through the guide cannula and microdialysis testing was performed for 160 min. Rats were euthanized via rapid decapitation after behavioral testing and several brain regions were analyzed for levels of monoamines using HPLC. HPLC analysis of dialysate revealed that CFA reduced extracellular dopamine, DOPAC, norepinephrine, and 5HIAA levels in the nucleus

accumbens. M40 did not alter the effects of CFA. These results suggest that galanin does not mediate the effects of CFA on the mesolimbic dopamine system; however further research is needed to rule out a role for galanin in the effects of chronic inflammatory pain on the central nervous system.

Disclosures: J. Smith: None. **S.M. Mohankumar:** None. **P.S. Mohankumar:** None. **L.L. Miller:** None. **P.V. Holmes:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.03/UU17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01MH104261
NIDA Grant U01DA043098
ONR Grant: N00014-12-1-0366
Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Consortium

Title: Minocycline treatment reduces anxiety- and depressive-like behaviors in a genetic model of internalizing mood disorders

Authors: *P. M. MARAS[1], J. DAUGHERTY[1], E. HEBDA-BAUER[1], S. J. WATSON, Jr.[2], H. AKIL[2]
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Abstract: Many psychological disorders, such as anxiety and depression, are strongly influenced by genetic factors. Our laboratory uses a selective breeding technique to study the neurobiological mechanisms underlying the propensity to develop mood disorders. Specifically, we have found that rats bred for high locomotor responses when placed into a novel environment (bHRs) exhibit low anxiety and are resilient to depression, whereas rats bred for low locomotor responses to novelty (bLRs) are highly anxious and vulnerable to depression. Among the possible factors underlying bHR/bLR differences in affective temperament, recent mRNA expression studies in our lab suggest that bLRs have elevated expression of key microglia-related genes within their hippocampus compared to bHRs, and these differences emerge as early as postnatal day 14. To test whether elevations in microglia activation are functionally related to the vulnerability of bLRs, we administered the antibiotic drug minocycline, which has been shown to suppress microglia, for 2 weeks in adult bLRs. We examined the behavioral effects of minocycline treatment under non-stress conditions (basal), as well as when it was administered

concurrently with chronic mild stress. Whereas minocycline reduced anxiety in the elevated plus maze in non-stressed bLRs, the drug was ineffective when bLRs were challenged with stress, suggesting that microglia may play a role in the basal anxiety phenotype of bLRs, but not their anxiety response to stress. In contrast, minocycline reduced immobility time in the forced swim test regardless of stress exposure, indicating a robust anti-depressant effect of the drug in genetically vulnerable rats. Taken together, these studies reveal that natural variations in affective temperament may be at least partially explained by underlying differences in microglia gene expression and/or activation. To determine the role of microglia in the organization of emotional brain circuits, ongoing studies are examining the effects of early-life minocycline treatment on the emergence of the bLR phenotype.

Disclosures: P.M. Maras: None. **J. Daugherty:** None. **E. Hebda-Bauer:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.04/UU18

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: CIHR Grant MOP-142308

Title: Neuroplastic and neuroimmune correlates of chronic stress exposure in female mice: Modulatory roles of estrogen receptor subtypes

Authors: *R. MAHMOUD[1], P. DUARTE-GUTERMAN[1], S. E. LIEBLICH[1], S. J. WONG[1], J. A. CHAITON[1], C. CHOW[1], L. A. GALEA[2]
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Abstract: The hippocampus displays remarkable plasticity across the lifespan and is particularly sensitive to the effects of chronic stress. Notably, chronic stress alters hippocampal plasticity and the neuroimmune environment. Importantly, previous research indicates that the outcomes of chronic stress in females are dependent on ovarian hormones. Here, we examined the receptor mechanisms underlying the modulatory effects of estradiol on the neuroplastic and neuroimmune consequences of stress. Adult female mice (C57BL/6J) were ovariectomized or sham-operated, then given six weeks of daily subcutaneous injections of the ERα-selective agonist propylpyrazole-triol (PPT), ERβ-selective agonist diarylpropionitrile (DPN), estradiol (E2), or vehicle. Two weeks into hormone treatment, all mice received two injections of the DNA synthesis marker, bromodeoxyuridine (BrdU), then were assigned to four weeks of Chronic Unpredictable Stress (CUS), or to non-CUS conditions. The density of BrdU+ cells in the

granule cell layer was examined, and hippocampal cytokine levels were quantified. Preliminary results suggest that CUS reduced the survival of BrdU+ cells, but this effect was prevented by E2, suggesting a combined role of ER α and β. Further, CUS increased hippocampal interleukin-6 in ovariectomized mice, but this effect was prevented by E2 or PPT treatment, indicating that ERα activation may ameliorate inflammation in the hippocampus under chronic stress. Thus, estrogen receptor subtypes may differentially contribute to the neurogenic and neuroimmune consequences of chronic stress. Analyses of microglial density and morphology and other markers of synaptic plasticity are ongoing.

Disclosures: R. Mahmoud: None. **P. Duarte-Guterman:** None. **S.E. Lieblich:** None. **S.J. Wong:** None. **J.A. Chaiton:** None. **C. Chow:** None. **L.A. Galea:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.05/UU19

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIDA grant DA032895

Title: Chronic variable stress disrupts reward encoding and motivated behavior

Authors: *M. G. SPRING[1], E. PANTHER[1], E. VAN NEWENHIZEN[1], B. WINDSOR[1], B. KURTOGLU[1], C.-L. CHAN[2], J. MANTSCH[1], P. J. GASSER[1], R. WHEELER[1]
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Abstract: The nucleus accumbens (NAc) has long been known to play a critical role in both hedonic processing and motivation and is likely involved in the development of depression-relevant symptoms. Recent reports have detailed disruptions in NAc function and its dopaminergic input that are correlated with altered reward sensitivity in stress models of depression. To study the effect of stress on the encoding of primary rewarding and aversive stimuli by NAc neurons, adult male Sprague Dawley rats were implanted with intraoral catheters for tastant delivery and stainless steel microwire electrode arrays targeting the NAc core and shell for electrophysiological recordings. Single unit firing rates were recorded in response to intraoral infusions of sucrose and quinine both before and after a 14 day chronic variable stress (CVS) paradigm. Units were classified as excited, inhibited, or unaltered by the tastant infusion. A taste reactivity analysis of orofacial responses reflective of the hedonic perception of the tastants was performed offline. Consistent with prior studies, intraoral infusion of sucrose was found to reduce the firing rates of most responsive NAc neurons (68% inhibited, 32% excited). CVS experience reduced the number of neurons inhibited by sucrose in the shell of the nucleus accumbens (48% inhibited, 52% excited). Such inhibitory responses are typically associated with

hedonic behavioral responses. However, following CVS, animals did not show a corresponding decrease in appetitive taste reactivity. Since hedonic perception appeared to be unchanged, we hypothesized that the altered encoding of sucrose could result in a disruption in the ability of rewarding stimuli to guide motivated behavior. This was tested with a Pavlovian autoshaping task in which the presentation of a CS+ or CS- lever predicted the delivery of a sucrose pellet or no reward delivery, respectively. Animals rapidly acquired a learned interaction with the CS+ lever. However, CVS experience delayed acquisition and produced reduced approach even after acquisition. Together, these data indicate that chronic stress alters the encoding of primary reinforcers in a manner that disrupts their ability to incentivize behavior. Ongoing experiments are examining the role of dopamine in this process.

Disclosures: M.G. Spring: None. **E. Panther:** None. **E. Van Newenhizen:** None. **B. Windsor:** None. **B. Kurtoglu:** None. **C. Chan:** None. **J. Mantsch:** None. **P.J. Gasser:** None. **R. Wheeler:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.06/UU20

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: VA grant 1101 BX001374 (MAW)
VA grant 121 BX002085 (LPR)
VA grant IO1 BX001804 (LPR)
USC Research Development Fund (LPR)
NSF grant IOS-1656626 (CAG)

Title: High fat diet differentially impacts endocrine, metabolic and inflammatory markers: Relationship to depressive-like behaviors

Authors: *J. L. WOODRUFF[1,2], M. N. HERSEY[1], F. L. ROSADO[1], C. A. GRILLO[1,2], L. P. REAGAN[1,2]
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Abstract: More than 36% of adults in the United States are considered to be obese. Obesity is comorbid with many other complications including depression and chronic inflammation. However, the relationship between diet, weight gain, and the development of inflammation and depression is not well understood. To further investigate this relationship, we placed male Sprague Dawley rats on either a control diet (15% fat) or a high fat diet (HFD; 45% fat) for three months and then tested their immune, endocrine, and behavioral differences. Furthermore,

because some animals are resistant to weight-gain on the HFD, this group was subdivided into diet resistant (DR) and diet induced obesity (DIO) groups based on whether their weight gain was either above or below the control group mean. Consistent with previous observations, access to a HFD produces increases in weight gain, body fat (kidney, epididymal), and plasma leptin in some (DIO) but not all (DR) rats. From a behavioral perspective, while total fluid intake did not change, DIO rats exhibited decreases in sucrose preference compared to DR and control rats. DIO rats also exhibited decreases in latency to immobility in the forced swim test (FST). However, DR rats exhibit increases in immobility and decreases in active behaviors, specifically climbing behaviors, compared to DIO and control-fed rats. Collectively, these results suggests that beyond eliciting differential effects on endocrine and metabolic parameters, access to a HFD also differentially impacts the development of depressive-like behaviors. Moreover these results are consistent with the heterogeneous symptomatology of patients with major depressive illness, and thereby may provide insight into more targeted treatment strategies for patients with comorbid depressive illness and obesity.

Disclosures: J.L. Woodruff: None. **M.N. Hersey:** None. **F.L. Rosado:** None. **C.A. Grillo:** None. **L.P. Reagan:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.07/UU21

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Va Grant I21 BX002085 (LPR)
VA Grant IO1 BX001804 (LPR)
the University of South Carolina School of Medicine Research Development Fund (LPR)
NIH grants R01MH106563
R21MH109959 (PH)
Horiba Award for Analytical Chemistry (PH)

Title: The role of acute and chronic neuroinflammation in depression: Uncovering the relationship between histamine and serotonin transmission

Authors: *M. HERSEY, J. L. WOODRUFF[1], A. ABDALLA[3], L. P. REAGAN[2], P. HASHEMI[4]
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Abstract: Changes to the central nervous system (CNS) are often reflected via neuroinflammation, which consequently plays a role in the pathology of many neurological diseases, including depression. In order to understand the neurochemical underpinnings of depression we are targeting the neurotransmitter systems of serotonin and histamine. We are interested in serotonin because of the long hypothesized notion that serotonin signaling is impaired during depression. We are interested in histamine because of this messenger's well-established role in peripheral inflammation and new data from the Hashemi lab showing that histamine release inhibits serotonin signaling. In this work, fast-scan cyclic voltammetry (FSCV) is used to simultaneously measure histamine and serotonin, in the posterior hypothalamus and fast-scan controlled adsorption voltammetry (FSCAV) is used to measure serotonin in the hippocampus of rodents following acute (peripheral injection of lipopolysaccharide) or chronic (high fat diet; 45 kcal % fat) neuroinflammation. Our results indicate that these inflammation models correspond to an increased histamine release, thereby further inhibiting serotonin release. We believe this relationship to be responsible for the decreased capacity of escitalopram to increase extracellular serotonin that we observe in these models. These results suggest that histamine plays a fundamental role in modulating serotonin during inflammation, thereby providing novel insights into the neurochemical basis for depressive illness.

Disclosures: J.L. Woodruff: None. **A. Abdalla:** None. **L.P. Reagan:** None. **P. Hashemi:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.08/UU22

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIHMH RO1 RMH099384A (A.A.)

Title: Chronic stress compromises the NG_2-glial cellular homeostasis in a murine depression model

Authors: *A. KOKKOSIS, M. MULLAHY, B. SUAREZ, G. LUCIANO, P. ALVAREZ, A. AGUIRRE
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Abstract: Background & Objective Major depressive disorder (MDD) is a chronic debilitating illness affecting yearly 350 million people worldwide. While most of the studies focus in neuronal malfunction during stress and MDD, we have recently established an important association of NG_2-glia with MDD in a murine depression model of chronic stress (repeated social defeat stress, RSDS) in the adult CNS. The aim of the present study is the time-dependent

characterization of the effects that RSDS has on the cellular dynamics of NG_2-glia. **Methods** RSDS paradigm (10 days) was utilized to characterize the NG_2-glial dynamics during the early (5 days) and post RSDS stages (10+2 days and 10+15 days), in 8-12 weeks old male mice (C57BL/6J and *CSPG4*-$EGFP^+$ mouse lines). Throughout the RSDS paradigm all groups were given access *ad libitum* to thymidine analog BrdU (5-bromo-2'-deoxyuridine) dissolved in drinking water, for monitoring cell proliferation. Social interaction test was performed at the end of the paradigm to categorize the defeated mice to susceptible and resilient mice. Mice were then euthanized, and brains were isolated to study the MDD-affected areas of Prefrontal Cortex (PFC) and Hippocampus (HPC) (n=4-6/per group). Cell quantification and data analysis were blinded and performed by 2 different investigators in each experiment. **Results** Significant time-dependent decrease in NG_2-glial density (PDGFRα marker and *CSPG4*-$EGFP^+$ reporter line) was observed in the PFC and CA1 region of the HPC in susceptible (S) mice compared to control (C) and resilient (R) animals at 5d, 10d+2d and 10d+5d. Given the highly active proliferation profiles of NG2 glia in adult CNS, the mitotic capacity (BrdU and Ki67) was examined during chronic stress. Both markers indicated reduced proliferation capacity at the S groups during and post the RSDS paradigm. In addition, BrdU labeling retention allowed us to monitor the NG_2-glial responses to the chronic stress-induced depression and determine their fate as well. Remarkably, the S groups indicated decreased differentiation rates of BrdU-labelled NG_2-glia towards oligodendrocytes (GST-pi) and a concomitant switch towards NG_2-glial production during the post RSDS stages. In addition, chronic stress also induced alterations in the NG_2-glial morphology and branching in the S groups; features which are crucial for communication of NG_2-glia with rest of glia as well as neurons. **Conclusions** NG_2-glial cell homeostasis was swiftly compromised by chronic stress leading to significant time-dependent alterations of NG_2-glial proliferation capacity, cell density, viability and progeny contributing to the onset of depressive-like behavior in mice.

Disclosures: A. Kokkosis: None. **M. Mullahy:** None. **B. Suarez:** None. **G. Luciano:** None. **P. Alvarez:** None. **A. Aguirre:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.09/VV1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Brain and Behavioral Research Foundation Grant BBRF22296
National Institute of Mental Health Grant K23MH091254
Natural Science Foundation of China/Shenzhen Grant 31671169/000099

Title: Inflammation is associated with decreased functional connectivity between the amygdala and ventromedial prefrontal cortex in depressed patients with comorbid PTSD

Authors: *N. MEHTA[1,2], Z. LI[3,4], B. WOOLWINE[2], E. HAROON[2,5], J. C. FELGER[2,5]
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Abstract: Biomarkers of inflammation are reliably elevated in patients with both major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). Our recent studies showed that plasma inflammatory cytokines and C-reactive protein (CRP) correlated with decreased functional connectivity in corticostriatal reward circuitry in association with anhedonia and reduced motivation. These findings are consistent with previous work from our group and others demonstrating that exogenous administration of peripheral inflammatory stimuli affects the striatum and prefrontal cortical regions to drive relevant depressive symptoms. In addition to targeting corticostriatal circuitry, peripheral inflammation has also been shown to affect fear and anxiety-related brain regions, and particularly the amygdala. Many patients with MDD have comorbid PTSD or anxiety disorders; however, it is unknown whether increased inflammation in these patients is associated with altered functional connectivity within fear and anxiety circuits. Therefore, we investigated whether increased inflammation affects fear and anxiety-related circuitry to lead to symptoms of anxiety in MDD patients with or without comorbid PTSD. Resting-state functional magnetic resonance imaging was conducted on 48 medically-stable, unmedicated outpatients with major depression, 19 of whom had a secondary diagnosis of PTSD. Whole-brain, voxel-wise functional connectivity was examined as a function of plasma CRP concentrations using seeds for the right and left amygdala. In the group as a whole, increased CRP was associated with decreased functional connectivity between the right amygdala and the ventromedial prefrontal cortex (vmPFC; corrected p < 0.05) which in turn correlated with increased symptoms of anxiety (r=-0.33, df=46, p=0.022). In addition to CRP, increased plasma IL-6 and IL-1 receptor antagonist also predicted decreased connectivity between the right amygdala and vmPFC (p's < 0.05). Of note, the relationship between inflammation-related decreases in amygdala-vmPFC connectivity and increased anxiety was significant only in patients with a secondary diagnosis of PTSD (r=-0.45, df=17, p=0.005) compared to those without PTSD (p=-0.10, df=27, p=0.646), and these findings were driven by females with PTSD (r=-0.60, df=15, p=0.011). These results suggest that increased inflammation compromises amygdala-prefrontal circuitry in association with increased anxiety in patients with depression, particularly those with comorbid PTSD.

Disclosures: N. Mehta: None. **Z. Li:** None. **B. Woolwine:** None. **E. Haroon:** None. **J.C. Felger:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.10/VV2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH (R01-MH111604, Robison PI)
NIDA (R01-DA040621, Rudenko PI)

Title: The *in vivo* effects of redox state on ΔFosB complex formation and interaction partners

Authors: *H. LYNCH[1], E. J. NESTLER[3], A. J. ROBISON[2], G. RUDENKO[4]
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Abstract: Brain function is regulated by a variety of intrinsic and extrinsic factors, and this regulation occurs, at least in part, at the level of gene expression within neurons. Many of these regulating factors alter the reduction/oxidation balance within brain cells (redox state). This effect is associated with a variety of neuropathologies, but the mechanisms by which redox state controls gene expression in neurons is unknown. Many neurons critical for such activities as memory, mood, and motivated behaviors orchestrate expression of select critical genes through a transcription factor called ΔFosB, a stable splice variant of the *FosB* gene. We show that the redox-dependence of the structure-function relationship of fos-family proteins found *in vitro* (Abate et al., 1990) is found in ΔFosB *in vivo* as well. Furthermore, this characteristic is preserved across the brain.
Under non-reducing (oxidizing) fully denatured conditions, immunoprecipitation followed by Western blot reveals a shift in the molecular weight of ΔFosB from 37kDa to ~75kDa and ~150 kDa. This could represent the binding of ΔFosB to other proteins through disulfide bridge formation between cysteine residues that has been demonstrated *in vitro (*Kouzarides and Ziff et al., 1988). We demonstrate that JunD and Smad3 are examples of potential binding partners. In contrast, under reducing conditions, ΔFosB remains at 37kDa, indicative of no covalent complex formation. Taken together, these data suggest that ΔFosB complex formation in the brain is directly regulated by redox state. Having a better understanding of how the structure-function relationship of ΔFosB is regulated by redox state may ultimately allow us to use ΔFosB as a therapeutic target for diseases that are associated with an altered redox state.

Disclosures: H. Lynch: None. **E.J. Nestler:** None. **A.J. Robison:** None. **G. Rudenko:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.11/VV3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Brain and Behavior Research Foundation NARSAD Young Investigator Award to GEH

Title: Sub-chronic and chronic variable stress induces sex specific effects on glutamatergic synapses in the nucleus accumbens core and shell sub-regions

Authors: *M. TSYGLAKOVA, K. A. UNROE, B. H. SMITH, J. R. RAINVILLE, G. E. HODES
Virginia Tech., Blacksburg, VA

Abstract: Depression and anxiety are common and debilitating mood disorders, and they are more prevalent in females than males. Previously, we showed that 6 days of sub-chronic variable stress (SCVS) induced behavioral stress susceptibility in females but not males. These behavioral effects were accompanied by sex specific changes in circuit-specific pre-synaptic changes in synapses containing VGLUT1 and VGLUT2 in the nucleus accumbens shell sub-region (NAc) (Brancato et al., 2017). Here, we examined synaptic changes in the NAc shell as well as core sub-regions of male and female mice following 6 days of SCVS and 28 days of chronic variable stress (CVS). The NAc was examined as it shows sex specific regulation of plasticity that has been associated with the effects of stress on behavior (Brancato et al., 2017, Christoffel et al, 2011, 2012). We hypothesize that different synaptic changes will emerge at 6 and 28 days within NAc shell and core. In particular, we are studying whether the synaptic changes in males and females after CVS follow the same or opposite patterns found after SCVS, and whether there are differences in the synaptic changes between the core and shell sub-regions. Specifically, we are using immunohistochemical analysis for expression of VGLUT1 and VGLUT2, presynaptic markers of glutamatergic inputs to the NAc, and PSD95, an excitatory postsynaptic marker, in the NAc core and shell sub-regions following 6 and 28 days of stress. Analysis of chronic and sub-chronic stress effects on synaptic plasticity in NAc sub-regions is ongoing.

Disclosures: M. Tsyglakova: None. **K.A. Unroe:** None. **B.H. Smith:** None. **J.R. Rainville:** None. **G.E. Hodes:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.12/VV4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NARSAD Young investigator award from the Brain & Behavior Research foundation to GEH

Title: Elucidating the contribution of sex differences in the peripheral immune system to stress susceptibility and depression

Authors: *J. R. RAINVILLE[1], J. W. MURROUGH[2], G. E. HODES, 24061[1]
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Abstract: Sex differences in the prevalence, symptomology, and response to treatment in patients diagnosed with major depressive disorder (MDD) suggest the possibility that the underlying biological mechanisms of depression may differ between men and women, who are more than twice as likely to be diagnosed with depression. The immune system is altered in patients with MDD, with changes to numbers and ratios of immune cells as well as differences in inflammation, many of which appear to be oppositely regulated in men and women. Interestingly, women are also more susceptible to autoimmune diseases, and women with autoimmune disease are at an even higher risk of developing depression. Here, we compare sex differences in cytokine profiles for humans with MDD to a stress-based animal model. Serum was sampled from pre-menopausal women and age matched men with a diagnosis of MDD and from healthy controls. Cytokine protein levels were detected using multiplex enzyme-linked immunosorbent assays. Sex differences were examined by group effects and by correlation to quick inventory of depressive symptomology (QIDS) scores. In mice, subjects were given a 6- or 28-day course of variable stress. Mice were exposed to a combination of foot shock (0.45 mA/ 2 sec/ 100 in 1 hour), tail suspension and restraint stress, one stress per day, repeated for 6 or 28 days. Following 6 days of stress, only females express behavior across a test battery consisting of splash test, novelty suppressed feeding, and forced swim. Both male and female mice display depression-like behavior following 28 days of variable stress. In mice, blood was sampled immediately after the final stress exposure, one day prior to behavioral testing, in order to examine cytokine levels and behavior in the same subjects. In both humans and mice, we determined that the overall pattern of peripheral cytokine expression in response to MDD or stress was different between males and females. In mice, a composite stress susceptibility score, calculated from individuals' scores on the three behavior tests, was negatively correlated with GM-CSF in females following 6-days of stress, but positively correlated in males following 28

days of stress. IL-9 expression was correlated with stress susceptibility following 6 days of stress in females only. In patients with MDD we found that IL-17a and MCP-1 significantly correlated with QIDS scores. When male and female data were analyzed separately, 12 cytokines were significantly regulated by depression in women and only 2 were significantly regulated in men. Additional cytokine analysis is ongoing.

Disclosures: J.R. Rainville: None. **J.W. Murrough:** None. **G.E. Hodes:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.13/VV5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NARSAD Young Investigator Award

Title: Examining individual differences in susceptibility and resilience to the variable stress model

Authors: A. P. JOHNSON[1], J. R. RAINVILLE[2], *G. E. HODES[1]
[1]Neurosci., [2]Virginia Tech., Blacksburg, VA

Abstract: Stress is a risk factor for mood disorders such as depression, but not all individuals that experience stress go on to develop depression. The social defeat stress model has indicated that individual differences in behavior can identify which animals are stress susceptible, and which are stress resilient. Using this behavioral endpoint, numerous studies have identified molecular and circuit related mechanisms that contribute to individual differences in the stress response. However, the majority of this work was performed on male subjects, as there are difficulties associated with performing social defeat in females. The variable stress model allows researchers to expose both sexes to the exact same stress paradigm and examine behavioral responses across a test battery. The stress paradigm consists of 3 different stressors each given for an hour a day: foot shock (100, 0.45mA/ 2 seconds), tail suspension and restraint stress. After 6 days of variable stress there are group effects on females but not males, following 28 days of stress both sexes engage in depression associated behaviors. Here we expand upon these studies to examine a longer timeline of stress exposure, the lasting effects of stress, and develop behavioral indicators that can be used to identify individual differences in the stress response within sex. Following extension of the stress paradigm to 56 days, female mice, as a group, expressed a resilient behavioral phenotype, whereas males responded to the stress in a similar fashion to that of 28 days of stress. When both the 6- and 28-day stress paradigms were altered to include a 30-day recovery period prior to behavioral testing, both female and male mice exhibited behaviors suggesting spontaneous recovery. Ongoing work examining individual

responses across multiple studies to identify individual behavioral indicators of stress susceptibility and resilience will also be discussed.

Disclosures: A.P. Johnson: None. **J.R. Rainville:** None. **G.E. Hodes:** None.

Poster

234. Depression and Bipolar Disorders: Neural Mechanisms: Inflammation and Depression

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 234.14/VV6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: The effects of altered gut biome in a ketamine-sensitive model of treatment-resistant depression

Authors: *S. W. WHITE[1], K. J. SUFKA[2]
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Abstract: Gut dysbiosis is thought to play a role in the development of stress-related disorders, including major depressive disorder (MDD). Whether dysbiosis also plays a role in resistance to antidepressant treatment is unknown. Utilizing a novel avian model of treatment-resistant depression (TRD), we manipulated the gut biome using non-medicated vs medicated (with antibiotics) feed to study stress-responsivity and ketamine sensitivity. Socially raised chicks were exposed to either non-medicated or medicated feed for four days. On days 6-7, chicks were exposed to an isolation stressor for 90 min under increasing doses of ketamine (0, 5.0, and 10.0 mg/kg IP). Patterns of distress vocalizations across the 90 min session representing anxiety and depression phases served as the dependent measure. No differences were detected across all conditions in the anxiety phase (0-5 min of isolation). Under saline, both medicated and non-medicated groups displayed similar decrease in distress vocalizations as they entered into behavioral despair (i.e. depression phase, 30-90 min of isolation). Ketamine produced a dose-dependent antidepressant effect in the non-medicated groups but was ineffective in the medicated group. These findings suggest antibiotic-induced dysbiosis influences response to the novel antidepressant ketamine and prompts further investigation into the relationship between antibiotic-induced gut dysbiosis and response to typical monoaminergic antidepressants.

Disclosures: S.W. White: None. **K.J. Sufka:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.01/VV7

Topic: G.08. Drugs of Abuse and Addiction

Support: ADARP DMAC Award (2938-0435)

Title: Maternal cannabis vapor exposure dose-dependently impairs behavioral flexibility in adult offspring

Authors: H. R. WRIGHT, C. R. WARRICK, J. R. KUYAT, J. W. RODRIGUEZ, J. M. LUGO, *R. J. MCLAUGHLIN
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Abstract: Cannabis is the most commonly used illicit substance among pregnant women, yet the effects of prenatal cannabis exposure on cognitive functioning in offspring remain largely unknown. With recreational cannabis laws now in effect in 8 states and counting, there is growing concern that maternal cannabis use during pregnancy could increase dramatically in the coming years. Thus, there is an urgent need to better understand the impact of prenatal cannabis exposure on cognitive functioning later in life. We investigated whether chronic exposure to vaporized cannabis during pregnancy alters cognitive flexibility in male and female offspring using an automated attentional set-shifting task. Female dams were passively exposed to vaporized cannabis extract (29.2% THC; 50 or 400mg/mL; 1 puff every 2 min for 1 hr, twice daily) or vehicle vapor throughout mating and gestation. Separate cohorts of dams were not exposed to any vapor during pregnancy. Beginning at postnatal day 55, all offspring were trained to press a lever that was paired with delivery of a cue light to receive a sugar pellet reward. On the day after learning criteria were reached, rats were tested in the set-shifting task, whereby they had to disregard the previously learned strategy in favor of an egocentric spatial strategy. On the final day of testing, rats were tested in a reversal-learning task that required them to press the lever opposite of the previous task. The number of trials required to meet criterion and the number errors, along with error type (perseverative, regressive, or never reinforced) were tabulated and compared across groups.Results indicate that rats prenatally exposed to cannabis vapor showed no impairment in visual cue discrimination, suggesting that they are capable of learning rule contingencies in a manner comparable to non-exposed rats. However, exposure to high (400 mg/ml) but not low (50 mg/ml) concentrations of vaporized cannabis extract resulted in significant impairment in attentional set shifting compared to no vapor control rats. Specifically, high-dose prenatal cannabis exposure led to an increased number of never-reinforced and regressive errors, which is indicative of an inability to acquire and maintain the new rule. There were no deficits in reversal learning at either dose of cannabis and no significant

sex differences in any endpoints. These data indicate that maternal cannabis vapor exposure dose-dependently impairs behavioral flexibility in adult offspring. Ongoing research is exploring differences in ventral striatal function and prenatal cannabis-induced alterations in dopamine- and endocannabinoid-related gene expression.

Disclosures: H.R. Wright: None. **C.R. Warrick:** None. **J.R. Kuyat:** None. **J.W. Rodriguez:** None. **J.M. Lugo:** None. **R.J. McLaughlin:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.02/VV8

Topic: G.08. Drugs of Abuse and Addiction

Support: The John Templeton Foundation

Title: Paternal THC exposure in rats impacts neurobehavioral effects in the offspring

Authors: *E. D. LEVIN[1], A. B. HAWKEY[2], E. YAZDANI[1], B. KENOU[1], H. WHITE[1], C. WELLS[1], M. CAULEY[1], A. H. REZVANI[3], S. K. MURPHY[1]
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Abstract: Developmental neurotoxicity with maternal exposure during gestation is very well established for a wide variety of toxicants. In contrast, the effects of paternal exposure on offspring neurotoxicity is much less well studied. Preconception exposure to toxicants can have intergeneration effects via altering sperm epigenetic marks. Most, but not all of the genomic DNA methylation in sperm is normally removed after fertilization. Any remaining methylation may result in abnormal gene regulation and expression in the offspring. In the current study, we investigated the potential intergenerational effects of a 12-day exposure to 0 or 2 mg/kg/day (PO) of delta9-tetrahydrocanabinol (THC) in young adult male rats. These males were mated with drug naive females. Neurobehavioral function in their male and female offspring were examined in a battery of tests to assess locomotion, emotional function and cognition. This paternal THC exposure was not found to significantly impact the viability and growth of the offspring. However, it did cause a significant impairment in attentional performance in the offspring relative to controls when they were tested in adulthood. There was also a significant increase in locomotor activity in the offspring of the males exposed to THC prior to mating. This study shows that premating THC exposure can cause deleterious behavioral effects in the offspring. Further research should be conducted to determine the degree to which this type of risk is seen in humans and to investigate the mechanisms underlying these effects and possible treatments to ameliorate these adverse behavioral consequences of paternal THC exposure.

Disclosures: E.D. Levin: None. **A.B. Hawkey:** None. **E. Yazdani:** None. **B. Kenou:** None. **H. White:** None. **C. Wells:** None. **M. Cauley:** None. **A.H. Rezvani:** None. **S.K. Murphy:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.03/VV9

Topic: G.08. Drugs of Abuse and Addiction

Support: Philip Morris International Inc. Grant 100197
Brazilian National Council of Research Grant 201542/2014-5
Drug Design and Pharmacology Department at the University of Copenhagen (Grant Number Not Applicable)

Title: Prenatal nicotine exposure is associated with functional changes of NMDA receptors within the laterodorsal tegmental nucleus (LDT) of juvenile mice

Authors: *F. S. POLLI, K. A. KOHLMEIER
Drug Design and Pharmacol., Univ. of Copenhagen, Kobenhavn O, Denmark

Abstract: Nicotine acts as a stimulant in the mammalian brain, and exhibits powerful dependency-inducing properties, with women less likely to quit than men. The difficulty in quitting is reflected in the staggeringly high number of pregnancies which are associated with smoking, or with the well-intentioned use of non-combustible abstinence aids which still include nicotine exposure. During brain development, nicotine acts as a teratogen, and disturbs the trajectory of neural development, including glutamate transmission. Changes in glutamate receptor function by prenatal nicotine exposure (PNE) have been linked to negative behavioral outcomes, such as learning and memory deficits. The LDT has been suggested to play a role in processes underlying learning and memory via cholinergic, glutamatergic, and GABAergic afferents directed to midbrain and thalamic centers. We have recently demonstrated functional changes of AMPA receptors in the LDT of young PNE mice. In the current study, we investigated potential PNE effects on the functionality of NMDA receptors (NMDARs) using *ex vivo,* whole-cell patch clamp recordings. In order to putatively phenotypically-identify LDT cells, we categorized LDT neurons into three types, as previously described. Type I neurons exhibit a fast after-hyperpolarization T-type calcium current and are mostly small cells, which are likely fast spiking, GABAergic interneurons. Type II cells exhibit an A-type transient outward potassium conductance and represent most of the cholinergic neurons. The type III LDT neuronal population exhibits both A and T type currents, and likely includes glutamatergic and cholinergic cells. Relative NMDA-mediated inward currents evoked at +20 and 0 mV in Mg^{+2}-containing ACSF were greater in Type 1 PNE LDT neurons vs. controls, and a significantly slower decay kinetic was seen in PNEs at -60 mV in Mg^{+2}-free ACSF. In type III neurons, PNE

induced a greater relative NMDAR-mediated, evoked outward current at +40 mV and a smaller relative inward current amplitude at +20 and 0 mV, with faster deactivation kinetics. No current/voltage or deactivation time constant differences were present in type II neurons between PNEs and controls. The observed changes in NMDAR function within the LDT could be associated with reduced output from excitatory projection neurons due to smaller direct excitation, as well as to enhanced local inhibition. Reduced output to cortical and subcortical targets could be expected to contribute to cognitive deficits observed in offspring exposed to nicotine during gestation. Further studies of PNE-associated alterations in glutamate signaling through NMDARs in the LDT are ongoing.

Disclosures: F.S. Polli: None. **K.A. Kohlmeier:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.04/VV10

Topic: G.08. Drugs of Abuse and Addiction

Support: Internal Grant

Title: Prenatal opioid exposure results in decreased myelination and facilitates a pro-inflammatory microenvironment in offspring

Authors: *J. MAXWELL[1], T. R. YELLOWHAIR[2], J. NEWVILLE[3], C. L. SHROCK[4], A. M. ALLAN[6], L. N. BAKHIREVA[3], F. J. NORTHINGTON[7], S. ROBINSON[5], L. L. JANTZIE[8]
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Abstract: Substance use disorder among pregnant women reached epidemic proportions, with nearly 6 out of 1000 hospital births affected by prenatal opioid exposure (POE). Opioid use during pregnancy can result in multiple complications including premature labor, intrauterine growth restriction and intrauterine death. The impact of POE on the developing fetus, and specifically on the developing brain, is incompletely characterized. To facilitate mechanistic inquiries, we created a preclinical model of POE. We hypothesized that POE in rats would alter brain and body development of offspring, characterized by increased inflammation, decreased myelination, and growth restriction. On embryonic day 16 (E16), osmotic mini pumps were implanted in pregnant Sprague Dawley rats for continuous methadone infusion with 16 mg/kg methadone or saline. Pups were born at E22 and remained with their dams, receiving methadone

exposure via milk. Maternal and pup urine methadone levels were determined using a methadone ELISA. Pups were weighed daily. Pup serum and brains were collected at intervals from postnatal day 0-21 (P0-P21). Serum pro-inflammatory biomarkers were assayed using multiplex electrochemiluminescent immunoassays. Diffusion tensor imaging and Western blots were used to assess white matter microstructure, myelination and axonal injury. Group differences were compared with Student's t-test or one-way ANOVA with posthoc correction; $p<0.05$ was considered significant. Methadone levels in urine were confirmed in dams (mean 11 ng/mL) and pups (mean 3.5 ng/mL). Pups exposed to methadone were significantly smaller at P0 and P21 compared to saline controls (all $p<0.05$). At P10, significant increases in serum interleukin-1beta (IL-1β, $p<0.001$), IL-6 ($p<0.05$) and tumor necrosis factor alpha (TNFα, $p<0.01$) were observed in methadone exposed pups compared to saline, with continued elevations through P21. Additionally, POE resulted in a persistent 30% decrease in myelin basic protein expression in methadone pups compared to controls at P14 and P21 ($p<0.001$) concomitant with a decrease in the phosphoneurofilament/neurofilament ratio ($p<0.05$). Together, these data support the hypothesis that POE causes myelination and axonal injury concomitant with reduced body weights in pups similar to what is observed in human neonates following opioid exposure. Opioid exposure resulted in an increased inflammatory signature in pup serum throughout the first 3 postnatal weeks. Additional studies are necessary to characterize the effects of POE on the brain so that targeted interventions can be implemented to improve the long-term outcomes in this vulnerable patient population.

Disclosures: J. Maxwell: None. **T.R. Yellowhair:** None. **J. Newville:** None. **C.L. Shrock:** None. **A.M. Allan:** None. **L.N. Bakhireva:** None. **F.J. Northington:** None. **S. Robinson:** None. **L.L. Jantzie:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.05/VV11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Training Grant 5K12GM000680-18
NIH Grant MH101477
NIH Grant DA044297

Title: β1-integrin during adolescence supports complex decision making and confers resilience to cocaine-seeking behavior in adulthood

Authors: A. J. WHYTE[1], *S. L. GOURLEY[2]
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Abstract: Adolescent brain development is a dynamic process during which dendritic spines - the primary sites of excitatory synapses - in the prefrontal cortex undergo rapid proliferation, pruning and then refining into adulthood. This process creates a window of vulnerability during which disruption of dendritic spine stability and maturation may contribute to long-term susceptibility to drug addiction and related deficits in decision making. Of interest then, are molecular targets that promote dendritic spine stability in the postnatal prefrontal cortex. Here, we investigated whether β1-integrin, one subunit of the heterodimeric integrin cell adhesion receptor that has been implicated in postnatal cytoskeletal stability, is involved in cocaine seeking and action-consequence-based decision-making behaviors dependent on the orbitofrontal prefrontal cortex (oPFC). We hypothesized that loss of Itgb1 (the gene encoding β1-integrin) within the adolescent oPFC would: 1) exaggerate the reinstatement of cocaine seeking in cocaine self-administering mice; 2) impair action-consequence decision making, biasing mice toward habit-based behavior at the expense of oPFC-dependent goal-directed actions; and 3) that these neurobehavioral effects could be ameliorated by pharmacologically manipulating the β1-integrin signaling partners, Abl2/Arg kinase (Arg) and Rho-kinase 2 (ROCK2), during an adolescent sensitive period. In support of our hypothesis, adolescent-onset viral-mediated knockdown of Itgb1 selectively within the oPFC exaggerated cue-induced reinstatement of cocaine seeking and impaired action-consequence decision making, biasing mice towards engaging inflexible in habits. Further, pharmacological treatment with an Arg stimulator or a ROCK2 inhibitor during a sensitive period in adolescence blocked long-term deficits in decision making, facilitating goal-directed action selection even after the cessation of drug treatment. Thus, developmental β1-integrin-Arg-ROCK interactions appear to support action-consequence decision making and cocaine resilience. Activation of β1-integrin signaling events may correct maladaptive decision making in addiction.

Disclosures: A.J. Whyte: None. **S.L. Gourley:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.06/VV12

Topic: G.08. Drugs of Abuse and Addiction

Support: Virginia Youth Tobacco Programs
Virginia Foundation for Healthy Youth

Title: Sex- and age-dependent expression of Cdk5, p35, and p25 proteins, their lateralization in adolescent and adult mice, and the effects of repeated nicotine injections

Authors: A. D. HUDSON[1], *K. J. FRYXELL[2]
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Abstract: Cyclin-dependent kinase 5 (Cdk5) is a proline-directed kinase with critical roles in neuronal development, synaptic regulation, and drug abuse. Cdk5 enzyme activity is regulated primarily through binding to its protein partner p35, which can be cleaved by the calcium-dependent protease calpain to produce a more stable subunit called p25. We measured Cdk5, p35, and p25 mRNA and protein levels in the ventral striatum of early adolescent and young adult male and female C57BL/6J mice, who were treated by repeated injections of either nicotine or saline. Overall, we found that the expression of Cdk5 and its regulators was highly sex- and age-specific. Moreover, Cdk5 expression was clearly asymmetric in adolescents (differed between the left vs. right hemispheres of the brain). For example, Cdk5 protein was 60% higher in the left (vs. right) hemisphere of adolescent females, the differences being highly significant. In adolescent males, it was 30% higher in the right (vs. left) hemisphere. In adolescent females, nicotine injections downregulated Cdk5 and eliminated its lateralization. In adolescent males, nicotine injections *increased* lateralization and reversed the direction of their lateralization, the differences again being highly significant. In adult males and females there was little, if any, lateralization of Cdk5 expression, and only small (but significant) changes in Cdk5 expression levels in response to nicotine (up in females, down in males). In adolescent males, the expression of p35 protein was increased 60% by nicotine injections, but this expression was symmetric between left vs. right hemispheres. Adolescent females and adults of either sex showed only minor (nonsignificant) changes in p35 expression after nicotine injections. We also observed pronounced, sex- and age-dependent differences in the formation of p25. Taken together, our observations of adolescent-specific asymmetry in Cdk5 protein levels, and age- and sex-dependent differences in p35 and p25 protein levels, indicate that fundamental and sex-specific changes in this crucial signaling pathway are occurring during adolescent development. Nicotine injections profoundly altered the lateral asymmetry of Cdk5 expression in adolescents, presumably due to bilateral stimulation of the midbrain dopamine pathway by nicotine. However, nicotine affected Cdk5 lateralization in opposite directions in adolescent males vs. adolescent females, suggesting that sex-specific factors continued to modify the lateralized activity of the midbrain dopamine pathway even during bilateral activation by nicotine.

Disclosures: A.D. Hudson: None. **K.J. Fryxell:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.07/VV13

Topic: G.08. Drugs of Abuse and Addiction

Support: UCI Department of Emergency Medicine
Undergraduate Research Opportunity Program

Title: CRISPR/Cas9 knockdown of alpha 6 nicotinic acetylcholine receptor subunit in the adolescent rat brain

Authors: *M. REN[1], J. CHANG[1], S. LOTFIPOUR[1,2]
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Abstract: While drugs of abuse have different mechanisms of action, they all provide reinforcing effects through activation of mesolimbic dopamine neurons in the ventral tegmental area (VTA). VTA dopamine neurons express a majority of the neuronal nicotinic acetylcholine receptors (nAChRs) in the brain. Alpha 6 (α6) nAChR subunits (encoded by the CHRNA6 gene) modulate dopamine release and regulate psychostimulant use in adults. It is currently unknown whether CHRNA6 influences psychostimulant use during adolescence, a sensitive developmental period when α6 peaks in expression and may lead to unique developmental drug effects on the maturing limbic system. To investigate the role of CHRNA6 in adolescent psychostimulant use, we developed an adeno-associated virus (AAV) CRISPR/Cas9 method to selectively knock down CHRNA6 in the rat adolescent brain (postnatal day (P) 28-42)). In order to inject the packaged AAV into the VTA, we first determined exact stereotaxic coordinates in preadolescent (P24-25) rats using intracranial injections of cresyl violet. We then confirmed that our CRISPR/Cas9 system disrupts the coding sequence of CHRNA6 by analyzing restriction enzyme-digested DNA banding patterns from gel electrophoresis. Our results show that CHRNA6-targeting guide RNA (gRNA) changes the base pair length of isolated DNA compared to control scramble gRNA, suggesting formation of indels. Future experiments using DNA sequencing, immunohistochemistry, and gene expression analysis will confirm these results. This experiment provides anatomical stereotaxic coordinates needed for VTA injections in preadolescent rats and the feasibility of CRISPR/Cas9-mediated knockdown approach, which will assist in identifying the molecular mechanisms mediating adolescent substance use.

Disclosures: M. Ren: None. **J. Chang:** None. **S. Lotfipour:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.08/VV14

Topic: G.08. Drugs of Abuse and Addiction

Title: Effect of pharmacological interaction between methylphenidate and citalopram on locomotor activity and voluntary consumption of methylphenidate

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Abstract: Methylphenidate (MPH) is a weak psychostimulant which is used in the treatment of attention deficit hyperactivity disorder (ADHD), its effect is exerted by blocking reuptake of dopamine (DA) and noradrenaline (NA), and practically it has not effect on the serotonin (5-HT) transporter, unlike other psychostimulants as cocaine. It has been described that MPH may have some addictive potential, which has not been truly supported. Serotonin (5-HT) is a monoamine that has been linked to various affective disorders, particularly depression and anxiety; so that, citalopram (CIT), a serotonin reuptake inhibitor is one of the drugs of choice to treat such conditions. It is common the prescription jointly of these two substances in clinic for the treatment of disorders in comorbidity such as ADHD and depression and/or anxiety. In order to study if treatment with CIT is able to increase the psychostimulant effect of MPH on locomotor activity and promotes or increase its voluntary consumption, adult male Wistar rats of 60 postnatal days were treated chronically (16 days), with either co-administered with methylphenidate (10mg/Kg) and citalopram (3mg/kg), or just methylphenidate (10mg/Kg), or just citalopram (3mg/kg), 40 min before evaluating the motor activity. Afterwards, the semi- and voluntary consumption of methylphenidate was evaluated. The co-administered group presented greater motor activity than the control group and those administered with a single drug. The group previously treated with only MPH, presented lower semi- and voluntary MPH consumption than the control group, and that the treated with only CIT, respectively. The co-administration of MPH + CIT enhanced the effect on motor activity (greater distance wandered and number of explorations); however, no sensitization effect was observed due to chronic treatment for any group. The lowest semi-voluntary and voluntary MPH consumption observed in the group treated with only this drug (VEH + MPH) suggests that chronic administration of methylphenidate not only does not facilitate its further consumption, rather, it could prevent the high consumption of this drug.

Disclosures: C.C. Álvarez-Padilla: None. **J. Juarez:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.09/VV15

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA041708
NIH Grant GM103436

Title: Early-life risperidone administration enhances amphetamine-conditioned place preference in adult rats

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Abstract: Antipsychotic drugs are used to treat pediatric psychiatric disorders, but little is known about the effects of these drugs on brain development. We have shown in rats that early-life administration of the most widely prescribed antipsychotic drug in children, risperidone, leads to greater sensitivity to the locomotor effects of amphetamine in adulthood. The purpose of this study was to determine if early-life risperidone administration enhances the rewarding effects of amphetamine in adulthood. Female and male Long-Evans rats received daily injections of 3.0 mg/kg of risperidone or vehicle on postnatal days 14 through 28. Beginning on postnatal day 70, all rats were tested for amphetamine-conditioned place preference (CPP) - two doses of amphetamine (0.5 and 1.5 mg/kg) were compared. Adult rats administered risperidone early in life demonstrated a modest yet significant increase in the percentage of time spent in the amphetamine-conditioned chamber, mainly towards the end of the test period. A similar study in rats administered risperidone in an identical manner during adulthood did not reveal any significant effects on amphetamine CPP. These results suggest that developing brains are uniquely sensitive to antipsychotic drug administration and raise concerns about the impact of early-life use of these drugs on substance abuse liability later in life.

Disclosures: T. Downnen: None. **E.C. Baltes Thompson:** None. **C. Crane:** None. **M.E. Bardgett:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.10/VV16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA022340
NIDA Grant DA039690

Title: Cannabinoid exposure in adolescence alters cocaine reward in adulthood to expedite binge use

Authors: *J. M. WENZEL, V. M. AYVAZIAN, J. CHEER
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Abstract: Cannabinoids (CBs) are the most commonly abused illicit drugs among adolescents, and regular use of CBs during development is associated with adulthood psychiatric disease, including cocaine abuse/addiction. However, the underlying cause of this phenomenon is

unclear. Research shows that CB exposure in adolescence has long-lasting effects on monoamingeric systems. Given the well-documented role of dopamine in cocaine reward, it is possible that CB exposure during this critical time window affects dopamine system maturation and may result in long-term effects on dopaminergic response to cocaine and cocaine reward. Indeed, we have previously shown that adolescent exposure to the synthetic cannabinoid WIN 55,212-2 (WIN) dose-dependently attenuates conditioned place preference (CPP) for cocaine, and, in fact, adolescent treatment with a moderate dose of WIN results in cocaine conditioned pace aversion (CPA) in adulthood. However, it is counterintuitive that adolescent exposure should abolish cocaine reward, considering the reported increased incidence of cocaine abuse in individuals with CB experience. Human and animal studies outline opponent processes of cocaine administration: an initial period of cocaine reward/euphoria which then gives way to dysphoria and anxiety. Indeed, rats develop a CPP to the immediate effects of IV cocaine (0-5min after administration) and a CPA to the delayed effects of the drug (15-20 min after administration). Thus, cocaine experience is the sum of these positive and negative effects, of which either may lead to future use through positive and negative reinforcement processes, respectively. Here we sought to examine how adolescent WIN exposure may expedite the switch from positive to negative experience of cocaine. Male rats were treated with WIN or vehicle in adolescence, and in adulthood they underwent place conditioning for the immediate effects of cocaine, however here we shortened the conditioning session (from 5 to 2min). Interestingly, when exposed to the conditioning environment for only 2min, both WIN-treated and control rats developed a CPP for cocaine, suggesting that adolescent CB treatment does not abolish cocaine reward in adulthood, but hastens the switch from positive to negative experience of the drug. It remains unclear how these alterations in cocaine reward translate to cocaine-seeking. However, cocaine-induced anxiety/dysphoria is hypothesized to promote binge use of the drug and reduced cocaine reward is associated with increased cocaine intake. Current research investigates the role of mesolimbic dopamine in these phenomena using fast scan cyclic voltammetry.

Disclosures: J.M. Wenzel: None. **V.M. Ayvazian:** None. **J. Cheer:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.11/VV17

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA-IRP
FDA-CTP Grant

Title: Nicotinic acetylcholine receptor density in the rat brain changes in response to nicotine dose and exposure age

Authors: *M. E. PRILLAMAN[1], R. J. KEELEY[1], J. L. GOMEZ[1], T. E. MAYER[2], P.-J. TSAI[1], H. LU[1], M. MICHAELIDES[1], Y. YANG[1], E. A. STEIN[1]
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Abstract: Smoking directly causes 18% of all deaths in the United States, and most smokers begin their habit during adolescence. Adolescence itself is a time of vulnerability to the effects of multiple drugs of abuse, including nicotine, the main addictive compound in tobacco. Therefore, to understand tobacco smoking and resultant nicotine addiction, modeling adolescent exposure to nicotine is required. To this end, male Sprague-Dawley rats were chronically infused with nicotine for 6 weeks, beginning either in adolescence (postnatal day (p) 33) or adulthood (p68). Saline or nicotine at either a low (1.2mg/kg/day) or high (4.8mg/kg/day) dose was chronically infused via osmotic minipump. Beginning prior to and continued throughout the exposure period, behavioral tests and MRI scanning occurred at 2-week intervals. Immediately following the last behavior and scanning session, brains were removed and flash frozen. Using autoradiography techniques, we quantified nicotinic acetylcholine receptors (nAChR). [3H]-nicotine was used to measure receptor binding to all nAChRs, while [3H]-A-85380 specifically examined the α4β2 receptor subtype, which comprises over 90% of all mammalian nAChRs. Regions of interest included those relevant to addiction, such as insula, caudate putamen, and ventral tegmental area, as well as regions known to undergo significant changes throughout the course of development, including frontal cortical regions. Preliminary quantification of prelimbic and insula cortices revealed nicotine dose-dependent increases in total nAChR density, and an interaction between nicotine exposure age and nicotine dose specifically in the prelimbic cortex, a region that undergoes significant changes over the course of regular development and is functionally homologous with the human prefrontal cortex. Since the prefrontal cortex regulates emotional cognitive control, which modulates tendencies like impulsivity and compulsivity, our preliminary data suggests nicotine exposure during adolescence may delay or inhibit prefrontal cortex development and lead to further drug-seeking behaviors.

Disclosures: M.E. Prillaman: None. **R.J. Keeley:** None. **J.L. Gomez:** None. **T.E. Mayer:** None. **P. Tsai:** None. **H. Lu:** None. **M. Michaelides:** None. **Y. Yang:** None. **E.A. Stein:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.12/VV18

Topic: G.08. Drugs of Abuse and Addiction

Title: Long-term effects of weight fluctuation during adolescent cannabinoid exposure

Authors: G. D. MEDLEY[1], R. D. LUNDY[1], D. L. CASHEL[1], H. M. PARRISH[1], N. A. STELLY[1], *P. A. JACKSON[2]
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Abstract: While there have been many studies observing the effects of natural and synthetic cannabinoids, relatively few have focused on the long-term effects of adolescent cannabinoid exposure on memory, sociability, and anxiety. As pointed out in Schneider's (2009) review, perinatal exposure to cannabinoids often results in cognitive deficits in adulthood, but emotional changes exhibit a much greater degree of variability. For example, Biscaia et al. (2003) found anxiolytic-like responses after adolescent cannabinoid exposure whereas O'Shea et al. (2006) reported increased anxiety in adulthood. One possible explanation for this inconsistency is reduced food consumption and lack of comparable weight gain in cannabinoid exposed animals (see Biscaia et al., 2003; Schneider, 2009). The current study addresses this factor by providing half of the cannabinoid animals with supplemental Ensure, and yoking each control animal to a drug animal in terms of the availability of food and supplement. Male adolescent Long-Evans rats were injected with the synthetic cannabinoid, CP 55,940, for a two-week period beginning at puberty. Throughout the injection period, body weight and amount of food consumed were measured in half of the animals, and the other half were supplemented with Ensure in order to match the weight gain exhibited in untreated siblings. Four weeks following the last injection the animals were subjected to a battery of behavioral tests, including elevated plus-maze, social interaction, and object recognition on an open-field. Preliminary results suggest that reduced weight gain during adolescent exposure to cannabinoids may account for the emotional fluctuations observed in adulthood but not the cognitive deficits.

Disclosures: G.D. Medley: None. **R.D. Lundy:** None. **D.L. Cashel:** None. **H.M. Parrish:** None. **N.A. Stelly:** None. **P.A. Jackson:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.13/VV19

Topic: G.08. Drugs of Abuse and Addiction

Support: 1F31AA026498
1R01AA018834
1R01AA024695
1R21AA023723
R01AA023508
NIGMS/NIH IDeA Program P30GM110702
UTHSC/UAMS CORNET Award

Title: Genetic contributions to the neuroinflammatory response following alcohol exposure in a mouse model of Fetal Alcohol Syndrome Disorders

Authors: *J. A. BAKER[1], C. J. M. KANE[2], J. W. JOHNSON[2], K. M. HAMRE[1]
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Abstract: Fetal Alcohol Syndrome Disorder (FASD) remains the leading developmental disorder in the U.S., occurring in 5% of births. It causes long-term behavioral deficits including many serious aspects of cognitive function, musculoskeletal function, and others. Neuroinflammatory responses have been linked to the neurotoxic effects of neonatal alcohol exposure. Because 1) genetics have been shown to have a role in the severity of alcohol's effect on the developing brain and 2) genetics can influence neuroimmune response, in the present study, we aim to test whether there is an interaction between genetics and neuroimmune responses following neonatal ethanol exposure using C57Bl/6J (B6) and DBA/2J (D2) mice. Neonatal ethanol exposure was examined because neonatal brain development in mice is equivalent to human brain development in the third trimester of human gestation. Postnatal day (P) 4-9 mice were treated by intra-esophageal gavage. Three groups were examined: 1) ethanol-treated at 4 g/kg/d ethanol in Intralipid®, 2) vehicle-gavage controls, and 3) non-gavage, handled controls. On P10, mice were sacrificed and the hippocampus was dissected and flash frozen. Expression of pro- and anti-inflammatory cytokines and chemokines, expressed by microglia, were examined in the hippocampus, including IL-1β, TNF-α, IL-6, CX3CR1, and TGFβ1. Dependent variables were treatment, strain, sex, and interactions between these. Changes in expression were molecule-specific. Some markers showed differential expression with ethanol exposure in both strains or in a strain-specific manner. In contrast, some markers showed differential expression between strains or sexes but were not affected by ethanol exposure. As we have published previously, no differences were observed between handled and vehicle-gavage control groups.
These results demonstrate a complex interaction between genetics, neuroinflammatory markers, and developmental alcohol exposure. Interestingly, sex appeared to be a factor in the level of change in expression after ethanol exposure. Therefore, genetics and sex should be considered when designing therapeutics targeting neuroinflammatory molecules for treatment of developmental alcohol exposure. Future studies are examining whether there are concomitant changes in protein expression as well as comparisons across other brain regions.

Disclosures: J.A. Baker: None. **C.J.M. Kane:** None. **J.W. Johnson:** None. **K.M. Hamre:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.14/VV20

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA025674

Title: Insulin sensitivity and intergenerational transmission of opioid-induced risk for metabolic syndrome

Authors: *E. M. BYRNES, A. M. TOORIE, D. N. TECENO, T. D. PATTON, C. M. SCHONHOFF, F. M. VASSOLER
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Abstract: The development of insulin resistance is a normal adaptation of pregnancy that ensures adequate carbohydrates for the developing fetus. These changes promote nutrient storage in maternal fat and allow shunting of high energy nutrients to the developing fetus by reducing their uptake in maternal tissues. We have recently demonstrated significant multigenerational effects of adolescent morphine exposure on metabolic outcomes, including an increased risk for metabolic syndrome in offspring. The current study examined potential modifications in maternal insulin resistance as a potential mechanism for the transmission of this risk. Females were administered morphine from age 30-39 days (MORF0) or received a matched volume of saline (SALF0). Following this 10-day exposure females remained drug free and as adults were mated with drug naïve males. On gestation day 20, fasting glucose and insulin levels were measured in dams. Additional glucose measurements were obtained from male and female fetuses. Data indicate normal glucose levels in both SALF0 and MORF0 dams, however, MORF0 dams demonstrated significantly reduced insulin levels, suggesting altered insulin sensitivity as a function of adolescent morphine exposure. Additionally, female but not male MORF1 fetuses had significantly blunted glucose levels. Such alterations could impact neurodevelopment given the critical role of glucose in this process. These outcomes will be discussed in the context of potential alterations in dam insulin receptor expression as well as sex-specific placental gene expression. Together these data will be used to advance hypotheses regarding the forward transmission of epigenetic effects mediated by adolescent opioid exposure.

Disclosures: E.M. Byrnes: None. **A.M. Toorie:** None. **D.N. Teceno:** None. **T.D. Patton:** None. **C.M. Schonhoff:** None. **F.M. Vassoler:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.15/VV21

Topic: G.08. Drugs of Abuse and Addiction

Support: National Institute of General Medical Sciences (GM084854)
National Center for Research Resources (5R25GM061838-15, 2G12-RR003051)
National Institute on Minority Health and Health Disparities (8G12-MD007600)
NSF Partnerships in International Research and Education (PIRE) program Neural Mechanisms of Reward & Decision (OISE-1545803)
National Institute on Alcohol Abuse and Alcoholism, P50 AA022538 and AA05846.

Title: Decrease in hyperpolarization- activated cation current (I_h) after cocaine administration: Evidence of epigenetic regulation

Authors: R. VAZQUEZ-TORRES[1], M. S. BRODIE[2], C. YOU[2], F. ARENCIBIA-ALBITE[3], K. Y. BOSQUE- CORDERO[4], A. VAQUER-ALICEA[1], J. C. VICENTY-PADILLA[5], *C. A. JIMENEZ-RIVERA[1]
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Abstract: Epigenetic regulation of gene expression occurs as a response to exposure to drugs of abuse including cocaine and alcohol; epigenetic changes (chromatin remodeling and DNA methylation, for example) contribute to pathological long-term neuroadaptations in the brain. One type of chromatin remodeling is histone acetylation, which is under the control of histone acetyl transferases and histone deacetylases (HDACs). Cocaine sensitization alters the intrinsic properties of dopaminergic neurons (DA) of the ventral tegmental area (VTA), which in turn alters dopaminergic transmission in the mesocorticolimbic network. One intrinsic properties of VTA neurons affected by exposure of drugs of abuse is the cation current activated by hyperpolarization called Ih, which is mediated by HCN channels. Previously, our laboratory has demonstrated that Ih current is reduced by ~40% in VTA neurons from cocaine-sensitized rats. The relationship between epigenetic modifications and alteration of intrinsic neuronal properties in VTA neurons by cocaine has not been characterized. Recent studies demonstrate that some behavioral and molecular changes induced by chronic alcohol can be reversed by histone deacetylase inhibitors (HDACi). However, it is not known whether HDACs regulate cocaine-induced changes in Ih conductance of DA VTA neurons. Using the whole-cell patch clamp technique, we investigated the effect of an HDACi (SAHA, vorinostat) on cocaine-induced

changes in Ih current. Additionally, we explored changes in rebound excitation and temporal summation in cocaine-sensitized rat slices treated with HDACi. In vitro incubation of midbrain slices with SAHA (3 μM for two hours) reversed the cocaine-induced reduction in VTA Ih current (cocaine-control 250 ± 5.0 pA vs cocaine-SAHA 460 ± 8.3 pA, **p<0.001). Current clamp traces also demonstrated HDACi reversal of cocaine-induced reduction of Ih concomitant with reduced AP firing (cocaine group 5 ± 1.4 pA vs cocaine HDACi group 1 ± 0.34 pA, *p<0.01). These results support the idea that the reduction of Ih current in VTA DA neurons after cocaine sensitization is epigenetically regulated, and suggests the possibility that HDAC inhibition could reverse some cocaine-induced neuroadaptations in reward circuits.

Disclosures: R. Vazquez-Torres: None. **M.S. Brodie:** None. **C. You:** None. **F. Arencibia-Albite:** None. **K.Y. Bosque- Cordero:** None. **A. Vaquer-Alicea:** None. **J.C. Vicenty-Padilla:** None. **C.A. Jimenez-Rivera:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.16/VV22

Topic: G.08. Drugs of Abuse and Addiction

Support: Swiss National Science Foundation (SNSF) grant
ETH Grant

Title: Transgenerational effects of maternal overnutrition on offspring's hedonic and metabolic phenotypes

Authors: G. SARKER[1], R. BERRENS[2], J. VON ARX[1], P. PELCZAR[3], W. REIK[2], C. WOLFRUM[1], *D. PELEG-RAIBSTEIN[1]
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Abstract: Maternal overnutrition has been associated with increased susceptibility to develop obesity and neuropsychiatric disorders later in life. So far, most studies have focused on the metabolic consequences across generations following an early developmental nutritional insult. Recently, maternal high-fat diet (HFD) exposure was shown to alter offspring's reward circuitry, which may be a risk factor for the development of addiction. Here we investigated the possible transmission of addictive-like and obesogenic phenotypes induced by maternal HFD in mice through the paternal lineage over three generations. We observed that offspring born to HFD ancestors displayed addictive-like behaviors as well as obesity and insulin resistance up to the third generation in the absence of any further exposure to HFD. This implicates that, the male

germ line is a major player in transferring these phenotypic traits. These behavioral and physiological alterations were paralleled by reduced striatal dopamine levels and increased dopamine 2 receptor density. Interestingly, by the third generation a clear gender segregation emerged, where females showed addictive-like behaviors while male HFD offspring showed an obesogenic phenotype. However, methylome profiling of F1 and F2 sperm revealed no significant difference between the offspring groups, suggesting that the sperm methylome may not be the major carrier for the transmission of the phenotypes observed in our mouse model. Together, our study for the first time demonstrates that maternal HFD exposure causes sustained alterations of the mesolimbic dopaminergic system up to third generation and leads to a predisposition to develop obesity and addictive like behaviors across generations.

Disclosures: G. Sarker: None. **R. Berrens:** None. **J. von Arx:** None. **P. Pelczar:** None. **W. Reik:** None. **C. Wolfrum:** None. **D. Peleg-Raibstein:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.17/WW1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA029815

Title: Effects of amphetamine exposure during adolescence or adulthood on cognitive flexibility and synaptic plasticity in the prefrontal cortex and nucleus accumbens

Authors: *S. KANG[1], M. L. HAYNES[2], T. M. BARROS[2], J. M. GULLEY[2]
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Abstract: Our previous studies suggested that high frequency stimulation (HFS) in the superficial layers of the rat medial prefrontal cortex (mPFC) typically induces long-term depression (LTD) in the deep layer mPFC. This LTD relies on intact $GABA_A$ receptor function and only occurs in adult rats (≥ 65 days old). Here, we investigated the potential role of dopamine receptors in the ontogeny of this LTD, the effects of amphetamine (AMPH) exposure on the expression of this LTD in adulthood, and the association between AMPH effects on synaptic plasticity and cognition in a behavioral flexibility task. In experiment 1, naïve male Sprague Dawley rats were sacrificed during peri-adolescence [postnatal day (P) 35 to P65] or young adulthood (P65 to P75 and P90+) for *in vitro* brain slice field potential recordings. We investigated the effect of D_1 and D_2 antagonists on HFS-induced LTD and the effect of D_1 and D_2 agonists on the field potential. We found that both antagonists blocked HFS-induced LTD and the emergence of this LTD in young adulthood coincided with a functional upregulation in both D_1 and D_2 receptors. In experiment 2, male and female rats were pre-treated with 3 mg/kg

AMPH or saline (i.p.) every other day from P27 to 45 or P85 to 103. Approximately four weeks after the last injection, cognitive flexibility was assessed in a strategy set-shifting paradigm. Lastly, HFS-induced plasticity within the mPFC or in the mPFC-nucleus accumbens (NA) pathway was measured *in vitro* 1-7 days after the behavioral assessment. We found that in the mPFC, HFS triggered LTD in controls but LTP-like responses in AMPH-exposed rats. In the mPFC-NA circuit, HFS was more likely to induce LTP in AMPH-exposed rats vs. controls. These effects were more pronounced in adolescent-exposed rats and were associated with a greater deficit in strategy set-shifting behavior compared to controls and adult-exposed rats. Together, these results demonstrate that dopamine plays an important role in the ontogeny of HFS-induced LTD in the mPFC and that adolescent exposure to AMPH disrupts its development and is associated with deficits in behavioral flexibility.

Disclosures: S. Kang: None. **M.L. Haynes:** None. **T.M. Barros:** None. **J.M. Gulley:** None.

Poster

235. Drugs of Abuse and Addiction: Developmental Effects of Addictive Drugs

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 235.18/WW2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA029815

Title: Age-of-onset and sex influence escalation of methamphetamine self-administration and drug-induced deficits in recognition memory in Sprague-Dawley rats

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Abstract: Drug users who are female and begin their use during adolescence often suffer greater consequences than male and adult-onset users. Although some studies using rodent models suggest that sex and age-of-onset are factors that confer increased vulnerability to problem drug use and its associated consequences on cognitive functioning, there has been limited research investigating these potential vulnerability factors in combination. We recently published studies showing rats that acquired methamphetamine (METH) self-administration (SA) under limited-access conditions displayed stable METH intake that did not differ by sex or age-of-onset. In subsequent tests of strategy-shifting, we found drug-induced deficits in adolescent-onset females only. Here, we sought to extend these findings by using a long access (LgA) paradigm for SA that has been shown previously to encourage escalation of intake over time, which is a common drug-taking pattern in human abusers. Sprague-Dawley rats of both sexes were implanted with an indwelling jugular catheter on postnatal day (P) 32 or P82 for adolescent- and adult-onset

groups, respectively. Starting on P41 or P91, rats were allowed 7 daily METH SA sessions under short access (ShA) conditions (2 h duration); this was followed by 14 daily LgA (6 h) sessions. After 7 days of abstinence, novel object (OR) or object-in-place (OiP) recognition was assessed. After an additional 7 days, rats were tested on the cognitive task they did not perform at the first assessment. We found that during LgA sessions, adolescent-onset rats escalated METH intake more rapidly than adult-onset rats, with adolescent-onset females earning the most infusions. Adolescent-onset rats exhibited modest deficits in OiP compared to adult-onset rats, but there was no sex difference in this effect and no groups differed in OR. Our findings in rats suggest that age-of-onset and sex may confer additive vulnerability to problematic patterns of drug-taking, but not drug-induced cognitive dysfunction, that may contribute to the worse outcomes of drug use in these populations.

Disclosures: S.R. Westbrook: None. **M.R. Dwyer:** None. **L.R. Cortes:** None. **J.M. Gulley:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.01/WW3

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant: DA009064
NIDA Grant DA026795

Title: AM7438, a novel controlled deactivation cannabinoid with reduced tolerance and dependence profiles

Authors: *J. G. RAGHAV[1,1], K. VEMURI[2], S. P. NIKAS, 02115[2], S. R. KULKARNI, 02115[1], A. MAKRIYANNIS[3]
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Abstract: Classical cannabinoids such as Δ^9-THC and its analogs display potent analgesic effects that are CB1 receptor (CB1R) mediated. However, they are also known to produce rapid tolerance along with dependence. Here we report the *in vivo* pharmacological properties of a novel short-acting CB1R agonist, AM7438, as a controlled deactivation compound displaying improved efficacy and safety profiles. In this study we show that AM7438 is a novel short-acting cannabinoid with potent analgesic properties, and diminished *in-vivo* tolerance and dependence profiles compared to its long acting congener, Δ^8-THC-DMH, a classical cannabinoid. We determined the potency and duration of action of AM7438 and Δ^8-THC-DMH using the tail-flick latency analgesia assay in male CD-1 mice. The corresponding ED_{50} values (in mg/kg with 95% CI) were 0.21 (0.1692, 0.2767) for AM7438 and 2.2 (0.614, 3.053) for Δ^8-THC-DMH.. Onset of

effects for Δ^8-THC-DMH was slow with an extended time-course; with functional, perpetual *in-vivo* half-life of 17 hours. AM7438 had a quick onset of effect and short duration of action; with functional perpetual *in vivo half-life of 5 hours.* We also evaluated the tolerance profiles of AM7438 and Δ^8-THC-DMH in male CD-1 mice using the tail-flick analgesia and hypothermia assays. Animals when administered with Δ^8-THC-DMH (10mg/kg) chronically over 6 days, developed tolerance rapidly as seen in both assays. Beginning day-2, Δ^8-THC-DMH produced no hypothermic or analgesic effects while AM7438 (1mg/kg) continued to produce significant analgesic effects and hypothermic effects until day-5 with a relatively slower onset of tolerance. Additionally, we looked at CB1R antagonist (rimonabant) precipitated withdrawal by measuring head-shakes and paw tremors in mice treated chronically with either AM7438 (1mg/kg) or Δ^8-THC-DMH (10mg/kg). Notably, mice treated with the short-acting CB1R agonist AM7438 over 6 days displayed reduced rimonabant-precipitated withdrawal symptoms as compared to animals treated with Δ^8-THC-DMH. Based on these data, we propose that controlled deactivation cannabinoids represented by one of our lead compounds AM7438, may act as promising pharmacotherapies for treating pain without producing tolerance or dependence.

Disclosures: J.G. Raghav: None. **K. Vemuri:** None. **S.P. Nikas:** None. **S.R. Kulkarni:** None. **A. Makriyannis:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.02/WW4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant 1R21DA038381
NIH Grant U54 EB 020403

Title: Mapping subcortical surface morphometry in substance use: An ENIGMA addiction working group study

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Abstract: Problematic substance use poses a huge social and economic burden globally. Numerous imaging studies of SUDs to date have demonstrated MR volumetric alterations common across various substances of abuse. However, gross volumetric measures are unable to

capture more localized subcortical differences that may either be generalizable across SUDs, or substance-specific. We quantified and examined subcortical shape variability across SUD groups (alcohol, nicotine, cocaine, meth, or cannabis) and controls, in a large multinational dataset from the ENIGMA Addiction working group. T1-weighted images from 1628 controls and 2277 individuals with SUD across 34 imaging sites were processed with FreeSurfer 5.3. The segmented subcortical structures were then transformed to a mesh surface and reviewed for quality using a standardized protocol. Two vertex-level metrics - (i) the radial distance (RD) of structure surface from a medial curve, and (ii) the log of the Jacobian determinant (JD), that respectively describe (i) local thickness and (ii) surface area dilation/contraction, were then extracted for all subcortical regions. Mega-analyses were performed on measures of RD and JD, to test for the main effect of SUD, controlling for subject age, sex, intracranial volume, and imaging site. All outputs were corrected using a regional searchlight false discovery rate (FDR) method at q=.005. We found widespread differences across subcortical structures in SUDs relative to controls, driven primarily by users with an alcohol use disorder (AUD). AUD was associated with localized lower RD and JD across most structures (Fig. 1). Given the confounding influence of smoking status across both SUDs and controls, subcortical morphometry was further examined across a subset of NUD subjects (n = 565), others SUDs with nicotine use (n = 734), and non-smoking controls (n = 1001). NUD was associated with a greater RD and JD relative to non-smoking controls in multiple regions, particularly the bilateral hippocampus and left accumbens, reflecting substance-specific effects on subcortical structures.

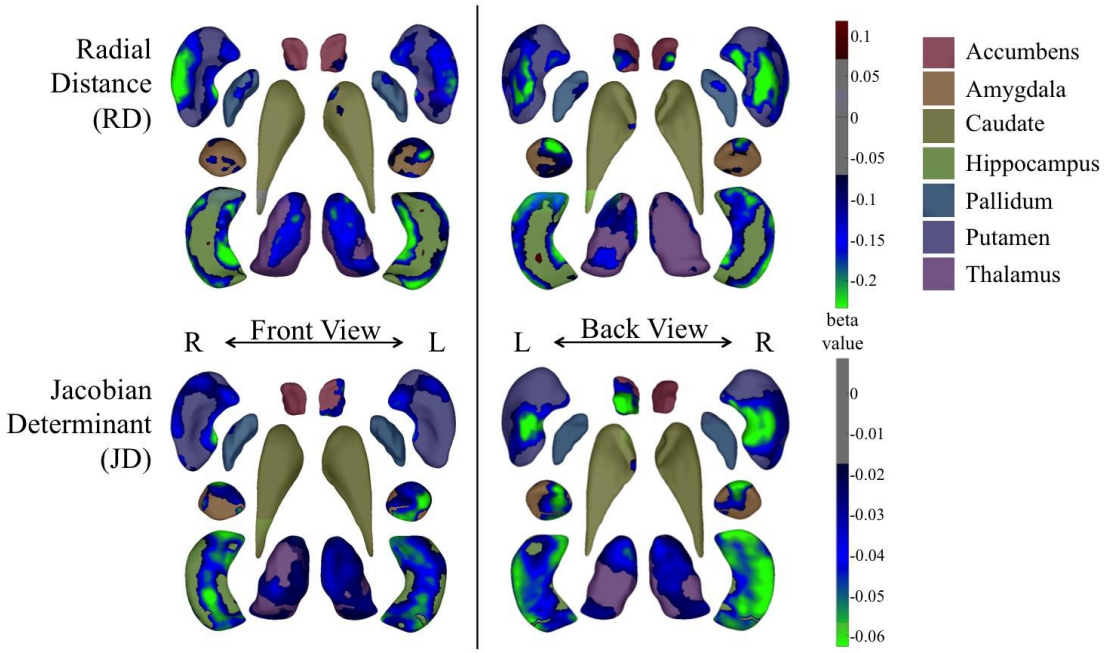

Fig. 1. Front and back view of local surface thickness (i.e. radial distance, RD) and local area (i.e. natural logarithm of the jacobian determinant, JD) differences across subcortical structures (i.e. bilateral accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus) in users with alcohol use disorder relative to controls. All effects have been controlled for imaging site, gender, and age. Heat map represents beta-values of the significant regions after searchlight FDR-control (Langers et al. 2007) at q=.005, conservatively treating the 14 subcortical structures and 2 metrics as a single family of tests. 'R' and 'L' denote the right and left hemisphere respectively.

Disclosures: Y. Chye: None. **S. Mackey:** None. **B. Gutman:** None. **P.M. Thompson:** None. **A. Uhlmann:** None. **P. Conrod:** None. **H. Garavan:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.03/WW5

Topic: G.08. Drugs of Abuse and Addiction

Support: China MOST 2012YQ03026005
China MOST 2013ZX0950910
China MOST 2015BAI08B02
National Basic Research Program of China 2015CB553504
National Key R&D Program of China 2017YFC1310404

Title: Response dynamics of midbrain dopamine neurons and serotonin neurons to heroin, nicotine, cocaine, and MDMA

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Abstract: Heroin, nicotine, cocaine, and MDMA are abused by billions of people. They are believed to target midbrain dopamine neurons and/or serotonin neurons, but their effects on the dynamic neuronal activity remain unclear in behaving states. By combining cell type-specific fiber photometry of Ca^{2+} signals and intravenous drug infusion, here we show that these four drugs of abuse profoundly modulate the activity of mouse midbrain dopamine neurons and serotonin neurons with distinct potency and kinetics. Heroin strongly activates dopamine neurons, and only excites serotonin neurons at higher doses. Nicotine activates dopamine neurons in merely a few seconds, but produces minimal effects on serotonin neurons. Cocaine and MDMA cause long-lasting suppression of both dopamine neurons and serotonin neurons although MDMA inhibits serotonin neurons more profoundly. Moreover, these inhibitory effects are mediated through the activity of dopamine and serotonin autoreceptors. These results suggest the responses of dopamine neurons and those of serotonin neurons are more closely associated with drug reinforcing property and drug euphorigenic property, respectively. We envision that this methodology will facilitate further in-vivo interrogation of neural dynamics using animal models of drug addiction.

Disclosures: C. Wei: None. **X. Han:** None. **D. Weng:** None. **Q. Feng:** None. **X. Qi:** None. **J. Li:** None. **M. Luo:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.04/WW6

Topic: G.08. Drugs of Abuse and Addiction

Support: CIC-UMSNH 26.10
CIC-UMSNH 2.36
CIC-UMSNH 30.2

Title: Xylene and diazepam co-administration potentiates anticonvulsant effect in rats

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Abstract: Intentional solvent exposure constitutes a serious worldwide health problem which mainly affects children and adolescents. Volatile organic solvents, such as xylene (XYL), share effects with central nervous system depressants and are commonly inhaled to produce an altered state of consciousness. Volatile solvents may potentiate the activity of $GABA_A$ receptors, as well as benzodiazepines, such as diazepam (DZP), producing an anticonvulsant effect. On the other hand, pentylenetetrazole (PTZ) is a chemical convulsant and acts as a $GABA_A$ receptor antagonist, inhibiting $GABA_A$-induced Cl^- currents. However, the effect of co-administration of XYL and DZP on PTZ-induced convulsions is not known. The purpose of this study was to analyze the effect of co-administration of sub-effective doses of XYL and DZP on PTZ-induced seizures. Male Wistar rats were i.p. injected with either PTZ (50 mg/kg) or PTZ and DZP (0.3 mg/kg), placed in a static exposure chamber and observed for 30 min during air or XYL exposure (1000 ppm). The parameters registered were the percentage of animals that presented tonic-clonic seizures, the number of clonic and tonic-clonic seizures, as well as the latencies to these responses. The results showed that exposure to XYL (1000 ppm) produced a tendency to protect against seizures produced by PTZ. In contrast, DZP (0.3 mg/kg) was not able to significantly protect against seizures. On the other hand, the combination of XYL + DZP had a greater protective effect against PTZ-induced convulsions. In conclusion, these results suggest that XYL and DZP co-administration produces a potentiation of anticonvulsant effect and that this effect could be mediated through $GABA_A$ receptors.

Disclosures: J. Serna-Vazquez: None. **D. Godinez-Hernandez:** None. **L. Ortega-Varela:** None. **M.Y. Gauthereau-Torres:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.05/WW7

Topic: G.08. Drugs of Abuse and Addiction

Support: R01 DA013951
F32 DA042518

Title: Self-administration of toluene vapor produces functional adaptations in the nucleus accumbens core of rats

Authors: *W. N. WAYMAN, M. P. OKAS, K. M. BRAUNSCHEIDEL, J. J. WOODWARD
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Abstract: Inhalants continue to be one of the most prevalent, and often first drugs abused by adolescents. Toluene, an archetypal inhalant, affects the function of neurons within key brain reward circuits including the prefrontal cortex, ventral tegmental area, and nucleus accumbens similar to other drugs of abuse. However, preclinical models used to study these toluene-induced adaptations employ passive exposure paradigms that do not mimic human abuse patterns. To address this shortcoming, we developed a self-administration paradigm (TOL-SA) and coupled this with whole-cell slice electrophysiology to examine changes in neuronal function in animals voluntarily administering toluene vapor. A custom-built self-administration apparatus containing active and inactive nose-pokes, flow-through vaporizers, and solenoid valves controlled by Med-Associates software was used to train adolescent (~P28) male rats to nose poke for toluene vapor. Rats were first conditioned to low levels of toluene vapor delivered non-contingently for 2 weeks prior to TOL-SA training. They were then allowed to nose poke for 15-second infusions (which also served as a time-out period) of toluene vapor (~750 ppm) using a fixed ratio 1 (FR1) schedule during 1-hour sessions. After 3 weeks of TOL-SA, slices containing the nucleus accumbens (NAc) were prepared and current-evoked spiking was measured in medium spiny neurons (MSNs) in the NAc core (NAcc). A second group of rats went through the TOL-SA paradigm followed by a 45-day withdrawal (WD) and an additional week of toluene vapor self-administration. Rats quickly learned to self-administer toluene vapor and received an average of 10.5 vapor infusions during each hour-long session. This increased to approximately 13.5 infusions in rats that experienced a 45-day WD. These rats also exhibited significantly more nose pokes throughout the 15-second infusion during reinstatement than during the initial 3 weeks of TOL-SA training. Across all animals, NAcc MSN firing did not correlate with lifetime toluene exposure. However, spike firing was enhanced in rats that underwent withdrawal and reinstatement of TOL-SA. This is the first study to demonstrate self-administration of toluene

vapor in rats and the findings suggest that adaptations in the NAcc may contribute to the development of toluene dependence in adolescents similar to other drugs of abuse.

Disclosures: W.N. Wayman: None. **M.P. Okas:** None. **K.M. Braunscheidel:** None. **J.J. Woodward:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.06/WW8

Topic: G.08. Drugs of Abuse and Addiction

Support: Pre-Doctoral Fellowship in Pharmaceutical Sciences
Generous funding from the University of Utah

Title: Effects of methamphetamine-induced dopamine toxicity on striatal plasticity

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Abstract: Methamphetamine (METH) is a highly addictive psychostimulant. Cognitive deficits are apparent in individuals with a history of METH abuse, and targeting cognitive function may be an efficacious approach to managing METH abuse and addiction. However, in order to develop a successful treatment for METH abuse, the consequences of METH-induced neurotoxicity must be better understood. METH exposure is known to be associated with damage to central monoamine systems, particularly dopamine signaling. Rodent models of such damage have revealed a decrease in the amplitude of phasic dopamine signaling and significant striatal dysfunction, including changes in molecular, systems, and behavioral functions of the striatum. Importantly, phasic dopamine signaling activates dopamine D1 receptors, which are involved in striatal synaptic plasticity, particularly long-term potentiation in D1 receptor-expressing striatal medium spiny neurons. We therefore hypothesize that METH-induced dopamine neurotoxicity will diminish D1 receptor-dependent striatal plasticity in mice. To test this hypothesis, mice were treated with a binge regimen of METH to induce neurotoxicity. This binge regimen (4 x 10 mg/kg *d,l*-methamphetamine, s.c.) provides a reliable rodent model that recapitulates all of the known METH-induced neurotoxic effects observed in humans, including dopamine toxicity. Three weeks later, plasticity was tested using white matter high frequency stimulation (HFS) and striatal field recordings in coronal slices. While analysis is ongoing, we expect that HFS will result in long-term potentiation (LTP) in the dorsomedial striatum of control mice. However, we expect this LTP will be diminished in mice with METH-induced neurotoxicity, due to a METH-induced disruption in phasic dopamine and consequently, D1 receptor signaling. Furthermore,

we expect that HFS will result in long-term depression (LTD) in the dorsolateral striatum of both control mice and mice with METH-induced neurotoxicity, as this form of plasticity is not dependent on D1 receptor signaling.

Disclosures: A. Gibson: None. **K.A. Keefe:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.07/WW9

Topic: G.08. Drugs of Abuse and Addiction

Support: VIEP-BUAP-2018
Extraordinary Federal Support to BUAP for research

Title: Chronic clobenzorex administration induce damage in motor activity and glial reactivity in striatum of rats

Authors: *G. A. DEL ROSAL[1], A. PATRICIO-MARTÍNEZ[2,4], I. MARTÍNEZ-GARCÍA[3], I. D. LIMÓN[2]
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Abstract: Clobenzorex (CLBX) it´s an amphetamine-like compound widely used in the treatment of obesity. Long-term use of amphetamines can cause the loss of dopamine neurons in the nigrostriatal pathway and result in motor impairment. The neurotoxic mechanisms of amphetamines induce a neuroinflammatory response. This neuroinflammation is marked by reactive microglia and astrocytes, characterized by the overexpression of Iba1 and GFAP, respectively. However, the effect of CLBX on motor behavior and neuroinflammatory response is not known. The aim of this study was to evaluate the effect of chronic administration of CLBX on the motor behavior and the reactivity of astrocytes and microglia in the striatum. Twenty four Male Wistar rats (380-450 g) were used. Three experimental groups were formed; vehicle (SSI), amphetamine (AMPH; 2 mg/kg) and CLBX (30 mg/kg). All experimental groups received oral administration every 24 hours, for thirty-one days. Motor activity in open field test (Columbus Instruments, Columbus Oh.) was evaluated on day 2, 10, 20 and 30. Motor coordination was measured in the beam-walking test on day 3, 11, 21 and 31. All the motor behavior tests were evaluated before the drugs administration. The brains were obtained to assess the immunoreactivity of both GFAP and Iba1 in the striatum. The results show that chronic administration of AMPH or CLBX doesn´t impair motor coordination, evaluated in the beam-walking test. However, AMPH administration decreased motor activity on day 10 (32%), 20

(31%) and 30 (41%). CLBX administration decreased motor activity on day 20 (35%) and 30 (31%). Finally, we observe that AMPH administration increase the immunoreactivity of GFAP (162%) and Iba1 (72%) in dorsal striatum. CLBX administration also increase the immunoreactivity of GFAP (300%) and Iba1 (117%) in dorsal striatum. In summary, the chronic administration of clobenzorex damage motor activity, but not motor coordination, and induce a neuroinflammatory response in striatum in a similar manner that amphetamine. These results suggest that clobenzorex is a neurotoxic amphetamine-like drug that affects nigrostriatal pathway.

Disclosures: G.A. Del Rosal: None. **A. Patricio-Martínez:** None. **I. Martínez-García:** None. **I.D. Limón:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.08/WW10

Topic: G.08. Drugs of Abuse and Addiction

Title: Drug Seeking like Effect of Pregabalin using conditioned place preference paradigm

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Abstract: Drug addiction is considered one of the most common and dangerous health, social, and economic problems in Saudi Arabia and worldwide. This disorder is expanding in trend especially among young population. It has been reported that some drugs have been consumed illicitly, because they are easily available, relatively inexpensive and they can be used without prohibition. Noteworthy, Pregabalin is one of the recent drugs that has been found to be abused by young population in Saudi Arabia and worldwide. In this study, we examined the hypothesis that pregabalin has an abuse potential; different doses were tested using conditioned place preference (CPP) paradigm to assess pregabalin-seeking like behavior. Male BALB/c mice were separated into three groups; the first group was given vehicle (1ml/kg/day, i.p.) for 8 days during the acquisition phase. The second group received four i.p. injections of pregabalin (30mg/kg) every other day during the acquisition phase. The third group received four injections of pregabalin (60mg/kg, i.p.) every other day during the acquisition phase. The dose of 30mg/kg did not significantly change the time spent in drug-paired chamber as compared to the vehicle-paired chamber. Nonetheless, the time spent in drug-paired chamber as compared to the vehicle-paired chamber was significantly increased in animal treated with (60mg/kg) of pregabalin. These results demonstrated for the first time the abuse potential of pregablin in animal model of drug addiction.

Disclosures: A. Almalki: None. **Y.S. Althobaiti:** None. **O. Alzahrani:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.09/WW11

Topic: G.08. Drugs of Abuse and Addiction

Support: Alkermes, Inc

Title: *In vivo* EEG signatures during chronic fentanyl exposure, spontaneous withdrawal, and protracted abstinence

Authors: *A. M. PATINO, C. B. PURYEAR, C. SANCHEZ
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Abstract: Preclinical studies in rodent models of opioid addiction are commonly used to characterize long-term effects on brain function. However, understanding the effects opioid agonists on cortical circuit activity may better elucidate the functional impact of opioids. Chronic opioid exposure and withdrawal has been shown to produce dynamic changes in oscillatory activity in brain areas central to the pathophysiology of drug addiction. Therefore, it is important to understand whether these dynamic changes can be observed in skull-level EEG recordings, which hold greater translational potential to clinical EEG studies. As such, we characterized the effects of chronic fentanyl exposure, withdrawal and abstinence on cortical EEG patterns. Fentanyl-treated rats exhibited significant physical dependence, as evidenced by transient weight loss and somatic phenotypes during withdrawal. Cortical EEG dynamics displayed distinct oscillatory signatures that varied according to the phase of fentanyl exposure or withdrawal. Fentanyl exposure caused a transient increase in delta (1-4Hz) and alpha (8-12Hz) power, and a transient decrease in gamma (30-80Hz) power. In contrast, spontaneous withdrawal was characterized by acute, transient increases in multiple frequency bands. Interestingly, alpha power remained increased above baseline levels during the subsequent three weeks of abstinence. These results demonstrate the profound impact of fentanyl on cortical circuit function. Normalization of opioid-induced changes in oscillatory dynamics, and subsequent rebound during withdrawal suggests the engagement of allostatic mechanisms that may compensate for the persistent activation of mu-opioid receptors. The persistent elevation of alpha power during protracted abstinence suggests that chronic fentanyl exposure has a long-term impact on cortical circuitry.

Disclosures: A.M. Patino: A. Employment/Salary (full or part-time):; All authors are full time employees at Alkermes Inc. **C.B. Puryear:** A. Employment/Salary (full or part-time):; All

authors are full time employees at Alkermes Inc. **C. Sanchez:** A. Employment/Salary (full or part-time):; All authors are full time employees at Alkermes Inc..

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.10/WW12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA R21 DA037728
Minneapolis Medical Research Foundation #07637
Minneapolis Medical Research Foundation #07434
T32 DA007097

Title: Greater anhedonia during withdrawal from acute opioid exposure is associated with greater sensation-seeking in rats

Authors: Y. SWAIN[1,2], P. MUELKEN[2], A. SKANSBERG[2], M. KRUEGER[2], D. MOTZ[3], Z. HAAVE[2], M. G. LESAGE[2], J. C. GEWIRTZ[1], *A. C. HARRIS[3,1]
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Abstract: Greater sensitivity to the acute agonist effects of opioids and other addictive drugs has been associated with greater sensation-seeking in both humans and animals. However, the relationship between sensitivity to *withdrawal* from acute drug exposure and sensation-seeking has not been studied. The current study evaluated the relationship between morphine withdrawal-induced anhedonia and sensation-seeking in rats. Rats were first tested for withdrawal sensitivity as measured by elevations in intracranial self-stimulation (ICSS) thresholds during both antagonist (naloxone)-precipitated and spontaneous withdrawal from acute morphine exposure (5.6 mg/kg, s.c.). After recovery from drug effects, rats were tested for sensation seeking as measured by spontaneous locomotor activity in a novel environment. Peak and average ICSS thresholds during both naloxone-precipitated and spontaneous withdrawal were positively correlated with distance traveled during locomotor testing (all $r > 0.37$, all $p < 0.05$). These results indicate that higher sensitivity to the anhedonic component of withdrawal from acute opioid exposure is related to higher sensation-seeking, consistent with previous evidence linking sensitivity to the acute agonist effects of drugs to sensation-seeking. Further work with this model could help identify common neurobiological pathways or genetic factors underlying vulnerability to addiction and comorbid mental disorders associated with sensation seeking (e.g,, manic depression).

Disclosures: Y. Swain: None. **P. Muelken:** None. **A. Skansberg:** None. **M. Krueger:** None. **D. Motz:** None. **Z. Haave:** None. **M.G. LeSage:** None. **J.C. Gewirtz:** None. **A.C. Harris:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.11/WW13

Topic: G.08. Drugs of Abuse and Addiction

Support: Betty J. Neitzel Award

Title: Binge-like toluene exposure during periadolescence alters behavioral responsiveness to later ethanol and cocaine drug challenges in Swiss-Webster mice

Authors: *C. J. DAVIDSON, M. M. NADDAF, D. L. HOLCOMB, S. E. BOWEN
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Abstract: Inhalants, such as toluene, are one of the most commonly reported drugs of abuse among early adolescents. Drug use during adolescence can have lasting neurobiological and neurobehavioral consequences including impaired decision-making, increased risk taking and increased drug use. Despite toluene's potent CNS depressant effects, there is a dearth of systematic investigations on what effect binge-toluene exposure during adolescence may have on the effect of other drugs of abuse later in life. This study exposed adolescent male Swiss-Webster mice (N=364) during postnatal days (PND) 28-32 to 0, 2000, or 4000 parts per million (ppm) of toluene vapor for 30 min/day using a static exposure chamber. These mice then had their locomotor activity recorded during cumulative dosing of ethanol (0, 0.5, 1, 2, 4 g/kg), cocaine (0, 2.5, 5, 10, 20 mg/kg) or saline (5 control injections) at one of two time points (PND 36 or PND 44). Results demonstrated that repeated toluene exposure dose-dependently increased locomotor behavior with repeated exposure to 4000 ppm producing sensitization and increasing locomotor activity across all 5-exposure sessions. When later challenged with other drugs, previous toluene exposure resulted in decreased activity (characterized as desensitization) to higher cocaine doses (10 and 20 mg/kg). Mice previously exposed to 4000 ppm and later challenged with ethanol showed a downward shift in locomotor activity at 4 g/kg as compared to air-exposed mice. These results are in agreement with the thesis that toluene exposure during adolescence, especially in "binge-like" patterns, can alter the effects of drugs of abuse later in life. This difference in drug effect may impact the propensity for drug use and addiction and increase the risk of later drug-related disorders.

Disclosures: C.J. Davidson: None. **M.M. Naddaf:** None. **D.L. Holcomb:** None. **S.E. Bowen:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.12/WW14

Topic: G.08. Drugs of Abuse and Addiction

Support: CNPq
CAPES
INNT

Title: Chronic treatment does not cause tolerance to diazepam's effect of reducing dopamine release induced by amphetamine

Authors: *J. Y. ESAKI[1], C. DA CUNHA[2]
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Abstract: Most drugs of abuse increase dopamine release in the nucleus accumbens. However, we have recently shown that an acute injection of the addictive drug diazepam not only causes the opposite effect, but also prevents amphetamine from increasing dopamine release in the nucleus accumbens of mice. The aim of the present study is to test whether rats develop tolerance to this effect. We used subsecond fast-scan cyclic voltammetry recordings at carbon-fiber microelectrodes to measure phasic release of dopamine in the nucleus accumbens evoked by electrical stimulation of the ventral tegmental area in urethane-anesthetized adult male Wistar rats. We observed that both acute and chronic administration of 2 mg/kg diazepam injected intraperitoneally once a day for 15 days decreased dopamine release and prevented the increase of dopamine induced by a single intraperitoneal injection 5 mg/kg amphetamine administered 30 min before the last dose of diazepam. Control groups received vehicle instead of diazepam and saline instead of amphetamine, which did not affect electrically evoked dopamine release. Neither the diazepam nor the amphetamine vehicles affected electrically evoked dopamine release. These results show that a chronic administration of diazepam does not cause tolerance to the attenuation it causes in dopamine release induced by stimulant drugs. This finding presents a promising use of diazepam as a treatment for substance abuse disorder.

Disclosures: J.Y. Esaki: None. **C. Da Cunha:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.13/XX1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA025560

Title: Transcriptional control of alcohol-induced behavioral change

Authors: *A. LANGE[1], P. ADHIKARI[2], F. W. WOLF[3]
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Abstract: Drug naïve animals given a single dose of ethanol show changed responses to subsequent doses, including the development of ethanol tolerance and ethanol preference. These simple forms of behavioral plasticity are due in part to changes in gene expression and neuronal properties. Surprisingly little is known about how ethanol initiates changes in gene expression or what the changes do. Here we demonstrate a role in ethanol plasticity for Hr38, the sole Drosophila homolog of the mammalian Nr4a1/2/3 class of immediate early response transcription factors. Acute ethanol exposure induces transient expression of Hr38 and other immediate early neuronal activity genes. Ethanol activates the Mef2 transcriptional activator to induce Hr38, and the Sirt1 histone/protein deacetylase is required to terminate Hr38 induction. Loss of Hr38 decreases ethanol tolerance and causes precocious but short-lasting ethanol preference. Similarly, reduced Mef2 activity in all neurons or specifically in the mushroom body α/β neurons decreases ethanol tolerance; Sirt1 promotes ethanol tolerance in these same neurons. Genetically decreasing Hr38 expression levels in Sirt1 null mutants restores ethanol tolerance, demonstrating that both induction and termination of Hr38 expression are important for behavioral plasticity to proceed. These data demonstrate that Hr38 functions as an immediate early transcription factor that promotes ethanol behavioral plasticity.

Disclosures: A. Lange: None. **P. Adhikari:** None. **F.W. Wolf:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.14/XX2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA R01-DA021274
NIDA R25-DA033613

Title: Examination of the relationship between ovarian hormones and the magnitude of the nicotine withdrawal syndrome in female rats

Authors: *R. J. FLORES GARCIA, K. P. URIBE, B. CRUZ, V. L. CORREA, L. M. CARCOBA, L. E. O'DELL
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Abstract: The negative affective states elicited during smoking abstinence are more intense in women than men, and the intensity of the withdrawal syndrome varies with peak levels of estradiol and progesterone. The present study compared sex differences and the role of ovarian hormones in the physical signs and negative affective states produced by nicotine withdrawal in female, ovariectomized (OVX) female, and male rats. We also assessed whether the magnitude of the behavioral effects of nicotine withdrawal was associated with peak levels of estradiol and progesterone. Briefly, female rats received either a sham or OVX surgery and 15 days later, all rats were implanted with an osmotic pump that delivered nicotine for 14 days. On the test day, separate groups received vehicle or a non-selective nicotinic receptor antagonist (mecamylamine) to precipitate withdrawal. Rats were then given a series of behavioral tests including the physical signs of withdrawal and 2 tests of anxiety-like behavior, including the elevated plus maze (EPM) and light/dark transfer (LDT) tests. After testing, trunk blood was collected and analyzed for plasma levels of the stress hormone, corticosterone and the ovarian hormones, estradiol and progesterone. Female rats also received vaginal lavage procedures to verify the phase of the estrous cycle on the test day. Our results revealed that nicotine withdrawal produced similar physical signs of withdrawal across all groups of rats. However, female rats displayed greater anxiety-like behavior in both the EPM and LDT tests and greater plasma levels of corticosterone during withdrawal as compared to OVX female and male rats. Interestingly, the magnitude of anxiety-like behavior in female rats was greater in rats that displayed lower progesterone and higher estradiol levels. In conclusion, these data suggest that female rats display intense negative affective states during nicotine withdrawal, and this effect was stronger during phases of the estrous cycle when progesterone levels are relatively low and estradiol levels are high.

Disclosures: R.J. Flores Garcia: None. **K.P. Uribe:** None. **B. Cruz:** None. **V.L. Correa:** None. **L.M. Carcoba:** None. **L.E. O'Dell:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.15/XX3

Topic: G.08. Drugs of Abuse and Addiction

Support: FRM Grant DPA20140629795
EquipEx Grant ANR-10-EQX-008-1
INSERM - Aquitaine Region Fellowship 2015-1R30105

Title: Evidence and characterization of individual variations in the mechanisms of nicotine seeking in the rat

Authors: *V. GARCIA-RIVAS[1,2], N. CANNELLA[1,2], J.-F. FIANCETTE[1,2], P. RENAULT[1,2], M. CARBO-GAS[1,2], B. CHAPPIS[1,2], J. TOSTAIN[1,2], V. DEROCHE-GAMONET[1,2]
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Abstract: Tobacco use leads to 6 million deaths every year due to severe long lasting diseases. Alleviating tobacco dependence is therefore a major public health concern. While the main component of tobacco, nicotine, is recognized as one of the most addictive drugs, available therapies for smoking cessation have limited efficacy. This warrants the need for developing better therapeutic strategies, which depend on understanding the mechanisms that underlie tobacco dependence.
Clinical and preclinical studies have demonstrated consistently that nicotine seeking is a complex behaviour controlled by complex interactions between nicotine and environmental cues associated to nicotine delivery. In particular, nicotine-associated cues can promote nicotine seeking due to their Pavlovian association with the primary reinforcing effects of nicotine. Nicotine can also enhance the reinforcing value of stimuli that are already reinforcing. Importantly, there is evidence that individuals may be differently responsive to these nicotine-cue interactions, and this could explain the differences in smoking behavior, withdrawal symptoms, relapse timing and success to a quit attempt reported in the literature. Clinical studies suggest that the speed of nicotine metabolism may be a possible contributor to these nicotine-cue interactions. However, the exploration of the psychopharmacological mechanisms behind these individual differences in nicotine-cue interactions remains largely ignored.
Here, using an intravenous nicotine self-administration paradigm in rats (n=59), we have evidenced subpopulations of individuals with distinct contributions of nicotine-cue interactions that drive their nicotine seeking. Rats were trained to self-administer nicotine paired with a discrete cue light, and then tested for nicotine seeking when (a) the cue was omitted during one session [cue-omission], (b) the dose was reduced by 50%, and (c) when the cue was omitted at this lower dose. In the first subgroup (n=22), cue-omission effects appear dose-independent, and appear predicted by the speed of nicotine metabolism. In the second subgroup (n=24), cue-omission effects are strongly dose-dependent, with no association with nicotine metabolism. In the third subgroup (n=13), the contributions of cue and nicotine appear additive, with no association with nicotine metabolism. Altogether, this data supports that different psychopharmacological mechanisms at the intersection between nicotine and surrounding cues might support nicotine self-administration at the individual level.

Disclosures: V. Garcia-Rivas: None. **N. Cannella:** None. **J. Fiancette:** None. **P. Renault:** None. **M. Carbo-Gas:** None. **B. Chappis:** None. **J. Tostain:** None. **V. Deroche-Gamonet:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.16/XX4

Topic: G.08. Drugs of Abuse and Addiction

Title: The effect of caffeine on aversive symptoms of nicotine withdrawal in rats

Authors: *N. SWALVE[1], E. BIERLEIN[2], S. SOWA[2], M. YODER[2]
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Abstract: Tobacco use is the leading cause of preventable death in the United States and relapse rates remain extremely high. Aversive symptoms during withdrawal, including increased anxiety and anhedonia, are associated with a decline in successful quit attempts and increased risk of relapse. In humans, stimulants such as caffeine potentiate the aversive symptoms of withdrawal and caffeine precipitates reinstatement to nicotine, the primary psychoactive component in tobacco, in rats. However, the acute and chronic effects of caffeine on the anxiolytic and cognitive effects induced by nicotine withdrawal are relatively unknown. This study examined the effects of caffeine on aversive symptoms of nicotine withdrawal. Male Sprague-Dawley rats (n=8 per group) received nicotine (0.2 or 0.4 mg/kg) or saline daily via subcutaneous injections for two weeks. The acute and chronic effects of nicotine on anxiety were measured during the initial treatment phase to replicate the commonly found biphasic effect of nicotine on elevated plus maze responding. Nicotine treatment was stopped and caffeine (20 mg/kg) or saline was given for an additional two weeks, during which the impact of caffeine on anxiety (e.g. time spent in open and closed arms in an elevated plus maze) and memory deficits (e.g. errors in a radial arm maze) were examined. Additionally, somatic and anorectic effects of nicotine were compared between caffeine and saline groups. Both nicotine treatment and nicotine withdrawal altered elevated plus maze responding. Caffeine affected aversive symptoms of nicotine withdrawal, suggesting that co-use of stimulants may play a role in tobacco relapse.

Disclosures: N. Swalve: None. **E. Bierlein:** None. **S. Sowa:** None. **M. Yoder:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.17/XX5

Topic: G.08. Drugs of Abuse and Addiction

Support: DA036691
DA041839

Title: NicA2-J1 reverses nicotine dependence, prevents relapse and decreases compulsive-like intake in rats

Authors: *M. KALLUPI[1], S. XUE[2], B. ZHOU[2], K. JANDA[2], O. GEORGE[2]
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Abstract: Smoking is the leading cause of preventable illness in the world with tobacco use killing 6 million people per year. Novel pharmacokinetic approaches to prevent nicotine from reaching the brain have been tested using vaccines, but such efforts have failed because antibody affinity and concentration are not sufficient to completely prevent nicotine from reaching the brain. In this study, we provide preclinical evidence of the efficacy of an enzymatic approach to reverse nicotine dependence, reduce compulsive-like nicotine intake, and prevent relapse in rats with a history of nicotine dependence. Animals were trained for 12 consecutive days to self-administer nicotine (0.03 mg/kg/injection) for 21 h daily. Once a robust escalation of nicotine intake was established, treatment with NicA2-J1 started. Nicotine blood levels were measured and a battery of behavioral experiments was performed. Chronic administration of NicA2-J1, an engineered nicotine-degrading enzyme that was originally isolated from *P. putida* S16, completely prevented nicotine from reaching the brain and reversed somatic signs of withdrawal, hyperalgesia, and irritability-like behavior in nicotine-dependent rats with a history of escalation of nicotine self-administration. NicA2-J1 also decreased compulsive-like nicotine intake, reflected by responding despite the adverse consequences of contingent footshocks, and prevented nicotine- and stress (yohimbine)-induced relapse. These results demonstrate the efficacy of enzymatic therapy in treating nicotine addiction in advanced animal models and provide a firm grounding for the development of biological therapies for smoking cessation in humans.

Disclosures: M. Kallupi: None. **S. Xue:** None. **B. Zhou:** None. **K. Janda:** None. **O. George:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.18/XX6

Topic: G.08. Drugs of Abuse and Addiction

Support: UNSW Faculty Research Grant

Title: Pre-quit nicotine decreases nicotine self-administration and attenuates cue- and drug-induced reinstatement

Authors: *K. J. CLEMENS[1], S. FERGUSON[2]
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Abstract: Administration of smoking cessation medications in anticipation of a nominated quit date can promote abstinence. How this occurs is not widely understood, but may be due to the disruption of contingencies between smoking behaviour and acute drug effects. To explore this relationship, we examined the effect of pre-quit nicotine replacement therapy on susceptibility to relapse in an animal model of nicotine dependence. Sprague Dawley (n=24) and Long Evans (n=32) adult male rats were trained to intravenously self-administer nicotine across 20 days. Continuous low-dose nicotine was administered via a mini-osmotic pump either 7 days prior to, or at the beginning of, a 6 day extinction training period where nicotine was withheld. Cue- and drug-induced reinstatement of responding were then measured with minipumps retained, the day after minipump removal or one week later. Prequit nicotine administration markedly reduced self-administration across the last days of training as the response-associated cues no longer reliably predicted an acute drug effect. Pre-quit, but not post-quit, nicotine administration significantly attenuated cue-induced reinstatement once minipumps were removed, indicating that the contingency disruption across training reduced the conditioned reinforcing properties of the cue at test. Both pre-quit and post-quit nicotine attenuated nicotine-primed reinstatement. No significant strain differences were detected at any stage. Together these results suggest that administration of a nicotine replacement prior to a nominated quit date may enhance resistance to relapse via disruption of the contingency between nicotine and its cues.

Disclosures: K.J. Clemens: None. **S. Ferguson:** F. Consulting Fees (e.g., advisory boards); GlaxoSmithKline Consumer Healthcare, Chrono Therapeutics, Johnson and Johnson.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.19/XX7

Topic: G.08. Drugs of Abuse and Addiction

Title: Effects of bupropion or varenicline on responding for nicotine in a preclinical model of nicotine self-administration vary according to individual demand for nicotine reinforcement

Authors: *T. KAZAN[1], D. HERTIA[1], K. TRAINOR[1], A. LEBEL[1], K. ZEROKA[1], S. CHARNTIKOV[2]
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Abstract: Bupropion and varenicline are the only two non-nicotine pharmacological agents in the first-line of approved therapies for smoking cessation. Even with the help of these treatments, cessation rates remain marginally low. Preclinical research examining the effects of bupropion or varenicline primarily employ grouped subject designs. Current understanding of the effects of these drugs on an individual level is virtually unexplored. To start filling this gap, we began investigating individual differences in responding to bupropion or varenicline using preclinical animal model of drug self-administration. First, we used behavioral economics model to derive individual demand for nicotine (0.03 mg/kg/inf). Following acquisition of the demand for nicotine, we assessed the effects of bupropion (0, 10, 30, 60 mg/kg) or varenicline (0, 0.1, 1.0, 3.0 mg/kg) on responding for nicotine reinforcement on a progressive ratio schedule of reinforcement. In the next phase, responding for nicotine was extinguished and rats were subjected to 3 separate reinstatement tests with nicotine or non-contingent cue presentation as triggers. Finally, because both bupropion and varenicline share stimulus effects with nicotine, a fourth reinstatement with bupropion or varenicline was conducted. Our results show that both bupropion and varenicline dose-dependently attenuated responding for nicotine, and this responding varied according to individual demand for nicotine. Specifically, rats with higher demand for nicotine showed greater decreases in responding for nicotine following pretreatment with bupropion or varenicline. Furthermore, rats with higher demand for nicotine showed higher magnitude of initial reinstatement triggered by nicotine and final reinstatement triggered by bupropion. Our results suggest that responding to pharmacological cessation treatments may differ from individual to individual and that understanding these effects may be critical for the development of more efficacious treatment strategies.

Disclosures: T. Kazan: None. **D. Hertia:** None. **K. Trainor:** None. **A. LeBel:** None. **K. Zeroka:** None. **S. Charntikov:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.20/XX8

Topic: G.08. Drugs of Abuse and Addiction

Support: INCA TABAB 2016
Institut Pasteur
LABEX BIOPSY
ANR 2017

Title: Use of a transgenic rat model identifies key mechanisms of relapse to nicotine seeking

Authors: *U. MASKOS[1], M. BESSON[1], S. PONS[1], P. SCHOLZE[2], C. MOREL[3], S. MONDOLONI[3], A. HAY[3], B. LAMBOLEZ[3], L. TRICOIRE[3], P. FAURE[3], A. MOUROT[4], B. FORGET[1]
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Abstract: Tobacco addiction is a chronic and relapsing disorder with an important genetic component that represents a major public health issue. Meta-analysis of large-scale human genome-wide association studies (GWAS) identified a frequent non-synonymous single nucleotide polymorphism in the gene coding for the α5 subunit of nicotinic acetylcholine receptors (α5SNP), which significantly increases the risk for tobacco dependence. To dissect the neuronal mechanisms underlying vulnerability to nicotine, we created rats expressing this polymorphism using Zinc Finger Nuclease technology. α5SNP rats self-administered more nicotine at high doses and exhibited higher nicotine-induced reinstatement of nicotine seeking than wild-type animals. Higher reinstatement was associated with altered neuronal activity in several discrete areas that are interconnected, including in the interpeduncular nucleus, a GABAergic structure that strongly expresses α5-containing nicotinic receptors. Our results suggest that the α5SNP increases the risk for reinstatement of nicotine seeking by disinhibiting a neuronal network involved in relapse.

Disclosures: U. Maskos: None. **M. Besson:** None. **S. Pons:** None. **P. Scholze:** None. **C. Morel:** None. **S. Mondoloni:** None. **A. Hay:** None. **B. Lambolez:** None. **L. Tricoire:** None. **P. Faure:** None. **A. Mourot:** None. **B. Forget:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.21/XX9

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA P50 Center grant DA027840

Title: Acute and chronic memantine effects on nicotine self-administration in rats

Authors: *A. H. REZVANI, C. WELLS, L. YAO, E. PIPPEN, E. LEVIN
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Abstract: Neurobehavioral bases of tobacco addiction and nicotine reinforcement is complex, involving more than just nicotinic cholinergic or dopaminergic systems. A variety of neural systems are involved in tobacco addiction. This presents the opportunity for development of a variety of pharmacological approaches to aid smoking cessation. The current studies investigated the potential role of NMDA glutamate receptors in nicotine reinforcement, Memantine is an NMDA glutamate antagonist used to improve cognitive function in people with Alzheimer's disease. Glutamate may be an important component of the reinforcing effects of nicotine. Two studies were conducted, one testing acute effects of memantine over a range of doses for changing nicotine self-administration and the other testing the chronic effects of memantine over a series of sessions. Acute memantine injections slightly, but significantly, increased nicotine self-administration in a dose-related manner. In contrast, chronic memantine treatment significantly reduced nicotine self-administration. During the first week of the chronic treatment, memantine-treated rats did not show any significant effect vs. controls. Starting in the second week of the chronic treatment there was a significant reduction of nicotine self-administration relative to controls. This was seen because memantine treatment prevented the increase in nicotine self-administration shown by controls with continued access. This memantine-induced reduced nicotine self-administration continued during the resumption of nicotine access after a week of enforced abstinence. There even continued to be a memantine-induced lowered nicotine self-administration during the week after the cessation of treatment. While acute memantine modestly increased nicotine self-administration, possibly due to short-term behavioral compensation to diminished reinforcement, chronic memantine significantly reduced nicotine self-administration over the longer term. Memantine or other drugs affecting NMDA glutamate receptors may be useful aids to smoking cessation. Full efficacy was seen as the NMDA drug treatment was given chronically. This research was funded by NIDA P50 Center grant DA027840.

Disclosures: A.H. Rezvani: None. **C. Wells:** None. **L. Yao:** None. **E. Pippen:** None. **E. Levin:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.22/XX10

Topic: H.01. Animal Cognition and Behavior

Support: CONACyT Mexico (No. 338275)

Title: Chronic treatment of resveratrol ameliorates memory and hippocampus alcohol-induced changes in rats

Authors: *C. R. MENDOZA PEREZ[1], F. DE LA CRUZ[2], A. D. DIAZ[3], G. FLORES[4]
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Abstract: Alcohol (ethanol) is one of the most consumed substances in the world, its abuse has become in a public health problem (WHO, 2014). Ethanol is a central nervous system depressant; its prolonged use develops addictive disorders and toxicity (Liang and Olsen, 2014). This drug is capable to cross the blood brain barrier; it is the cause of characteristic effects of alcohol such as cognitive and neuronal impairments when there is a long-term consumption (Estruch, 2002). Several studies indicate that chronic alcohol consumption induces oxidative stress and inflammatory response in the brain, resulting in neurodegeneration. Recently, an alternative compound has been suggested to reduce the neurotoxicity that induces alcohol consumption, being the antioxidant molecules the most promise for this problem. Resveratrol (RSV) (trans-3, 5, 4´- trihydroxystilbene) is a polyphenol present in approximately 31 genera of plants such as grapes. It has antioxidant (Gonthier et al., 2012), anti-inflammatory and anti-carcinogenic (Signorelli et al., 2005; Fukui et al., 2010) properties. Currently, the action mechanism of RSV is not well established. Previous reports of our group showed that this polyphenol can to promote an increase in dendritic morphology and spine density of the hippocampus and cortex neurons of aged rats (Hernández-Hernández et al., 2016). This study attempts to evaluate the effect of chronic RSV treatment (20mg/kg/day for 30 days) on memory and neuronal morphology changes induced by alcohol in rats. The memory was evaluated with the novel object recognition test; the Golgi-Cox staining method was used to evaluate neuronal morphology in the hippocampus. Memory data showed improvement in the short-term memory in the alcohol rats treated with RSV. Besides the histological analysis of the hippocampus showed that RSV reduce dendritic atrophy induces by chronic alcohol consumption. Our results suggest that RSV reverses memory deficits by stimulation of neuronal plasticity in the hippocampus of these animals (Supported by: CONACyT grants (No. 338275) to C R Mendoza-Pérez).

Disclosures: C.R. Mendoza Perez: None. **F. De la Cruz:** None. **A.D. Diaz:** None. **G. Flores:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.23/XX11

Topic: G.08. Drugs of Abuse and Addiction

Support: Fundação para a Ciência e Tecnologia (FCT, Portugal) (Strategic Project 2015-UID/NEU/04539/2013)
COMPETE-FEDER (POCI-01-0145-FEDER-007400)
Centro 2020 Regional Operational Programmes (CENTRO-01-0145-FEDER-000012: HealthyAging2020 and CENTRO-01-0145-FEDER-000008: BrainHealth 2020)

Title: Early behavioral and glial signature of the new psychoactive substance MDPV in mice

Authors: *F. C. PEREIRA[1], L. FERNANDES[1], M. CAMPEÃO[1], I. PITA[1], C. LEMOS[2], S. F. ALI[3], F. CARVALHO[4], C. A. FONTES RIBEIRO[1], S. D. VIANA[1,5]
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Abstract: Aims: Methylenedioxypyrovalerone (MDPV), one of the most widely available synthetic cathinones (bath salts), has surfaced as a popular alternative to other amphetamine analogs such as methamphetamine (METH). In spite of MDPV posing growing neuropsychiatric complications, its neuropharmacological profile is dramatically less explored, comparing to classic amphetamines. This study determined the early behavioral (locomotor and emotional phenotype) and glial signature (WB and IHC analysis) of this new psychoactive substance in comparison with METH. **Methods:** Adult male C57BL/6 mice were injected with MDPV or METH binge (4x10 mg/Kg, two hours-apart, i.p.) and their striata and frontal cortices were analyzed after probing their locomotor and emotional phenotypes at 18-24 h post-injection, time-window known to encompass the onset of classical amphetamines neurotoxicity. Differences between experimental groups (SAL; MDPV; METH, n=8-9) were compared using one-way ANOVA followed by Tukey multiple comparisons or Kruskal-Wallis followed by Dunn multiple comparisons. Results: MDPV mice showed normal vertical and horizontal locomotor activity in the open field. This was paralleld by unchanged emotional parameters as assessed by elevated plus maze (anxiety-like behavior), splash test (index of well-being) and tail suspension (despair-like behavior). Molecular and cellular analysis showed that MDPV did not change glia as gauged

by normal densities in Iba1 (microglia), GFAP (astrocytes), and MPB (oligodendrocytes). Finally, striatal receptor for advanced glycation end-products (RAGE; early responder to dopaminergic toxins) density in MDPV mice was not statistically different from control animals. In sheer contrast with MDPV, METH decreased general motor activity in mice. This was paralleled by a significant striatal TH depletion which was accompanied by changes in microglia arborization (Scholl analysis) and astrocytic hypertrophy (increased GFAP labeling), but normal MPB density. In spite of glial changes, RAGE levels were not significantly different from control animals. Additionally, both MDPV and METH failed to produce frontal-cortex molecular and cellular changes at this early time-point. This confirms that the neurotoxic effects of amphetamine analogues on different brain regions are time-dependent. **Conclusion:** This comparative study newly highlights that binge MDPV exposure comes without evident behavioral and glial changes in regions involved in drug addiction at this early time-point, when striatal neurotoxicity is already evident in METH mice. However, neuropharmacological MDPV signature needs further profiling.

Disclosures: F.C. Pereira: None. **L. Fernandes:** None. **M. Campeão:** None. **I. Pita:** None. **C. Lemos:** None. **S.F. Ali:** None. **F. Carvalho:** None. **C.A. Fontes Ribeiro:** None. **S.D. Viana:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.24/XX12

Topic: G.08. Drugs of Abuse and Addiction

Title: Transient physical withdrawal and persistent reduction in morphine analgesia are detected following chronic fentanyl exposure in rats

Authors: *Y. LI, M. R. HUFF, C. B. PURYEAR, C. SANCHEZ
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Abstract: Chronic opioid exposure induces long lasting alterations in neurocircuitries, which may result in somatic and affective symptoms that make protracted abstinence a challenge to sustain in patients. While behavioral changes in affective domain and memory deficits have been reported in mice during the protracted abstinence period following opioids exposure, it is unclear whether there are other indications of an altered opioid system. To our knowledge, protracted opioid abstinence in rats has not been characterized, despite the routine use of rats in addiction studies. Furthermore, it is known that mice and rats respond to opioids differently. Current study focuses on rats chronically exposed to fentanyl, aims to confirm signs associated with physical dependence during the acute withdrawal period, as well as to assess nociception and response to opioid system stimulation during the protracted abstinence period. Adult male Sprague-Dawley

rats were exposed to fentanyl (0.6mg/kg/day, via osmotic minipump) for 2 weeks. Physical dependence was measured during the acute withdrawal period. Thermo nociception and morphine response in hot plate test were assessed during the protracted abstinence period. Experiments were repeated in separate cohorts of animals to confirm the reproducibility of the findings. Chronic fentanyl exposure led to a reduced body weight gain. Withdrawal from fentanyl induced a significant loss in bodyweight, accompanied by reduced food and water intake up to 48 hours after minipump explant. During the protracted abstinence period, fentanyl group had a significant reduction in morphine analgesia in hot plate test, compared to vehicle group. This change was detectable from week one to week nine post fentanyl withdrawal. These results support the hypothesis that chronic exposure to and subsequent withdrawal from opioids lead to physical dependence and long-lasting changes in opioid neurocircuitry in rats.

Disclosures: Y. Li: A. Employment/Salary (full or part-time):; Alkermes Inc. **M.R. Huff:** A. Employment/Salary (full or part-time):; Alkermes, Inc. **C.B. Puryear:** A. Employment/Salary (full or part-time):; Alkermes, Inc. **C. Sanchez:** A. Employment/Salary (full or part-time):; Alkermes, Inc.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.25/XX13

Topic: G.08. Drugs of Abuse and Addiction

Support: Texas Tech University Health Sciences Center Start-Up Funds

Title: Discovery of novel class of opioid receptor antagonist to overcome the opioid crisis

Authors: *M. HOSSAIN, A. SIFAT, T. ABBRUSCATO, N. A. GERMAN
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Abstract: Recent reports state that opioid overdose takes more than 115 lives every day in the United States. Current therapy includes naltrexone, a non-selective antagonist that has shown excellent results in clinical trials. However, hepatotoxicity and individual reactions to this compound caused a reduction in the number of patients remaining on the treatment. Therefore, it is crucial to develop novel, structurally dissimilar, non-selective opioid antagonists to have more choices of individualized therapy for patients. Gliotoxin is a fungal metabolite with reported anticancer, antibacterial, and antiviral activities, and the ability to suppress the immune system. Its toxicity is mainly attributed to the presence of the disulfide bridge. Gliotoxin contains a tricyclic system that includes a diketopiperazine ring, a naturally privileged structure known to modulate selected G-protein coupled receptors (GPCRs). We hypothesized that removal of the disulfide bridge from the gliotoxin structure would yield analogs with the activity such as GPCR

modulators, specifically at opioid receptors. Here, we report the design, synthesis and biological activities of gliotoxin-derived analogs lacking the disulfide bridge. All compounds were evaluated for their affinity to major groups of GPCR, using the primary binding assay. The secondary binding assay was performed for compounds that showed at least 40% of the inhibition of any GPCR. Our results identified several active analogs, where one was able to selectively inhibit the μ, δ, and κ-opioid receptor at 97.8% (*Ki* 262 nM), 97.4% (*Ki* 148 nM), and 99.3% (*Ki* 197 nM), respectively. Next, compounds with significant activity were assessed for their ability to cross the blood-brain barrier and induce cytotoxicity (bEnd.3 cells and neurons extracted from the mouse). Obtained data confirmed that removal of the disulfide bridge abolished gliotoxin-related cytotoxicity in all our analogs at the concentrations ranging from 100 nM to 100 μM. The blood-brain barrier permeability *in-vitro* assay (bEnd.3 cell monolayer) showed excellent penetration of tested compounds with the permeability coefficient (P_{app}) higher than selected CNS drugs. Finally, we have identified analogs with selective inhibition of opioid receptors at the nanomolar range. Because of the known overdose-reversing effect of the opioid antagonists, we believe that our analogs have potential for clinical implications in treating this condition. We envision that structure-activity-relationship studies of this new class of opioid antagonist will lead us to develop novel therapeutics that will significantly decrease the outcome of the existing opioid crisis.

Disclosures: M. Hossain: None. **A. Sifat:** None. **T. Abbruscato:** None. **N.A. German:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.26/XX14

Topic: G.08. Drugs of Abuse and Addiction

Support: Dean Faculty of Science Grant, University of Karachi

Title: Effects of environmental enrichment on dependence & withdrawal induced by abstinence of nicotine, caffeine and diazepam in rats

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Abstract: Rationale
Drug addiction is a chronic neuropsychiatric disorder which is linked to neurobehavioral deficits. One of the main problems that drug addicts experience when trying to quit the habit of addiction is the adverse neuropsychological and behavioral deficits collectively known as withdrawal

symptoms. Most prominently, these withdrawal symptoms include depression and impaired memory functions. It has been observed that the withdrawal symptoms increase the drug seeking behavior and chance of drug relapse with higher probability. Living in a healthy and enriched environment has powerful positive effects on physiological and pathological conditions. There are compelling data which represent the preventive effects of enriched environment against drug addiction. However, its effects on withdrawal symptoms during drug abstinence period are not explored so far. This study was, therefore, designed to investigate the effects of enriched environment on withdrawal symptoms during drug abstinence in rats.

Methods

After acclimation period, 48 rats were divided into four equally numbered groups (n=12) control, nicotine (0.6 mg/kg), caffeine (5 mg/kg) and diazepam (1 mg/kg). Addiction was induced in standard environment and half rats from each group were then reared in enriched environment during drug withdrawal for 21 days. Withdrawal symptoms were evaluated weekly using conditioned place preference (CPP) paradigm. Locomotor activity, depression and memory function were also monitored during withdrawal period using open field test, force swim test and Morris water maze, respectively.

Results

Drug injected rats kept in standard environment exhibited significantly increased drug seeking behavior, depression-like symptoms and impaired memory function during the time period of drug abstinence. Whereas, exposure to physically enriched environmental condition significantly reduced withdrawal symptoms in rats as evident by reduced time spent in drug-preferred area in CPP. Intensity of depression-like symptoms and impaired memory were also gradually reduced in rats kept in physically enriched environment during the exposure of three weeks.

Conclusions

Hence, this study highlights the significance of enriched environmental condition to diminish the severity of withdrawal symptoms and neurobehavioral deficits which are commonly observed during spontaneous withdrawal from addictive drug. It is, therefore, suggested from the present study that enriched environment diverts from addiction by providing healthy, intellectual and physical stimulation and thus may protect from drug relapse.

Disclosures: Z. Batool: None. **A. Nawaz:** None. **S. Haider:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.27/YY1

Topic: G.08. Drugs of Abuse and Addiction

Support: Veterans Affairs Grant IK2 BX003838-01A1
NIH/NIDDK Grant: T32 DK083250

Title: Nicotine and minor tobacco alkaloid effects on food intake, body composition, and neuronal activation

Authors: *P. E. BUNNEY[1], M. K. GRACE[2], C. M. KOTZ[3]
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Abstract: Nicotine has long been viewed as the primary active component in tobacco products responsible for their effects on body weight. However, the limited success of nicotine replacement therapies to prevent post-cessation weight gain suggests that there may be other compounds within tobacco products that facilitate smokers' reductions in weight gain. The nicotine-like compounds, minor tobacco alkaloids (MTA), which are found in low levels in tobacco products, may be such compounds. Like nicotine, the MTAs activate nicotinic acetylecholine receptors (nAChRs) within the brain, including the nAChR subtypes involved in mediating nicotine's effects on food intake. Their lower potency and affinity for the receptors reduces their addictive potential, making them superior candidates for obesity pharmacotherapy. Based on this, we hypothesized that chronic MTA administration could prevent weight gain. To test this, we administered saline, nicotine (0.5 mg/kg) and 3 minor tobacco alkaloids (nornicotine: 6.0 mg/kg; anatabine: 3.0 mg/kg; anabasine: 3.0 mg/kg) to male rats housed in indirect calorimetry chambers for seven consecutive days (i.p.; n = 10/group). All drugs reduced weight gain and food intake relative to saline. Faster and significantly greater delays in weight gain and reductions in fat mass were seen with nornicotine and anatabine, while nicotine and anabasine both prevented any additional body weight and fat mass gain. All drugs, except anatabine, increased physical activity (PA) on day 1, although only nicotine and nornicotine increased PA across the seven days. There was a trend for increases in energy expenditure for all drugs tested, although these failed to reach significance. Based on their ability to promote the greatest weight loss, nornicotine and anatabine were then further evaluated in a new set of male rats. Nornicotine or anatabine was administered bilaterally into the arcuate nucleus (AN) (n=8/group; 0.03 - 3.00 ug/ul at a volume of 1uL per side). At the highest dose, anatabine directly into the AN reduced food intake and produced increases in cFos expression within this area, whereas nornicotine did not have any effect. Combined, these results suggest that nornicotine and anatabine are potential pharmacotherapies for treating obesity, and that anatabine, but not nornicotine, affects food intake via neurons within the AN.

Disclosures: P.E. Bunney: None. **M.K. Grace:** None. **C.M. Kotz:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.28/YY2

Topic: G.08. Drugs of Abuse and Addiction

Support: P01 DA017259
RO1 AA020404 and a Research Supplement to Promote Diversity
K99 AA025393
R00 DA035865

Title: Enhanced nicotine reward in a mouse model of the P129T FAAH gene polymorphism

Authors: *L. A. NATIVIDAD[1], M. W. BUCZYNSKI[3], D. STOUFFER[1], I. Y. POLIS[1], A. VIADER[2], B. F. CRAVATT[2], L. H. PARSONS[1]
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Abstract: A single nucleotide polymorphism of the human fatty acid amide hydrolase (FAAH) gene leads to a missense mutation (C385A) that substitutes a proline residue for threonine (P129T). Carriers of this mutation are thought to have diminished FAAH influence in brain and peripheral lipid metabolism. Clinical studies report an association between the P129T mutation, reward-related pathologies and problem drug use. The current study employed a P129T knock-in (KI) mouse model to characterize the effects of this SNP on the rewarding effects of nicotine using conditioned place preference (CPP), operant intravenous self-administration (IVSA) and *in vivo* microdialysis procedures. For the CPP study, P129T KI and wild-type (WT) mice received 3 days of drug conditioning with both nicotine (0 - 0.7 mg/kg, sc) and saline injections paired with distinct environments in a 3-chamber maze each day. On test day, the mice were allowed to explore all chambers of the maze in a drug-free state, and the time spent in the drug-paired environment was indexed as a measure of drug reward. In the IVSA studies, the nicotine dose-effect function (0.05 - 0.25 mg/kg/inf.) was characterized under an FR-1 schedule, followed by evaluations of the motivation for nicotine under a progressive ratio (PR) schedule of reinforcement. Separate studies examined operant behavior under an extinction/reinstatement procedure. The microdialysis study employed a nicotine exposure regimen identical to the CPP study, with nucleus accumbens (NAc) microdialysates collected on the third day of drug exposure, and subsequently assayed for monoamines. The results revealed genotypic differences such that P129T KI mice exhibit enhanced sensitivity to low doses of nicotine reward relative to WT in the CPP paradigm. P129T KI mice also acquire nicotine IVSA more quickly, display an upward shift in the dose response, and achieve higher breakpoints during the PR probe. Operant behavior was rapidly extinguished in WT mice upon saline substitution, although P129T KI mice display “burst-like” responding during the first 2 saline substitution sessions that abated by the third session. Moreover, P129T KI mice exhibit enhanced nicotine-induced elevations in NAc dopamine levels than their WT counterparts. Preliminary findings using a chemo-proteomics approach reveal region-specific changes in FAAH activity in areas associated with nicotine reinforcement. Collectively, these data suggest that nicotine reward is enhanced in mice expressing the P129T mutation. The mechanisms by which genetic disruption of FAAH enhance sensitivity to nicotine likely involve dopamine transmission in terminal regions of the mesolimbic pathway.

Disclosures: L.A. Natividad: None. **M.W. Buczynski:** None. **D. Stouffer:** None. **I.Y. Polis:** None. **A. Viader:** None. **B.F. Cravatt:** None. **L.H. Parsons:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.29/YY3

Topic: G.08. Drugs of Abuse and Addiction

Title: Evaluating mechanisms of reward enhancement by nicotine in humans

Authors: *K. JENKINS, A. PALMISANO, A. ARNISTA, M. PADUA, O. OKIFO, R. LIVOTI, C. LOVE, R. S. ASTUR
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Abstract: In addition to acting as a primary reinforcer, nicotine has been shown in many nonhuman studies to enhance the incentive value of non-nicotine stimuli conditioned through Pavlovian associations. Recently, our lab has examined nicotine's reward-enhancing effects in humans using a novel virtual reality conditioned place preference (CPP) paradigm.
Using a virtual reality (VR) CPP task, thirty nicotine-using undergraduates were randomly assigned to receive either a 2mg nicotine or placebo lozenge prior to conditioning. During each of six, three-minute conditioning sessions, participants were confined to one of two VR rooms. In one room, they received real chocolate M&Ms, whereas no M&Ms were administered in the other room. Following conditioning, a 3-minute free-access test session occurred in which participants had unrestricted access to both rooms without reward. Only participants who received nicotine exhibited a CPP by spending significantly more time in the room previously-paired with M&Ms ($p = 0.02$).
A second study was then conducted to examine differences in reward responding between nicotine users and non-users. Participants were given questionnaires evaluating nicotine dependence, cravings, sensation-seeking, impulsivity, and sensitivity to reward and punishment. Participants were also asked to rate standardized images from the International Affective Picture System (IAPS), and pictures of nicotine-associated stimuli. Nicotine users scored significantly higher on both disinhibition ($p = 0.001$) and experience ($p = 0.001$) subscales of the Zuckerman Sensation Seeking Scale, suggesting that they are more likely to participate in risky behaviors. Nicotine users also scored higher on reward subscales ($p = 0.01$) of the Sensitivity to Punishment and Reward Questionnaire, suggesting that they are more prone to show approach behavior toward rewards. Finally, compared to non-users, nicotine users rated nicotine-related images ($p = 0.001$) and positively affective images as significantly more positive ($p = 0.01$).
Combined, these studies support evidence that nicotine enhances sensitivity to reward and demonstrate the efficacy of utilizing the virtual CPP paradigm to understand behavioral

mechanisms of substance dependence. These data also provide a foundation for future studies aimed at characterizing the reward mechanisms that underlie risks for maintaining nicotine use. Future studies will examine the effects of nicotine on human sympathetic nervous system responses via galvanic skin and electrocardiogram responses to determine whether CPP result in changes in the sympathetic response.

Disclosures: K. Jenkins: None. **A. Palmisano:** None. **A. Arnista:** None. **M. Padua:** None. **O. Okifo:** None. **R. Livoti:** None. **C. Love:** None. **R.S. Astur:** None.

Poster

236. Addictive Drugs: Reward Mechanisms, Tolerance, Dependence, and Toxicity

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 236.30/YY4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA040619 (YP/TR)

Title: Neurovascular and neuroinflammatory alterations following electronic cigarette exposure

Authors: *N. A. HELDT[1], S. GAJGHATE[1], A. SELIGA[1], M. WINFIELD[1], N. REICHENBACH[1], S. ROM[1], Y. PERSIDSKY[1,2]
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Abstract: The use of electronic cigarettes (e-cig) is projected to overtake traditional tobacco products within the next decade. Very little is known regarding the long-term impact of e-cig use, and several e-cig constituents are associated with deleterious health effects. Cigarette smoking is known to induce neuroinflammation, and the smoking population demonstrates increased risk for neuropathology and cognitive decline. In the present study, we assess the impact of e-cig exposure on neurovascular integrity and neuroinflammation using an *in vitro* blood brain barrier (BBB) model and murine *in vivo* model. C57BL/6 mice were exposed to 2 hours of daily e-cig vapor for a duration of up to 2 months, beginning at 8 weeks of age. Endothelial cell and pericyte cultures were treated with e-cig infused media diluted to physiologically relevant concentrations and barrier integrity and leukocyte-endothelial interactions were evaluated. The impact of e-cig exposure on cognitive function (Y-maze), affective state (plus-maze, marble bury), microglial activation, BBB permeability, endothelial cell gene expression, and infiltration of peripheral immune cells was examined. Exposure to e-cig induced gene expression alterations in brain microvascular endothelium and increased peripheral immune cells within the brain parenchyma. Our findings suggest that e-cig use has neuroinflammatory effects which are similar to traditional tobacco products. The impact of

sustained neuroinflammation associated with long-term e-cig use remains uncharacterized and may have neurocognitive and affective consequences.

Disclosures: N.A. Heldt: None. **S. Gajghate:** None. **A. Seliga:** None. **M. Winfield:** None. **N. Reichenbach:** None. **S. Rom:** None. **Y. Persidsky:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.01/YY5

Topic: G.08. Drugs of Abuse and Addiction

Support: P30 grant (P30 AR-070254) Rheumatic Disease Research Core Center.
NIDA Intramural Research Program (NIH)

Title: Fluorescence activated synaptoneurosome sorting (FASS) to study rat dorsal striatum glutamatergic inputs from prelimbic and motor cortices following acute methamphetamine injections

Authors: *E. M. HILAIRE, F. RUBIO[1], R. CIMBRO[2], R. QUINTANA FELICIANO[1], B. L. WARREN[1], K. LI[3], A. B. SMIT[3], B. T. HOPE[1]
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Abstract: Learning plays a large role in cue-induced drug craving. Long-lasting alterations within synapses that were strongly activated during learning are thought to encode the resulting memories. To identify and isolate activated synapses to identify their unique alterations during learning, we are developing a fluorescence activated synaptoneurosome sorting (FASS)-based proteomic approach to find markers of activated synapses in the dorsal striatum of the rat brain. Synaptoneurosomes contain the presynaptic terminal attached to a resealed post-synaptic spine. We injected a virus encoding the fluorescent protein eYFP (fused to channel rhodopsin) into either the motor and prelimbic cortices of rats to fluorescently tag synapses projecting to the dorsal striatum. Six weeks later, rats were administered a single injection of 5 mg/kg (IP) of methamphetamine. Following 0, 10, or 60 minutes, we then isolated synaptoneurosomes from the dorsal striatum using Percoll gradient centrifugation. Using calibration beads in a flow cytometer, we gated events around 0.7-1.4 μm and sorted them based on their eYFP fluorescence signal. We validated the synaptoneurosome characteristics before and after sorting by electron microscopy.
We were able to sort 20 million eYFP-positive events from the dorsal striatal synapses coming from the motor and prelimbic cortices (n=4) at each time point (0, 10, and 60 minutes). Further

proteomic analysis will be done using mass spectrometry to determine potential candidate markers of activated synapses.

Disclosures: F. Rubio: None. **R. Cimbro:** None. **R. Quintana Feliciano:** None. **B.L. Warren:** None. **K. Li:** None. **A.B. Smit:** None. **B.T. Hope:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.02/YY6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA IRP

Title: Functional alterations in Fos-expressing neuronal ensembles of the prelimbic cortex after cocaine place conditioning

Authors: *L. R. WHITAKER[1], C. N. MILLER[2], A. KESNER[3], S. A. GOLDEN[3], M. VENNIRO[3], B. T. HOPE[4]
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Abstract: Learned associations between environmental stimuli and rewards drive goal-directed learning and motivated behavior. The prelimbic cortex (PLC) is known to play a role in this type of learning, although there is debate as to its specific role. Learned associations are thought to be encoded by specific patterns of sparsely distributed neurons called neuronal ensembles that are selectively activated by reward-predictive stimuli. The fundamental question of how ensemble neurons are functionally altered during learning, and which of these changes encode learned associations is unknown. To address this question, we examined intrinsic excitability in prelimbic cortex neuronal ensembles that were selectively activated during exposure to a cocaine-paired context. We used FosGFP transgenic mice to identify activated ensemble neurons (FosGFP+) and non-activated (or weakly activated) non-ensemble neurons (FosGFP-) in an *ex vivo* brain slice preparation. Using whole cell recordings of layer V pyramidal neurons, we found alterations in excitability of FosGFP+ neurons and FosGFP- neurons following re-exposure to a context previously paired with cocaine. Overall, these data suggest that there are specific functional alterations within ensemble neurons of the PLC that encode learned associations.

Disclosures: L.R. Whitaker: None. **C.N. Miller:** None. **A. Kesner:** None. **S.A. Golden:** None. **M. Venniro:** None. **B.T. Hope:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.03/YY7

Topic: G.08. Drugs of Abuse and Addiction

Support: Financial support provided by NIDA IRP/NIH.
NIDA 1K99DA042102 - 01A1

Title: Projections from Fos-expressing neuronal ensembles in the ventromedial prefrontal cortex to nucleus accumbens shell are required for extinction of cocaine seeking

Authors: *B. L. WARREN[1], L. F. KANE[1], M. VENNIRO[1], V. SELVAM[1], R. QUINTANA FELICIANO[1], R. MADANGOPAL[1], L. R. WHITAKER[1], F. RUBIO[1], J. M. BOSSERT[1], D. CAPRIOLI[2], Y. SHAHAM[1]
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Abstract: Background: We previously found that functionally distinct neuronal ensembles in the ventral medial prefrontal cortex (vmPFC) mediate self-administration and extinction of cocaine-seeking. In the present study, we examined whether neuronal ensembles associated with cocaine self-administration or extinction project to different subregions of the nucleus accumbens (NAc). We then examined whether these activated projections differentially mediate the cocaine self-administration and extinction behaviors.
Methods: For both experiments, we trained rats to self-administer cocaine for 14 days. Separate groups of rats underwent 0 or 7 extinction training sessions prior to test day. On test day, drug seeking was assessed in the absence of cocaine reward. We had previously shown that the self-administration memory was reactivated in the 0 extinction session group while the extinction memory was reactivated in the 7 extinction session group. In the first experiment, we used fluorescent retrograde tracer cholera toxin B to label projections from the vmPFC to NAc core and shell and combined this with double-labeling for Fos in the vmPFC. In the second experiment, we performed a disconnection experiment where we combined Daun02 inactivaton of vmPFC neuronal ensembles associated with extinction of cocaine seeking followed three days later with inactivation of the NAc core or shell with SCH-39166 either ipsilaterally or contralaterally immediately prior to recall on test day.
Results: The tracing experiment indicated that self-administration ensembles project preferentially to the NAc core, while extinction ensembles project preferentially to the shell. Contralateral inactivation of the extinction-related ensemble and NAc shell increased cocaine seeking when compared to cocaine seeking in the ipsilateral inactivation and vehicle controls. We are now performing disconnection experiments following Daun02 inactivation of the self-

administration ensemble in vmPFC.
Conclusions: Different neuronal ensembles within the vmPFC mediate cocaine self-administration and extinction of cocaine seeking. These ensembles are functionally distinct, and project to different anatomical subregions of the NAc to exert their effects.

Disclosures: B.L. Warren: None. **L.F. Kane:** None. **M. Venniro:** None. **V. Selvam:** None. **R. Quintana Feliciano:** None. **R. Madangopal:** None. **L.R. Whitaker:** None. **F. Rubio:** None. **J.M. Bossert:** None. **D. Caprioli:** None. **Y. Shaham:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.04/YY8

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA/NIH

Title: Incubation of discriminative stimulus-induced cocaine craving

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Abstract: Background:
Environmental stimuli paired with cocaine experience can provoke craving and relapse in humans, and elicit cocaine seeking in rats. Previous studies have shown that discrete cue- but not context-induced relapse to drug seeking progressively increases after withdrawal (incubation of drug craving). Here we developed a trial-based discriminative stimulus (DS+/DS-) procedure and tested whether the rats' response to a DS that predicts cocaine availability incubates after withdrawal.
Methods:
We first trained rats to self-administer cocaine in the presence of a DS+ that signals cocaine availability (FR1 reinforcement schedule; 3-h continuous access; 0.75 mg/kg/infusion; 6 sessions) and then transitioned them to a trial-based design (30 trials/session; 60-s lever availability/trial; multiple infusions available per trial; variable inter-trial interval; 2 sessions). Next, we introduced a DS- that signals the absence of cocaine and trained the rats to discriminate between the two DSs within the same session (60 trials/session; 30 each of DS+ and DS-; 2 sessions of 3-h/day) for 6-10 days. Once the rats showed stable discrimination, we repeatedly

tested them for DS-induced relapse to cocaine seeking during both DS+ and DS- trials (60 trials/3-h; 30 trials each of DS+ and DS-) after 1, 21, 60, 120, 200 and 300 days of abstinence.
Results:
We observed reliable cocaine self-administration and discrimination in the trial-based procedure and robust DS-induced relapse to cocaine seeking at all time points. Further, we observed incubation of DS-induced cocaine seeking only during DS+ trials after 21, 60, and 120 days of abstinence.
Conclusions:
We have developed a trial-based procedure for studying incubation of DS-induced cocaine seeking. Future studies will investigate the role of DS-specific neuronal ensembles in mediating this new form of incubation of cocaine craving.
*Financial support provided by NIDA/NIH

Disclosures: S.J. Weber: None. **L.E. Komer:** None. **J.K. Hoots:** None. **B.J. Tunstall:** None. **J.M. Bossert:** None. **Y. Shaham:** None. **B.T. Hope:** None. **R. Madangopal:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.05/YY9

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Research Program, NIH
1K99DA042102-01A1

Title: Functionally distinct neuronal ensembles within the ventromedial prefrontal cortex mediate food and cocaine seeking

Authors: *L. F. KANE, B. L. WARREN, R. QUINTANA-FELICIANO, M. VENNIRO, R. MADANGOPAL, J. F. RUBIO, Y. SHAHAM, B. T. HOPE
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Abstract: Learned associations between cues and rewards play a major role in drug addiction. Different cues can become associated with the stimuli properties of different rewards such as cocaine and food. These separate learned associations are thought to be encoded by functionally distinct patterns of sparsely distributed neurons called ‘neuronal ensembles’. We previously demonstrated that neuronal ensembles in the ventromedial prefrontal cortex (vmPFC) mediate both food and cocaine seeking. However, it was currently unknown whether the neuronal ensembles mediating food-seeking are distinct from those mediating cocaine-seeking. In the current study, we hypothesized that functionally distinct neuronal ensembles within the vmPFC mediate food and drug memories. We trained all rats to lever press for palatable food pellets (3

h/d) and cocaine infusions (3 h/d; 1.0mg/kg/infusion) on alternating days (3 weeks). During training, we also exposed the rats to one discrete choice session per week in which rats had access to both food and cocaine levers. All rats learned to lever press for both rewards, and the number of lever presses increased over time. On induction day, one week after the last training session, rats were allowed to press for the food or cocaine-associated lever for 1 h under non-reinforced conditions to reactivate the reward-associated memory and related neuronal ensembles. Ninety minutes after the beginning of this induction session, Daun02 was injected into the vmPFC to selectively disrupt neuronal ensembles that were activated during the 1 h session. Three days later, all rats were tested for food and cocaine seeking. Selective inactivation of the food-associated neuronal ensemble decreased food lever-pressing on test day, without altering cocaine lever pressing. Likewise, inactivation of the cocaine-associated neuronal ensemble decreased cocaine lever-pressing without altering food lever pressing. Our results suggest that functionally distinct neuronal ensembles within the vmPFC encode the different operant memories for food and cocaine seeking.

Disclosures: L.F. Kane: None. **B.L. Warren:** None. **R. Quintana-Feliciano:** None. **M. Venniro:** None. **R. Madangopal:** None. **J.F. Rubio:** None. **Y. Shaham:** None. **B.T. Hope:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.06/YY10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA/NIH

Title: Fos mapping in whole mouse brain during food seeking relapse

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Abstract: Expression of immediate early genes (IEGs) are routinely used as an indicator of strongly activated neurons in rodent behavioral procedures. Our lab and others have shown that neuronal ensembles, identified using the activity marker Fos, mediate relapse to food and drug seeking. To investigate brain-wide circuitry that was activated during behavior, we adapted a whole brain clearing and immunolabeling technique, called iDISCO+, to generate whole brain

Fos maps in mice during relapse to food seeking. We trained mice to lever press for a palatable food pellet reward for seven days. We then tested the mice for relapse to non-reinforced food seeking (30 min test sessions) after 1, 15, or 60 abstinence days in homecage. We transferred these mice (test group) to their homecages immediately after the test session and perfused them 60 min later; we also perfused no-test mice (homecage group) at the same time. We modified the recently published iDISCO+ method for uniform labeling of the proteins Fos. We optimized acquisition parameters to image immunolabeled brains using light sheet fluorescent microscopy. We observed reliable food self-administration from the mice, as well as robust relapse to food seeking during both early and late abstinence. We acquired whole brain Fos data from the experimental brains and are currently optimizing parameters to use the open source analysis package WholeBrain for data analysis. We will quantify Fos expression by brain area, generate distribution maps, and analyze Fos activation patterns across the whole brain.

Disclosures: L.E. Komer: None. **M. Jin:** None. **S.J. Weber:** None. **R. Madangopal:** None. **S.A. Golden:** None. **C. Mejias-Aponte:** None. **Y. Shaham:** None. **B.T. Hope:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.07/YY11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA IRP

Title: Characterization of Fos-expressing neuronal ensembles in the prefrontal cortex following cocaine place condtitioning using the Fos-tTa system

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Abstract: Learned associations between rewards, such as food or drugs of abuse, and reward-predictive stimuli, are critical to motivated behavior. Associative learning is thought to be encoded by functional alterations within activity-dependent neuronal ensembles. The immediate early gene, Fos, can be used to identify these small, sparsely distributed populations of strongly activated neurons. The Fos-tTa transgenic mouse system in combination with viral technology can be used to identify, characterize, and ultimately manipulate Fos ensemble neurons. We used a cocaine conditioned place preference (CPP) procedure to study the association between an environmental context and cocaine reward in both wild type and Fos-tTa mice. To identify brain

regions active during expression of cocaine CPP we used Fos immunohistochemistry and identified the prelimbic cortex as a particularly active region. All groups tested (wild type males, Fos-tTa males, and Fos-tTa females) demonstrated significant cocaine CPP. There was no significant difference in CPP scores between male and female Fos-tTa mice. Future studies include the validation of the Fos-tTa system as well as experiments to determine the time course of functional alterations in Fos-expressing ensembles.

Disclosures: C.N. Miller: None. **A. Kesner:** None. **S.A. Golden:** None. **M. Venniro:** None. **B.T. Hope:** None. **L.R. Whitaker:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.08/YY12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA IRP / NIH

Title: *In vivo* calcium imaging of rat prelimbic cortex ensembles during different stages of palatable food seeking

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Abstract: *In vivo* calcium imaging of awake behaving rats provides a dynamic, spatio-temporal view of task-related ensemble activity during the course of learning. Previous studies using the rat reinstatement model have implicated prelimbic cortex in reinstatement of palatable food seeking induced by non-contingent pellet priming. However, how the underlying neuronal population code in prelimbic cortex relates to pellet priming-induced reinstatement is unknown. To this end, we developed a miniature epifluorescent microscope and optimized surgical and behavioral procedures for long-term calcium imaging in prelimbic cortex of awake behaving rats.
We trained rats to lever press for a palatable food pellet reward (FR1 reinforcement schedule; 3 pellet reward delivered after presentation of a 10-s discrete cue) in a modified trial-based design (100 trials/session; 20-s lever availability/trial; variable inter-trial interval). Next, we

extinguished the rats' lever pressing in the presence of the discrete cue. We then tested the rats under extinction conditions for pellet priming-induced reinstatement (1 priming pellet delivered/trial preceding lever presentation) of food seeking. We observed reliable food self-administration and extinction of food-reinforced responding in the trial-based procedure. We also observed robust pellet-primed reinstatement under extinction conditions.
We use a local factorization approach to extract neurons from individual fluorescence videos, and then apply a recently published probabilistic model for session-to-session cell registration. Following cell-identification and across-session registration, we track the evolution of single cell firing properties, as well as the stability/degeneration of neuronal ensembles active throughout operant food-seeking, extinction learning, and pellet-primed reinstatement.
*Financial support provided by NIDA/NIH.

Disclosures: R. Madangopal: None. **C. Heins:** None. **D. Caprioli:** None. **B. Liang:** None. **G. Barbera:** None. **L.E. Komer:** None. **S.J. Weber:** None. **J.M. Bossert:** None. **V. Priessemann:** None. **Y. Shaham:** None. **B.T. Hope:** None. **D. Lin:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.09/YY13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Research Program (NIH)
P30 (P30 AR-070254) Rheumatic Disease Research Core Center.

Title: Detection and quantification of Arc-positive synapses after acute cocaine injections using a flow cytometry approach

Authors: *F. RUBIO[1], P. V. SELVAM[1], S. ZHANG[1], E. HILAIRE[1], R. CIMBRO[2], B. T. HOPE[1]
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Abstract: Learning plays a central role in cue-induced drug craving. Long-lasting alterations within synapses that were strongly activated during learning are thought to form the engram that encodes the long-lasting memory. To identify and characterize these activated synapses, we first need to isolate them from the surrounding less activated synapses. Arc is an immediate early gene product whose mRNA is found constitutively at the base of dendritic spines. Arc mRNA is translated into Arc protein that accumulates in activated synapses. Thus Arc protein could be a useful marker for isolating activated synapses. Here we used immunohistochemistry and immuno-electron microscopy (EM) from brain sections and flow cytometry of

synaptoneurosomes to evaluate cocaine-induced Arc expression in activated synapses. Synaptoneurosomes contain the presynaptic terminal attached to a resealed post-synaptic spine. We administered one injection of 20 mg/kg (IP) of cocaine or the saline vehicle. Using immunohistochemistry, we detected an increase of Arc-positive cell bodies in the nucleus accumbens after cocaine but not saline injections. Using EM, we identified immunogold-labeled Arc protein within the postsynaptic compartment. Cocaine increased the number of post-synaptic densities associated with Arc (33% of all post-synaptic densities) compared with 20% in the saline vehicle group or 22% in a group of naïve rats. Finally, we developed a protocol to quantify Arc-positive synaptoneurosomes using PSD95 and Arc antibodies using flow cytometry. Within the gate chosen for synaptoneurosomes, 60-80% of them were PSD95-positive while only 4-11% were Arc positive. After further validations, we will use the flow cytometry approach to isolate and study molecular alterations in activated Arc-positive synaptoneurosomes associated with learning and cue reactivation in models of drug relapse.

Disclosures: F. Rubio: None. **P.V. Selvam:** None. **S. Zhang:** None. **E. Hilaire:** None. **R. Cimbro:** None. **B.T. Hope:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.10/YY14

Topic: G.08. Drugs of Abuse and Addiction

Title: Volitional social interaction prevents drug addiction

Authors: *M. VENNIRO[1], M. ZHANG[2], D. CAPRIOLI[3], S. A. GOLDEN[4], C. HEINS[2], D. H. EPSTEIN[5], M. F. MORALES[6], Y. SHAHAM[7]
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Abstract: Background: Prevention and treatment of addiction have not been appreciably improved by neuroscientific research. One problem is that mechanistic circuit- or molecular-related studies using rodent models do not incorporate social factors, which, for humans, play a critical role in addiction. Here we introduce an operant model of social choice in rats and demonstrate the profound impact of an alternative social reward on drug self-administration and relapse.
Methods: We first determined whether rewarding voluntary social interaction would prevent extended access self-administration of methamphetamine or heroin; we also determined the boundary conditions for this effect. Next, we used the rat DSM-IV-based addiction model to

determine whether such volitional social interaction would also prevent drug self-administration in the subpopulation of rats identified as “addicted.’’
Finally, we determined whether social-choice-based voluntary abstinence would prevent incubation of vulnerability to drug relapse and investigated brain mechanisms underlying that effect.
Results: Independent of sex, drug class, drug dose, training conditions, abstinence duration, housing conditions (including social housing), and “addiction score” (DSM-IV-based model), volitional social interaction prevented drug self-administration. Only when we introduced a long delay between lever-pressing and social interaction, or punished the operant response for social reward, did the rats resume drug self-administration.
Social-choice-based voluntary abstinence prevented incubation of drug craving and relapse, an effect associated with selective activation of central amygdala PKCδ-expressing inhibitory neurons.
Conclusion: Our results illustrate the profound impact of volitional prosocial interaction on addiction and support wider implementation of social-based contingency-management programs to addiction treatment.

Disclosures: M. Venniro: None. **M. Zhang:** None. **D. Caprioli:** None. **S.A. Golden:** None. **C. Heins:** None. **D.H. Epstein:** None. **M.F. Morales:** None. **Y. Shaham:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.11/YY15

Topic: G.08. Drugs of Abuse and Addiction

Support: Universitat Jaume I (PREDOC2014/11)
UJI (14I307.01/1)
Ministerio de Economía y Competitividad (MINECO) (PSI2015-68600-P)

Title: Back to front: How would the cerebellum control the activity of the addiction circuitry in order to establish conditioned preferences for drug-related cues?

Authors: *M. MIQUEL, I. GIL-MIRAVET, J. GUARQUE-CHABRERA, F. OLUCHA-BORDONAU, A. SANCHEZ-HERNANDEZ
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Abstract: Recent evidence from our laboratory has shown that cocaine-induced conditioned preference boosts both neural activity and the expression of perineuronal nets in the dorsal region of the posterior cerebellum. Moreover, the lesion of this region promotes the acquisition of preference for odour cues that predicts cocaine availability. Overall, these findings indicate that

the cerebellum would be critical for the inhibitory control of drug seeking after the establishment of drug-cue memories. In the present research, a possible explanation for this facilitation effect was investigated. The hypothesis was that the cerebellar lesion changes neuronal activity at the level of the striatum and medial prefrontal cortex (mPFC). Quinolinic acid was infused into the dorsal region of lobule VIII before conditioning trials. Then, associative cue-drug training alternated between 8 cocaine and 8 saline pairings. Neural activity was assessed 24 hours after the preference test using cFOS and vGlut expression in different regions of the basal ganglia, thalamus and medial prefrontal cortex. To propose a neuroanatomical model for our findings, we addressed a tracing study with Fluoro-Gold and biotinylated dextran amine, as retrograde and anterograde tracers, respectively. Tracers were infused into the dorsal region of lobule VIII in the vermis, mPFC cortex and ventral tegmental area (VTA) in order to map the interconnections between these regions. Double immunofluorescence was used for simultaneous identification of cell types. A dorsal lesion in the posterior cerebellum increased neuronal activity in mPFC and all striatal regions except the ventrolateral striatum. The neuroanatomical model that emerges is that the dorsal region of the posterior vermis might control striatal and mPFC activity throughout the direct projections from the deep cerebellar nuclei to VTA. These findings point to an important role of the cerebellum in controlling the activity of the addiction circuit with important behavioural effects on drug seeking.

Disclosures: M. Miquel: None. **I. Gil-Miravet:** None. **J. Guarque-Chabrera:** None. **F. Olucha-Bordonau:** None. **A. Sanchez-Hernandez:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.12/YY16

Topic: G.08. Drugs of Abuse and Addiction

Support: Alberta Gambling Research Institute
Alberta Innovates Health Solutions
Canadian Natural Sciences and Engineering Research Council Discovery Grant

Title: Chronic dopamine D_3 agonist administration induces compulsive reward seeking in rats

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Abstract: INTRODUCTION: Individuals treated for Parkinson's disease using dopamine agonists that preferentially target D_3 receptors develop behavioral addictions at rates much higher than in the general population. We tested whether chronic administration of a D_3

preferring agonist, pramipexole dihydrochloride (PPX), could induce addiction-like behaviors in rats.
METHODS: Thirty rats were implanted subcutaneously with either an osmotic or dummy pump after being trained to respond for reward delivered on a random ratio schedule of reinforcement requiring, on average, 50 responses for each reward. Osmotic pumps delivered PPX at a fixed rate over 28 days at doses of 1.0, 2.0, or 3.0 mg/kg/day. After implantation, animals were assessed for addiction-like behaviors using four behavioral assays. First, motivation for reward was assessed using a progressive ratio task in which response requirements to earn reward were increased gradually throughout the session. Second, difficulty limiting reward seeking was evaluated by calculating changes in rates of responding during periods when a cue light indicated that reward is no longer available. Third, persistence in the face of increasing negative consequences was evaluated using a progressive aversion task, during which reward was paired with increasing intensities of foot-shock. Finally, rates of relapse were assessed using a reinstatement paradigm which measured cue-induced response rates after a period of withdrawal.
RESULTS: Our data indicate that chronic PPX administration significantly increases both motivation (progressive ratio: $p = .032$) and the likelihood of relapse (reinstatement: $p = .032$). PPX administration also interferes with rats' ability to limit reward-seeking behavior when cues indicate that reward is not available ($p = .026$), but not when reward is paired with punishment (progressive aversion: $p = .123$).
CONCLUSIONS: These data show that PPX can induce compulsive, addiction-like behavior in rats exposed to random ratio reward schedules. PPX combined with long-term training may hence be useful as a model of behavioral addiction in the rat.

Disclosures: C.S. Laskowski: None. **K.M. Ward:** None. **D.L. Dorchak:** A. Employment/Salary (full or part-time):; Casino Lethbridge. **D.R. Christensen:** None. **D.R. Euston:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.13/YY17

Topic: G.08. Drugs of Abuse and Addiction

Support: DFG SFB1134

Title: Imaging neuronal ensemble activity in medial prefrontal cortex during operant self-administration using *in vivo* microendoscopy in rats

Authors: *I. SONNTAG[1], S. PFARR[2], J. BARROSO-FLORES[2], C. KÖRBER[1], W. SOMMER[2], T. KUNER[1]

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Abstract: The medial prefrontal cortex (mPFC) plays an important role in the regulation of complex behaviors and its dysfunction can lead to a range of aberrant behaviors such as excessive alcohol seeking. Reinforcement of behaviors involves the association of environmental cues with the availability of a reward, a learning process that is thought to engage groups of neurons - neuronal ensembles - that are sparsely distributed throughout the brain including the mPFC. Specifically in the infralimbic area (IL), we have recently identified and characterized a functional ensemble that controls the seeking of alcohol and is also involved in the processing of natural rewards. These findings were obtained using cFos-dependent activity tagging and chemogenetic ablation of cue-related ensembles in the IL of the mPFC. Because of the snapshot nature of the cFos method, insights into the dynamics of these ensembles are lacking. To further investigate formation, specificity, distinction and plasticity of prefrontal ensembles we established an *in-vivo* microendoscopy pipeline to track the calcium transients of 30-150 identified neurons across multiple behavioral sessions, while synchronously logging all relevant behavioral interactions of the rat with the operant conditioning chamber. Given the much greater behavioral flexibility compared to mice, rats are better suited for learning multiple or concurrent contingencies, but their strength and agility pose a challenge for microendoscopy. Here, male Wistar rats were trained in a customized operant conditioning chamber (Med Associates) to respond to cues associated with the availability of saccharin (0.2%) rewards. Recording was done using open source miniaturized epifluorescence microscopes (UCLA Miniscopes) that can be head mounted during the behavioral sessions. The miniscopes are coupled to implanted GRIN lenses (1 mm diameter) in the IL to allow optical access to neurons expressing GCaMP6f under the synapsin promotor. The data are analyzed using a combination of customized code and publicly available repositories (CNMF-E). Calcium traces of individual neurons synchronized with behavioral readouts permit high level analyses of neuronal ensemble activity during reward-related behaviors in single recording sessions as well as across multiple sessions. Thus, long-term observation of mPFC neuronal ensemble activity in different behavioral settings will enable new insights into the contribution of these ensembles to complex behaviors.

Disclosures: I. Sonntag: None. **S. Pfarr:** None. **J. Barroso-Flores:** None. **C. Körber:** None. **W. Sommer:** None. **T. Kuner:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.14/YY18

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R00 MH103531-03

Title: Characterization of ventral subiculum-nucleus accumbens projection circuitry

Authors: E. BOXER[1], *X. WANG[2], B. DUNN[2], J. AOTO[2]
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Abstract: Drug addiction and schizophrenia are complex brain disorders and pose tremendous socioeconomic challenges on individual productivity and the society. Nucleus accumbens (NAc) is the main reward center of the brain, while the hippocampus is essential for memory storage. The major output structure of the hippocampus is the subiculum. One role of ventral subiculum (vSUB) is thought to be in controlling context-dependent drug reinstatement. Consistent with this notion, vSUB provides substantial input to NAc. It is hypothesized that hyperactivity of vSUB-NAc circuit contributes to dopamine dysregulation associated with drug addiction and schizophrenia. Dopamine receptor type 1 (D1R)- or type 2 (D2R)-expressing medium spiny neurons (MSNs) in NAc count for 95% of the total neuronal population and their output onto ventral tagmental area (VTA), ventral pallidum (VP), prefrontal cortex (PFC), and amygdala drives reward behaviors. Despite mounting evidence supporting the importance of the vSUB-NAc projection circuit, little is known regarding its cell-type-specific wiring of the circuit. The subiculum is populated by two electrophysiologically distinct principle neurons, identified as regular- (RS) or burst-spiking (BS) neurons. BS neurons are more abundant than RS cells (70-30, respectively) and these two types of neurons project in an unknown distribution and proportion to D1R- or D2R-MSNs in NAc. Consistent with previous reports, we show that ~70% of NAc projecting vSUB neurons are RS neurons. We further demonstrate that D1R and D2R MSNs in NAc receive disproportionate input from RS and BS subicular neurons. Finally, we observed that basal synaptic transmission and activity-dependent synaptic plasticity at vSUB-D1R and vSUB-D2R synapses are fundamentally distinct. To the best of our knowledge, this study represents the first cell-type- and synapse-specific interrogation of the disease-relevant vSUB-NAc circuit.

Disclosures: E. Boxer: None. **X. Wang:** None. **B. Dunn:** None. **J. Aoto:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.15/YY19

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant R03DA044562

Title: Crossing an electric barrier to obtain rewards: A simple procedure to measure the persistence of reward taking in the presence of adversity

Authors: *M. MARINELLI[1], M. R. BREDDER[1], A. MUTTI[2], A. BATES[1], S. S. DESAIVRE[1], V. RAMACHANDRA[2], A. G. GORDON[1]
[1]Neurosci., Univ. of Texas at Austin, Austin, TX; [2]Div. of Pharmacol. and Toxicology, Col. of Pharm., Univ. of Texas At Austin, Austin, TX

Abstract: Inability to stop seeking and taking rewards despite adversity is one of the hallmarks of addictive behaviors. Many studies model this with operant responding in rats, by imposing a punishment upon each reward delivery, or by using conditioned aversive stimulus as deterrent for reward taking. While most of these approaches model the adverse *consequences* of obtaining rewards, few model adversity associated with the *action made* to obtain rewards. Here we measured the pursuit of reward taking in the presence of adversity, by modifying an existing procedure initially developed to produce abstinence (Cooper, Barnea-Ygael, Levy, Shaham, and Zangen, 2007).

We trained rats to self-administer a reward (sucrose pellets or cocaine, 1.2 mg/kg/infusion) for seven days. Then, we introduced adversity, in the form of "electric barrier" (a portion of electrified floor), which rats needed to cross in order to respond for and obtain the reward. The length of the electric barrier was proportional to the length of the rats (30% longer than the distance between the fore paws and hind paws, measured when the rat was gently stretched into a reaching posture). The intensity of the electric barrier (i.e. the level of adversity) was tailored to each rat's nociceptive threshold, and was increased daily, until rats stopped responding.

As the level of adversity increased, rats reduced intake of rewards. Data fitted a sigmoidal-curve, which allows calculating (a) the intensity at which intake starts decreasing, (b) the point at which intake is suppressed to half the initial intake, and (c) Hill slope. We can also examine (d) the latency to obtain the first reward for each session. This variable is known to correlate with escalation of drug intake and has been used to assess seeking and the level of "hesitation" (conflict) to obtain a reward. This procedure can also measure (e) the number of unsuccessful approaches (rat entering the electrified zone, without responding for the reward), which provides an index of approach-avoidance that is related to the anxiety state of the rat.

Overall, this procedure can be used to assess the amount of adversity that rats will withstand to reach a reward. This is different than the "breaking point" in the progressive ratio test, because it uses adversity (not workload) to modify behavior. Furthermore, the procedure has the advantage that can be tested over a short period of time (2 weeks), which allows studying behavior at distinct ages or after short-term interventions. In summary, this procedure represents a simple, practical, and short way to study responding for rewards in the presence of adversity, and could be used as an indication of addiction liability.

Disclosures: M. Marinelli: None. **M.R. Bredder:** None. **A. Mutti:** None. **A. Bates:** None. **S.S. Desaivre:** None. **V. Ramachandra:** None. **A.G. Gordon:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.16/YY20

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant: R01AA024526

Title: Glutamatergic modulation recovers multiple behavioral deficits in a model of AUD/PTSD comorbidity

Authors: *C. E. SMILEY, J. T. MCGONIGAL, S. MELTON, T. VALVANO, J. T. GASS
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Abstract: Post-Traumatic Stress Disorder (PTSD) and Alcohol Use Disorder (AUD) are theorized to be disorders of learning and memory that share many overlapping neural circuits. These disorders are highly comorbid with rates as high as 41-79%. PTSD/AUD can induce a variety of behavioral deficits in patients including stress induced alcohol consumption and cognitive inflexibility. This set of studies tested the ability of N-acetylcysteine (NAC), a glutamatergic modulator, to attenuate behavioral deficits in an animal model of PTSD/AUD comorbidity. The first set of experiments examined the ability of NAC to prevent stress-induced increases in alcohol consumption. Rats were first exposed to acute restraint stress paired with an odor cue, and then trained to self-administer ethanol. NAC treatment occurred for five days prior to and five days following the stressor. After acquisition of alcohol self-administration, all rats received extinction training in which lever presses were recorded but did not result in ethanol delivery. Following extinction training, alcohol-seeking behavior was reinstated by exposure to the stress-related odor. It was found that stress exposure significantly increased alcohol intake, and exposure to the stress-related odor induced relapse-like behavior. Importantly, treatment with NAC prevented the stress-induced increase in alcohol consumption and cue-induced reinstatement of alcohol-seeking behavior. The second set of experiments tested the ability of NAC to treat stress-induced cognitive inflexibility; a cognitive deficit commonly associated with PTSD and one of the main barriers to successful treatment in the clinical population. Cognitive inflexibility was measured in an animal model using a set-shifting task. Rats were first trained to lever press for sucrose under a specific rule, and then their ability to switch to a new rule to receive the reward was assessed. As in the first set of experiments, rats were exposed to restraint stress and treated with NAC for five days before and five days following the stressor. Set-shifting training began following the final treatment day. These results indicate that restraint stress was sufficient to induce deficits in cognitive flexibility and NAC treatment rescued this deficit. Further studies will seek to determine the mechanism by which NAC is working to achieve these effects. Together, these results suggest that NAC, a clinically available therapeutic,

is successful in preventing stressed induced alcohol consumption and relapse-like behavior and enhances cognitive flexibility in animal models of PTSD.

Disclosures: C.E. Smiley: None. **J.T. McGonigal:** None. **S. Melton:** None. **T. Valvano:** None. **J.T. Gass:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.17/YY21

Topic: G.08. Drugs of Abuse and Addiction

Support: PHS grant PO1 DA031656
NINDS Grant P50NS091856 (Morris K. Udall Center for Excellence in Parkinson's Disease Research).

Title: An addiction vulnerability trait impacts complex movement control: Evidence from sign-trackers and chemogenetically reversed goal-trackers

Authors: *C. LUSTIG[1], A. J. KUCINSKI[2], M. SARTER[3]
[1]Dept. of Psychology, [2]Psychology, Univ. of Michigan, Ann Arbor, MI; [3]Psychol, Univ. of Michigan Dept. of Psychology, Ann Arbor, MI

Abstract: Cognitive-motivational vulnerability traits are associated with increased risk for substance addiction and relapse. Sign-tracking (ST) behavior in rats is associated with poor attentional control, mediated by an unresponsive basal forebrain cholinergic system, and an increased risk for substance addiction/relapse. Goal trackers (GT), on the other hand, possess superior top-down cognitive control mediated by task-evoked increases in cholinergic neuromodulation. A separate literature links poor attentional control and cholinergic losses to increased fall risk in Parkinson's disease. We first tested whether the relatively inferior attentional control of STs extends to complex movement control and a propensity for falls. ST and GT were tested using a beam traversal apparatus, the Michigan Complex Motor Control Task (MCMCT), which has been used previously to develop a model of Parkinsonian falls. STs were found to fall more often than GTs while traversing a straight rotating rod and, similar to human fallers, when taxed by a secondary task. Furthermore, STs fell more often while traversing a more challenging rotating zig-zag rod. GTs exhibited fewer falls from this rod by avoiding entry to the rotating zig-zag sections when in, or rotating toward, a difficult traversal state. Goal-tracking rats approached risky movement situations using strategies indicative of superior top-down control. Next, non-selective DREADD-mediated inhibition of basal forebrain neuronal activity with CNO (5 mg/kg) was found to increase fall rates in GTs but not STs. Fall rates in GTs expressing a non-DREADD control construct were not affected by CNO. These

results suggest that the differential balance between bottom-up and top-down attention in STs and GTs, mediated by cholinergic mechanisms, extends to complex movement control. Thus, impairments in the cognitive-motor interface are likely to be comorbid with addiction vulnerability. Sign-tracking indexes an endophenotype that may increase the risk for a wide range of neurobehavioral disorders.

Disclosures: C. Lustig: None. **A.J. Kucinski:** None. **M. Sarter:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.18/YY22

Topic: G.08. Drugs of Abuse and Addiction

Title: The emergence of addiction in a computational model of goal-directed foraging

Authors: *E. D. GRIBKOVA[1], R. GILLETTE[1,2]
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Abstract: Addiction mechanisms emerge from reward learning and motivation. They are manifestations of the ancient circuitry of foraging behavior, in which generalist foragers, such as the predatory sea-slug *Pleurobranchaea californica*, establish preferences and aversions to specific prey. We used our agent-based foraging simulator, Cyberslug*****, which is based on the decision circuitry of *Pleurobranchaea*, to develop a simple model that captures the nature and course of the addictive process in terms of the foraging mechanisms from which it emerges. In this model, a single slug forages in a simulated environment with two different types of prey: *Hermissenda*, which are beneficial, and *Flabellina*, which are noxious, as well as one type of drug which provides very high reward when consumed. The prey and drug provide their own odor signatures which the slug can sense, track, and learn. By incorporating processes of homeostatic plasticity, manifested as habituation and sensitization, into the reward circuitry of Cyberslug, we could recreate the major hallmarks of the addictive process, as desensitization to reward received from drug consumption, withdrawal, and post-withdrawal cravings for the drug. It is interesting that, to fully simulate addictive mechanisms, it was necessary to distinguish between “liking” and “wanting” processes, as postulated by Robinson and Berridge's incentive-sensitization theory; in our model these correspond to incentive and total reward response, respectively. In this model of addiction, we have found that during withdrawal, defined as a negative reward state, the addiction process accentuates the effect of hunger, causing the virtual slug to demonstrate less selectivity towards the prey types of different values. During high reward states, nutritional needs are often ignored in favor of drug consumption, causing the virtual slug to demonstrate an increased selectivity, particularly for the drug. Thus, if there is

enough available drug in the environment, it inevitably leads to a high rate of drug consumption and a very low nutritional state, as seen in many physiological processes of addiction.
* Brown JW, Caetano-Anollés D, Catanho M, Gribkova E, Ryckman N, Tian K, Voloshin M, Gillette R. (2018) Implementing Goal-Directed Foraging Decisions of a Simpler Nervous System in Simulation. eNeuro, 5(1), ENEURO. 0400-0417.2018.

Disclosures: E.D. Gribkova: None. **R. Gillette:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.19/YY23

Topic: G.08. Drugs of Abuse and Addiction

Support: EJG was supported by DA035435-01S1
Doreen Shanteau Undergraduate Research Fellowship

Title: The effects of different abstinence periods and environmental protection on sucrose incubation and accumbal receptor expression

Authors: *B. A. HUMBURG, E. J. GARCIA, A. N. BEESLEY, M. E. CAIN
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Abstract: Abstinence period length positively correlates with drug seeking, termed incubation of craving. Environmental enrichment reduces cocaine and sucrose craving when compared to standard and isolated rats (Grimm et al, 2008; Chauvet et al, 2012). However, a full range of abstinence intervals has not been explored in differentially reared rats. Recent work suggests that incubation of craving of high fat food is accompanied by increased intracellular expression of AMPA subunit GluA1 without altering surface expression in the nucleus accumbens (NAc) (Dingess et al, 2017), and metabotropic glutamate receptor 5 (mGlur5) moderates cued sucrose reinstatement (Bobadilla, 2017). Therefore, the current experiments characterize glutamate receptor expression in the NAc following sucrose self-administration and varying abstinence intervals in differentially reared rats. Rats arrived 21 days of age and reared for 30 days in an isolated condition (IC) or an enriched condition (EC). The IC rats were housed singly in hanging metal cages and were not handled during the rearing period. EC rats were housed in a large cage with toys and cohorts, handled every day, and received daily toy changes. At 51 days rats lever press trained with 20% sucrose on an FR1 schedule and self-administered 20% sucrose for 15 days in daily 1-hr sessions. After day 15 of self-administration, rats rested for 1, 7, 21, or 40 days and were tested in a sucrose seeking test. In the test, active lever presses resulted in cues but no sucrose reward. After the seeking test the NAc was removed. The GluA1 subunit and mGlur5 expression was quantified with western blots. Our results indicate that sucrose craving is

dynamic and moderated by environmental housing condition. Sucrose seeking between IC and EC rats are similar after 7 or 40 days of incubation period. However, IC rats show intensified craving after 21 days when compared to EC rats. Preliminary western blot data suggest that membrane-bound NAc GluA1 did not change across groups, but mGlur5 increased in both EC and IC rats after the 40 day incubation period. Thus, our results agree that mGlur5 is implicated in cued sucrose seeking, and we are currently analyzing western blots for differentially reared rats that were tested at abstinence day 7 and 21.

Disclosures: B.A. Humburg: None. **E.J. Garcia:** None. **A.N. Beesley:** None. **M.E. Cain:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.20/YY24

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH P50 AA017072

Title: mTORC1 in the orbitofrontal cortex controls alcohol seeking and habits

Authors: *A. L. BERGER, N. MORISOT, S. LAGUESSE, K. PHAMLUONG, D. RON
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Abstract: The mammalian target of rapamycin in complex 1 (mTORC1) plays an important role in dendritic protein synthesis, synaptic plasticity, learning and memory [1]. We recently reported that excessive alcohol intake and withdrawal activate mTORC1 in the rat orbitofrontal cortex (OFC) [2], a brain region that plays a role in decision making and updating the value of predicted outcomes [3]. The aim of this study was to identify the role of mTORC1 in alcohol drinking behaviors. First, we tested whether inhibiting mTORC1 in the OFC alters alcohol self-administration. We found that intra-OFC administration of the mTORC1 inhibitor, rapamycin, did not alter alcohol intake per se, but attenuated alcohol seeking. Next, we hypothesized that mTORC1 in the OFC is required for either goal-directed or habitual alcohol seeking. To model goal-directed and habit-driven behaviors, respectively, we used an operant paradigm in which rats self-administered alcohol under a random ratio (RR) or a random interval (RI) schedule of reinforcement, and tested whether rapamycin administration or knockdown of raptor, a main component of mTORC1, in the OFC alters goal-directed or habitual responding. We found that intra-OFC infusion of rapamycin, prior the devaluation test did not affect goal-directed alcohol responding in RR-trained rats but restored the sensitivity to devaluation in RI-trained rats suggesting that mTORC1 in the OFC in driving habitual responding for alcohol. Similarly, knockdown of raptor in the OFC restored the sensitivity to alcohol devaluation i.e. maintained

goal-directed responding for alcohol. In contrast, intra-OFC infusion of rapamycin did not alter habitual responding for sucrose. Next, we elucidated the mechanism by which mTORC1 is activated by alcohol. Alcohol withdrawal enhances glutamatergic neurotransmission, and we found that mTORC1 activation during withdrawal was localized to c-Fos positive OFC neurons. We further observed that ex vivo activation of NMDAR stimulates mTORC1 in the OFC. Therefore, we hypothesized that the activation of NMDAR during withdrawal activates mTORC1 in the OFC which in turn drives habitual alcohol seeking. As predicted, we found that inhibition of NMDARs in the OFC attenuates both seeking and habitual responding for alcohol. Together, our data suggest that alcohol withdrawal promotes an NMDAR-dependent activation of mTORC1 in the OFC which in turn contributes to the expression of habitual alcohol responding. References 1. Buffington, Annu Rev Neurosci, 2014. 2. Laguesse, Addict Biol, 2016. 3. Wallis, Annu Rev Neurosci, 2007.

Disclosures: A.L. Berger: None. **N. Morisot:** None. **S. Laguesse:** None. **K. Phamluong:** None. **D. Ron:** None.

Poster

237. Drugs of Abuse and Addiction: Learning and Circuitry

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 237.21/ZZ1

Topic: G.08. Drugs of Abuse and Addiction

Support: DA035443
MH106972

Title: Contribution of direct and indirect medium spiny neurons in the dorsal striatum to action and habit learning

Authors: *M. D. MURPHY, M. MALVAEZ, K. M. WASSUM
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Abstract: Optimal behavior relies on a balance between two distinct strategies; one goal-directed in which the relationship between actions and their consequences is considered, and one habitual, which allows routine tasks to be conducted without forethought of their consequences. The balance between these systems allows maximally adaptive and efficient behavior, but disruption of this balance can lead to symptoms characteristic of many neurodegenerative and psychiatric diseases. The goal-directed and habit strategies are known to rely on the anatomically distinct dorsomedial striatum (DMS) and dorsolateral striatum (DLS), respectively. But very little is known about the subregion-specific contribution of the two major subtype of medium spiny projection neurons, the direct (dMSN) and indirect (iMSN) pathway projections. Using chemogenetics and DRD1a-cre and A2A-cre driver mice we selectively inactivated dMSNs or

iMSNs in either the DLS or DMS during instrumental lever press-->reward training. Behavioral strategy was assessed, manipulation free, with sensory-specific satiety devaluation. The data indicate both cell-type- and subregion-specific function of each striatal output pathway in goal-directed and habit learning, suggesting the direct and indirect pathways differentially contribute to these learning strategies and the transition to habit, and that their contribution depends on striatal subregion.

Disclosures: M.D. Murphy: None. **M. Malvaez:** None. **K.M. Wassum:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.01/ZZ2

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01EY027718

Title: Stimulus competition among more than two stimuli in the barn owl midbrain

Authors: *A. RAJAGOPALAN ECHAMBADI[1], J. H. HUNTLEY[3], S. P. MYSORE[2]
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD; [3]Div. of Gen. Intrnl. Med., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The superior colliculus (called optic tectum or OT in birds) plays a critical role in animals' ability to select the location of the most salient or behaviorally relevant stimulus in the environment. Previous work in the barn owl has indicated that the OT implements an elegant winner-take-all-like selection process that is supported by competitive inhibition originating from a midbrain GABAergic nucleus called the isthmi pars magnocellularis (Imc). This work, however, has focused on selection between only two competing stimuli. Here, we extend this work to selection among more than two stimuli. Using electrophysiological experiments and computational modeling, we test two competing hypotheses for how the Imc-OT circuit resolves competition among multiple stimuli. Results provide evidence in support of one of the hypotheses, and, in doing so, reveal new insights into how inhibitory inputs are pooled in the Imc-OT circuit. This finding yields a deeper understanding of how the OT implements stimulus selection in cluttered scenes (analogous to real-world conditions) and makes testable predictions on the nature of the underlying neuronal computations.
Funding: NIH R01EY027718

Disclosures: A. Rajagopalan Echambadi: A. Employment/Salary (full or part-time):; Johns Hopkins University. **J.H. Huntley:** A. Employment/Salary (full or part-time):; Johns Hopkins University School of Medicine. **S.P. Mysore:** A. Employment/Salary (full or part-time):; Johns

Hopkins 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.; NIH R01EY027718.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.02/ZZ3

Topic: H.01. Animal Cognition and Behavior

Title: Background homogeneity modulates saliency detection and neural activity in the optic tectum of the barn owl (Tyto alba)

Authors: *T. LEV-ARI, Y. ZAHAR, Y. GUTFREUND
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Abstract: Perceiving an object as salient from its surround often requires a preceding process of grouping the object (figure) and background (ground) elements as separate wholes. Homogeneity of background elements is a major cue for grouping, here we studied motion based grouping in barn owls. First, we performed behavioral experiments in owls trained for visual search tasks on a computer screen. Owls were shown displays of multiple circles on the screen with one circle moving oddly to the right while the remaining circles, either moved homogenously (all leftwards, all upwards or all downwards) or moved in mixed directions (each dot moving either leftwards, upwards or downwards). The owls spontaneously scanned the display while a head-mounted camera was used to track their point of gaze. Search time and number of head fixations until the owls fixate on the oddly moving dot were measured. We found that a dot moving relative to a homogenously moving background is perceived by barn owls as more salient compared to a dot moving relative to a non-homogenous background. Like in humans, the homogeneity of the surround was found to be a more powerful cue for saliency than the motion contrast between the target and the surround. In the second part of the research, we recorded multi-unit neural activity from the optic tectum (OT) of barn owls. Recordings were performed in head-fixed owls passively viewing similar displays of moving circles as in the behavioral experiments. We found that in the intermediate/deep layers of the OT (and not in the retinal recipient superficial layers), neural responses to the oddly moving circle were stronger when the background was homogenously moving compare to when the background elements moved in mixed directions. Importantly the neural responses in the OT matched the perceived saliency of the stimulus as measured in the behavioral experiments. The homogeneity or regularity of the surrounding area plays a factor in the modulation of the responses, consistent with motion-based grouping for figure-ground-segregation. Our findings show similar principles of saliency-by-

motion in an avian species as in humans and suggest a locus in the OT where the underlying neural circuitry may exist.

Disclosures: T. Lev-Ari: None. **Y. Zahar:** None. **Y. Gutfreund:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.03/ZZ4

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI JP (17H06063)

Title: Selective response of locus coeruleus neurons to extended live tutor singing in zebra finches during song learning

Authors: *J. KATIC, Y. YAZAKI-SUGIYAMA
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Abstract: Zebra finches learn to sing from vocalizations of conspecific adults, typically their fathers, during development. Juvenile song learning greatly improves through social vocal communication with tutors, while juveniles learn little from listening to recorded tutor songs. This suggests that social interactions modulate juvenile attention, leading to more effective song learning. The nucleus locus coeruleus (LC), in the pons of the brainstem, has been suggested as the control nucleus of attention and arousal level. We examined how social interaction with tutors affects LC neuronal activity of juvenile zebra finches, in order to determine its effect on song learning. We chronically recorded extracellular, single-unit activity from LC neurons of awake, freely behaving juvenile male zebra finches that were isolated from their tutors. LC neurons were tested with playbacks of several song stimuli, including tutor songs and songs of two conspecifics and one heterospecific. The majority of LC neurons responded to song stimulation (16 of 18 recorded LC neurons, from five birds), but none showed biased responses to particular songs. Juveniles were then introduced to a tutor and housed together for several days. Even after three days of tutoring, LC neurons showed no biased auditory responses to tutor song playbacks. However, LC neurons exhibited greater auditory responses to live tutor singing than to tutor song playbacks. Interestingly, LC neurons having high tonic spontaneous spiking activity showed offset responses to live tutor singing by decreasing firing rates, but not to playbacks of tutor, nor to other songs. Period duration of decreased neural firing to the song offset correlates with number of song motifs of tutor singing (it lasted from 0.5-1 sec for three or more song motif repetitions). We observed similarly decreased neuronal activity of LC neurons for several seconds upon tutor introduction into the cage, but not upon introduction of a control adult male bird. Previously we showed that auditory memories of tutor songs are formed in the

zebra finch caudomedial nidopalium (NCM), analogous to the mammalian higher auditory cortex, and that tutor presence modifies auditory responsiveness of NCM neurons (Yanagihara and Yazaki-Sugiyama 2016). Further anatomical analysis identified projections from LC neurons to the NCM. Taken together, we suggest that social interactions with tutors modulate neuronal activity of the LC, which affects auditory responses of the NCM, resulting in memory formation of tutor songs.

Disclosures: J. Katic: None. **Y. Yazaki-Sugiyama:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.04/ZZ5

Topic: H.01. Animal Cognition and Behavior

Title: Neural circuits for top-down visual attention

Authors: *F. HU, Y. DAN
Div. of Neurobiology, Dept. of Mol. and Cell Biol., Univ. of California, Berkeley, Berkeley, CA

Abstract: Top-down visual attention allows us to focus on the relevant stimuli and filter out irrelevant distractors. In mice, long-range corticocortical projections from the cingulate (Cg) region of the frontal cortex to the primary visual cortex (V1) exert powerful top-down modulation of visual processing. In addition to V1, Cg neurons also project to the superior colliculus (SC) and lateral posterior thalamic nucleus (LP). We found that activation of the projection pathways from the Cg to the SC and LP can also improve visual discrimination performance and induce gain increase in V1 cells.

Disclosures: F. Hu: None. **Y. Dan:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.05/ZZ6

Topic: H.01. Animal Cognition and Behavior

Title: Subcortical afferents to the claustrum in the mouse brain

Authors: *Q. WANG, A. CETIN, M. NAEEMI, J. KNOX, H. ZENG, J. A. HARRIS
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Claustrum, a thin sheet-like subcortical structure located between insular cortex and striatum, has widespread reciprocal connections with neocortical areas and has been hypothesized to play crucial roles in consciousness (Crick and Koch, 2005), cortical oscillation amplification (Smythies et al., 2012), salience detection (Remedios et al., 2014) and selective attention allocation (Mathur, 2014). A recent study combining transgenic and optogenetic techniques in mouse has demonstrated that claustrum coordinates cortical slow-wave activity (Shiozaki et.al., 2017). In contrast to extensive studies of its relationship with cortex, subcortical connections with the claustrum remain unclear or controversial, particularly as the claustrum border was recently reassessed with molecular markers (Mathur, 2014). To comprehensively understand subcortical afferents to the claustrum, we systematically analyzed subcortical injections (covering 178 brain structures) made in wild type C57BL/6J and Cre transgenic mice with anterograde viral tracers from the Allen Mouse Brain Connectivity Atlas (http://connectivity.brain-map.org/). We found that the claustrum receives input from most major brain divisions, including olfactory areas (8), hippocampal formation (4), cortical subplate (5), striatum (2), pallidum (4), thalamus (12), hypothalamus (6), midbrain (3), pons (3), and cerebellum (1) with different projection strengths. Projections to the claustrum were strongest from lateral amygdala nucleus, basolateral amygdala nucleus, dorsal piriform nucleus, nucleus of reunion, paraventricular nucleus, anterior olfactory nucleus, mediodorsal nucleus and anteromedial nucleus, moderately from postpiriform transition area, nucleus of the lateral olfactory tract, piriform-amygdalar area, posterior amygdala area, central medial nucleus and parataenial nucleus, and weakest from ventral tegmental nucleus, locus ceruleus and dorsal nucleus raphe. Two thirds of these structures innervate ipsilateral claustrum and one third are bilateral with ipsilateral dominance. We even identified weak innervation from a cerebellar nucleus to the contralateral claustrum. Results of the anterograde tracing data were confirmed with monosynaptic retrograde data in which starter cells were labeled in the claustrum. Our findings clearly show widespread subcortical afferents to the claustrum, with varying connection strengths, suggesting that the claustrum may act as a crucial hub gatekeeping information flow between cortex and subcortical structures.

Disclosures: Q. Wang: None. **A. Cetin:** None. **M. Naeemi:** None. **J. Knox:** None. **H. Zeng:** None. **J.A. Harris:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.06/ZZ7

Topic: H.01. Animal Cognition and Behavior

Title: Inter-areal synchronization in visual cortex during a divided attention task

Authors: *M. L. SCHOLVINCK, J. R. DOWDALL, G. SPYROPOULOS, P. FRIES
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Abstract: When processing a visual stimulus, neuronal ensembles in different brain areas along the visual hierarchy interact with each other. Attention is known to influence these interactions; attending to a visual stimulus increases the coherence between neuronal populations in V1 and V4 representing that stimulus (Bosman et al., Neuron 2011). It is unknown how dividing one's attention over several visual stimuli impacts these interactions. Behavioral evidence in humans suggests that attention switches rhythmically between the stimuli (Landau & Fries, Current Biology 2012), but attention could also be truly divided between the stimuli.
We recorded local field potentials (LFPs) from areas V1 and V4, as well as single and multi-unit activity (MUA) from higher visual areas in the superior temporal sulcus and on the prelunate gyrus, in two monkeys (*Macaca mulatta*) while they were engaged in a divided attention task. Two drifting gratings were presented, both of which had an equal probability of transiently changing their drift orientation slightly, after which the monkey was required to make an eye movement to this particular grating to obtain a fluid reward. LFP was recorded with 252- and 480-contact electrocorticography (ECoG) grids covering the superficial parts of V1 and V4 that correspond to the central 8 degrees of visual angle. The two gratings were placed such that they activated separate neuronal populations in V1, but fell within the same receptive field of a chosen V4 or higher-order area site. Therefore, the coherence between these separate V1 sites and the V4 / higher-order area site could be studied as both stimuli were attended to. To date, only the V1-V4 data have been analysed sufficiently.
When the stimuli were shown separately, many V1 sites were selectively activated by either stimulus, whereas V4 sites were activated by both stimuli. We trained a classifier on the LFP power in V4 during these separate presentations of the gratings, which resulted in 81% and 73% accuracy of determining which grating had been shown. We then applied the classifier to V4 LFP power during presentation of both stimuli simultaneously. This analysis is still ongoing for the second monkey; the data from the first monkey showed that when V4 LFP power resembled that of one stimulus more, coherence between V4 and the V1 sites representing that stimulus was stronger and reaction times to the stimulus shorter, than when V4 LFP power resembled that of the other stimulus more. These analyses enable us to determine whether attention can be truly divided over, or instead switches between, multiple visual stimuli. As such, they provide important insights into the neural implementation of attention.

Disclosures: M.L. Scholvinck: None. **J.R. Dowdall:** None. **G. Spyropoulos:** None. **P. Fries:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.07/ZZ8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Intramural research program

Title: A novel attention-related area in the macaque temporal cortex

Authors: *L. N. KATZ, A. R. BOGADHI, A. BOLLIMUNTA, R. J. KRAUZLIS
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Abstract: The ability to select one stimulus over others is commonly referred to as selective attention. In the nonhuman primate, the midbrain superior colliculus (SC) causally contributes to behavior in selective attention tasks, but how it interacts with cortical attention mechanisms remains unclear. Here, using electrophysiological recordings and pharmacological perturbations, we reveal a novel attention-related area in the primate temporal cortex that is causally linked to SC, as well as to behavior in an attention task.

Two monkeys performed a selective spatial attention task in which patches of motion were presented on either side of a central fixation point. In *"Attend to motion"* blocks, monkeys were rewarded for attending to the motion patches and releasing a joystick in response to a change in motion direction. In *"Ignore motion"* blocks, reward was delivered for ignoring the change in motion direction and instead, responding to a change in fixation point luminance. During performance in the attention task, we recorded from ensembles of neurons in a region previously identified by fMRI in the fundus of the superior temporal sulcus (aFST/IPa) of two macaques before (n = 244) and during (n = 223) SC inactivation.

We report three main findings. First, we found that neurons in the aFST/IPa exhibited substantial attention-related modulation (12.5%) during the attention task, showing significantly higher activity for stimuli in their receptive field during the *"Attend to motion"* condition compared to the *"Ignore"*, indicating that this region reflects behavioral manipulations of attention. Second, the attention-related modulation of aFST/IPa neurons was substantially reduced during SC inactivation (61% reduction), demonstrating a causal link between SC activity and attention-related modulation in aFST/IPa. Third, reversible inactivation in area aFST/IPa itself during task performance produced deficits in the monkeys' ability to detect changes in either one or both of our task stimuli, establishing a causal role for aFST/IPa in the selective attention task.

Together, our results demonstrate a novel attention-related area in the temporal cortex (aFST/IPa). The causal contributions of aFST/IPa to attention task performance - and its dependence on SC activity - indicate that it is a crucial link between the cortical and subcortical networks subserving the process of selective attention.

Disclosures: L.N. Katz: None. **A.R. Bogadhi:** None. **A. Bollimunta:** None. **R.J. Krauzlis:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.08/ZZ9

Topic: H.01. Animal Cognition and Behavior

Support: Funding provided by the Universidad Iberoamericana

Title: Manipulation of the endocannabinoid system and its effect in the performance of a temporal bisection attentional task

Authors: *M. CHAVEZ HERNANDEZ[1], M. H. BUENROSTRO-JAUREGUI[2], M. MENDEZ-DIAZ[4], H. SANCHEZ-CASTILLO[4], O. R. GALICIA-CASTILLO[3]
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Abstract: The attentional system (AttS) is important for the survival and behavioral performance of the species. Cannabinoids have become a research interest in light of possible adverse effects that the use of marijuana can have. These substances bind to CB1 and CB2 receptors of the endocannabinoid system. Studies have reported that the use of cannabinoids can have a negative effect in cognition (including AttS). The CB2 receptor has recently been described in the SNC and there is little known about the effect that agonism/antagonism of this receptor can have on cognition (including AttS). The aim of this exploratory study is observe the effect cannabinoids can have on a temporal bisection attentional task (TBAT) using selective agonists (Anandamide -AEA- and HU308) and antagonists (SR141716A and SR144528) of CB1 and CB2 cannabinoid receptors. Male adult wistar rats were trained in a TBAT using Skinner operant conditioning chambers. The TBAT has 2 phases: training and testing. Training phase: sessions consisted of 60 trials. Trials initiated presenting a tone of either 2s (short -S-) or 8s (long -L-), each of which associated to a specific lever. Correct responses resulted in reinforcer delivery. When 80% accuracy in both levers for three consecutive training sessions was presented, testing phase began. Testing phase: sessions included the previous two S and L sounds, and 5 probe duration values (2.52, 3.17, 4.00, 5.04, and 6.35 s). Reinforces were not delivered after probe trials. This phase registers how many of the 5 probe durations the rat discriminates as a long/short stimulus. After 15 base-line testing phase sessions, rats were injected i.p. with previously reported effective doses of either AEA (CB1 agonist), SR141716A (CB1 antagonist), HU308 (CB2 agonist), or SR144528 (CB2 antagonist). Rats were evaluated in testing phase under influence of these substances for 3 consecutive sessions. Results show that, when comparing to the control

group: AEA significantly increases the number of errors for the S sound and significantly increases the number of omission errors for S and L sounds. SR141716A does not significantly differ in the number of correct responses and omissions to S and L sounds. HU308 significantly increases number of errors for L sound. SR144529 presents significantly more correct responses to the L sound. These results show that CB1 and CB2 receptors agonism significantly decreases the performance of the TBAT. Antagonism of CB1 receptors does not affect the performance, while antagonism of CB2 improves it compared to the control group. This study was conducted in the Universidad Iberoamericana, for which we are thankful for all the support provided.

Disclosures: M. Chavez Hernandez: None. **M.H. Buenrostro-jauregui:** None. **M. Mendez-Diaz:** None. **H. Sanchez-Castillo:** None. **O.R. Galicia-Castillo:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.09/ZZ10

Topic: H.01. Animal Cognition and Behavior

Support: PHS DA031656
PHS P50NS091856

Title: Resource depletion versus increased opportunity costs: A test of competing theories in rats performing a sustained attention task

Authors: *K. B. PHILLIPS[1], L. RYSZTAK[2], M. SARTER[1]
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Abstract: Performance on sustained attention tasks declines over time, in response to distractors, and is generally more vulnerable in patients with impaired brain function. Traditionally, such performance decline has been interpreted as reflecting depletion of attentional or related cognitive resources. However, resource depletion models cannot explain invigorated performance following task switches or increased incentives to perform. An alternate hypothesis for this decline proposes that performers compute cost/benefit calculations for staying on task versus engaging in alternative action, termed opportunity costs (Kurzban et al., 2013). Increases in opportunity costs are subjectively experienced as increasing boredom, loss of motivation to perform, and attentional fatigue. Thus, task performance declines and alternative action becomes increasingly attractive. Here we employed manipulations of task variables to test conflicting predictions derived from these two theoretical perspectives in rats performing a Sustained Attention Task (SAT). The SAT requires the reporting of cues as well as non-cue events via separate levers, yielding four response categories (hits and misses; correct rejections and false alarms). Male and female rats trained to SAT criterion performed three versions of SAT: with

sequences of repeated trial types (during which only cued or non-cued trials occur), with blocks where the intertrial interval (ITI) is shortened, and with blocks where the ITI is lengthened. Importantly, the two competing theoretical perspectives predict opposed outcomes of these task manipulations: trial repetition and long ITIs should not tax attentional resources but they should be neutral to, or elevate, opportunity costs. Conversely, shorter ITIs are thought to tax processing resources but may be neutral with respect to, or even decrease, opportunity costs. The outcomes of these manipulations are being determined in rats with relatively poor versus relatively high cholinergic-attentional capacities (sign versus goal trackers, respectively) to further determine the nature of these animals' opponent cholinergic-attentional traits. Additionally, we are assessing the role of the basal forebrain cholinergic system on resource management versus opportunity cost tolerance by testing these parametric task manipulations in goal-trackers with cholino-selective basal forebrain lesions and thus with permanent impairments in SAT performance. Defining the precise cognitive and neuronal mechanisms mediating attentional decline is crucial for developing rational treatments of the cognitive instabilities that typify a wide range of disorders.

Disclosures: K.B. Phillips: None. **L. Rysztak:** None. **M. Sarter:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.10/ZZ11

Topic: H.01. Animal Cognition and Behavior

Title: Automated training of freely behaving rodents on touchscreen-based visual tasks

Authors: *B. HOLT[1], J. GARMON[2], S. P. MYSORE[1]
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Abstract: Behavioral training of animal models is typically time-consuming and labor intensive. More hands-off or automated methods of behavioral training are preferable for their increased efficiency. However, contemporary automated training systems for rodents often involve expensive components and substantial technical expertise to implement. Moreover, few systems are available to train rodents in an automated fashion on visually based behavioral tasks. We develop an inexpensive and scalable automated system for training rodents on touch-screen based visual behavioral paradigms. In this system, the training schedule is managed by networked Raspberry Pi microcontrollers. Commercially available components together with custom software provide an affordable and flexible solution for presenting visual stimuli, for delivering appropriate reward and punishments, and for rodent monitoring and identification. In addition, this system is potentially compatible with the training being conducted within the familiar environment of the animal's home cage. Modular in design, this system allows for

straightforward potential integration of visual perceptual and cognitive tasks with neural recording and manipulation.

Disclosures: B. Holt: None. **J. Garmon:** None. **S.P. Mysore:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.11/ZZ12

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant: DA R01 027222

Title: Concomitant behavioral and prefrontal cortex neuronal responses following acute and chronic methylphenidate exposure in adolescent and adult rats

Authors: S. S. VENKATARAMAN[1], C. REYES-VAZQUEZ[2], C. M. CLAUSSEN[1], *C. E. HULSEBOSCH[1], N. DAFNY[1]
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Abstract: There is growing concern that the psychostimulant Methylphenidate (MPD) is being abused for cognitive enhancement and recreation by healthy adults and adolescents seeking to improve their work or academic performance. This study concomitantly recorded the behavioral and prefrontal cortex (PFC) neuronal activity in freely behaving animals exposed to acute and chronic MPD doses (0.6, 2.5, and 10.0mg/kg MPD) in order to compare MPD effects on adult and adolescent rats. The PFC was selected because it is one of the primary brain areas affected by MPD and the drug of choice for treating ADHD. Moreover, the PFC is one of the last brain areas to complete development, suggesting that the behavioral and neurophysiological response to MPD may differ in adolescents and adults. In both adult and adolescent animals, it was observed that the same repetitive (chronic) dose of either 0.6, 2.5, or 10.0mg/kg MPD exposure elicited behavioral sensitization in some animals and tolerance in others, and the majority of PFC units recorded in animals expressing behavioral sensitization or tolerance to chronic MPD exposure responded by increasing and decreasing their neuronal firing rate, respectively. Behavioral sensitization and tolerance are experimental biomarkers indicating that the drug has the potential to elicit drug dependence. Overall, adult PFC units were more responsive to acute and chronic MPD exposure than adolescent PFC units. This difference may be related to the ongoing PFC development during the adolescent period. In addition, in both adult and adolescent animals, PFC neurons recorded from animals expressing behavioral tolerance exhibited a significantly ($p<0.05$) greater increase in PFC neuronal firing rate than PFC neurons recorded from animals expressing behavioral tolerance. This and the above observation suggest that it is

essential to record the acute and chronic effect of psychostimulants on brain activity concomitantly with the animals' behavior and to evaluate the neurophysiological responses from behaviorally sensitized animals separately from those recorded from behaviorally tolerant animals.
Acknowledge: This research was supported by a National Institutes of Health (NIH) grant, DA R01 027222

Disclosures: S.S. Venkataraman: None. **C. Reyes-Vazquez:** None. **C.M. Claussen:** None. **C.E. Hulsebosch:** None. **N. Dafny:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.12/ZZ13

Topic: H.01. Animal Cognition and Behavior

Title: Influence of prenatal exposure to valproic acid in rats on the performance of an auditory stimuli detection task

Authors: *D. T. HECTOR, S. MENESES-ORTEGA
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Abstract: Experiments in rodents have indicated that exposure to neurotoxins in pregnant rats has permanent adverse effects on the behavioral and cognitive functions of offspring. Prenatal exposure to VPA induces neural tube defects and impairment in social behaviors similar to that observed in patients diagnosed with autistic spectrum disorder**.** VPA can also induce fetal valproate syndrome, which has been associated with attention deficit hyperactivity disorder (ADHD).
In this study we evaluated the effect of exposure to different doses of VPA (200 mg/kg and 600 mg/kg) to pregnant Wistar rats on embryonic day 12 in order to analyze the effect in the performance of an auditory stimulus detection task in the pups when they reached the postnatal age of 60 days.
Pregnant rats were divided into three groups. Rats from the control group received i.p. saline solution on embryonic day 12 (E12). The second group of pregnant rats received at E12 a dose of 200 mg/kg of VPA, and the third group a dose of 600 mg/kg. Ten male pups from each group were selected and kept in separate boxes until the age of 60 days, which was the moment when the behavioral evaluation began.
The auditory stimuli detection task consisted in the following: rats had to press a lever and keep it pressed until an auditory stimulus appeared (4 kHz, 100 ms, 60dB). Rats had to release the lever when detecting the stimulus. If they did it with a reaction time of less than 1 sec, they obtained water as a reinforcer. Three levels of difficulty of the task were evaluated (fixed interval

1 sec, fixed interval 5 sec, variable interval of 2 to 5 sec).
The results showed that the prenatal exposure to both doses of VPA affected the reaction time ($F_{(2,54)}$= 7.70; 0.01) and produced an increase in the number of errors ($F_{(2,54)}$= 8.10; 0.001) during the execution of the auditory detection task. Regarding the number of correct answers, no effects of the VPA exposure were observed in any of the groups.
The VPA model provides a valuable tool to investigate the effects of prenatal exposure to neurotoxins (VPA) on cognitive processes such as attention.

Disclosures: D.T. Hector: None. **S. Meneses-Ortega:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.13/ZZ14

Topic: H.01. Animal Cognition and Behavior

Support: ERC grant 339244-FUSIMAGINE
ANR-10-LABX-24 LABEX WIFI
ANR-10-IDEX-0001-02
FLAG-ERA JTC FUSIMICE ANR-15-HBPR-0004-01

Title: Functional evidence for a default mode network deactivation in the mice brain using functional ultrasound imaging (fUS)

Authors: *J. FERRIER[1], E. TIRAN[3], T. DEFFIEUX[5], M. TANTER[4], Z. LENKEI[2]
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Abstract: The “Default Mode Network” (DMN) has been highlighted in brain imaging studies as a set of interacting brain areas which are active during wakeful rest and inactivated during task-based stimulation. The DMN is thought to be involved in a number of internal and self-related cognitive processes. Although the existence of an analogous network has been identified in small rodents using resting-state intrinsic functional connectivity (the so-called “DMN-like” network), there is no functional evidence supporting a deactivation of this network during high-demanding cognitive/sensory tasks. Such a demonstration requires a highly-sensitive brain imaging modality that can be applied to awake animals. Here we used functional ultrasound (fUS) imaging in head-restrained awake mice to properly visualize functional connectivity (FC) patterns and to investigate their modulation during whisker stimulation. We identified reproducible and highly symmetric resting-state networks in awake mice. However, sensory stimulation induced an increase in locomotion resulting in a higher signal-to-noise ratio which altered FC outcome. We hence used low-dose medetomidine to induce a mild sedation while

maintaining the animals alert. Under this state, we show that FC is similar to that in awake animals while significantly reducing epochs of activity during stimulation. Importantly, we find a decreased interhemispheric correlation within the restrosplenial cortex, a major hub of the DMN, during whisker stimulation compared to rest. Taken together, these results provide further evidence supporting an evolutionary preserved function of the DMN and could help improve translational relevance of preclinical models of neuropsychiatric diseases.

Disclosures: J. Ferrier: None. **E. Tiran:** None. **T. Deffieux:** None. **M. Tanter:** None. **Z. Lenkei:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.14/ZZ15

Topic: H.01. Animal Cognition and Behavior

Title: Dissociable effects of Noradrenergic and Cholinergic lesions of Anterior Cingulate Cortex on distractibility

Authors: *J. A. MCGAUGHY[1], D. J. HUTCHINS[2], A. J. PIMENTEL[2], C. S. PIMENTEL[2], J. A. SWAINE[2]
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Abstract: Prior data from our lab and others has shown that that the anterior cingulate cortex (ACC) of the rat is critically involved in many aspects of executive function and cognitive control. Previously, we have shown that excitotoxic lesions of the ACC produced deficits in the ability of male rats to filter salient distractors. Additionally, these same subjects were unable to reverse reinforcement contingencies when tested with complex stimuli (Newman and McGaughy 2011). These deficits in filtering were not attributable to impairments in conditional discrimination learning, impairments in reversal learning with uni-dimensional stimuli or a general distractibility to conspicuous, irrelevant stimuli. In the present study, male, Long-Evans rats were used to determine if lesions to the noradrenergic or cholinergic afferents to ACC could recapitulate the effects of excitotoxic lesions in the same area. Lesions were produced by infusion into rostral ACC of dopamine β hydroxylase saporin or 192 IgG-saporin to deplete norepinephrine or acetylcholine, respectively. After two weeks of recovery from surgery, rats were tested in an intradimensional/extradimensional set-shifting task. This test was selected because of it's utility in translational neuroscience and it’s sensitivity to several aspects of executive function including susceptibility to salient distractors, the ability to form an attentional set, the ability to shift an attentional set and reversal learning. Preliminary data show that noradrenergic, but not cholinergic lesions recapitulate some, but not all, of the impairments found after excitotoxic lesion of ACC. Specifically noradrenergic lesioned rats were more

susceptible to salient distractors than sham-lesioned rats. In contrast to the effects of excitotoxic lesions, noradrenergic lesions did not impair the ability to reverse reinforcement contingencies when using complex stimuli containing salient, irrelevant stimulus dimensions. The extent of the lesions to ACC were assessed using markers for norepinephrine transporters and acetylcholinesterase. Together these data support the hypothesis that norepinephrine in the ACC is critically involved in the ability to filter salient distractors. The significance of these findings will be discussed in terms of the relevance of these data to the treatment of several neuropsychiatric disorders including attention deficit hyperactivity disorder, depression and addiction.

Disclosures: J.A. McGaughy: A. Employment/Salary (full or part-time):; University of New Hampshire. **D.J. Hutchins:** None. **A.J. Pimentel:** None. **C.S. Pimentel:** None. **J.A. Swaine:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.15/ZZ16

Topic: H.01. Animal Cognition and Behavior

Title: Claustrum to medial prefrontal cortex glutamatergic projections control attentional shifts

Authors: *S. MUTEL[1,2], O. GSCHWEND[1,3], R. SALAZAR[1], C. HUBER[1,2], R. LEONE[1,2], J.-R. RENFER[1,2], L. FODOULIAN[1,2], I. RODRIGUEZ[2], A. CARLETON[1]
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Abstract: The claustrum, a subcortical structure located between the putamen and the insular cortex, forms extensive reciprocal connections with most cortical areas. Such a widespread pattern of connectivity drove several hypotheses about its function, which encompass saliency detection and attention. However, due to the difficulty to specifically alter CLA activity without affecting surrounding brain areas, we are currently lacking causal evidence to its role. We used a transgenic mouse line expressing a Cre recombinase in glutamatergic CLA neurons to specifically study CLA connectivity and to modulate its activity. Viral tracing showed that while CLA neurons project to the entire neocortex, they preferentially innervate associative areas, such as the medial prefrontal cortex (mPFC). Using channelrhodopsin-assisted circuit mapping, we showed that CLA neurons exert a direct excitatory drive on mPFC pyramidal neurons. Calcium imaging of the CLA during the attentional set-shifting test (ASST), a task that evaluates cognitive flexibility, revealed the recruitment of specific ensembles of CLA neurons. To confirm the critical involvement of CLA neurons in this task, we either chemogenetically inhibited or optogenetically stimulated these neurons. All of these manipulations specifically impaired extra-

dimensional shifts. Given the established role of the mPFC to cognitive flexibility, we further characterized the role of CLA projections into the mPFC. First, we optogenetically stimulated CLA terminals in the mPFC, a modulation which disrupted ASST extra-dimensional shifts performance. Second, we demonstrated a monosynaptic excitatory drive on mPFC pyramidal neurons using channelrhodopsin-assisted circuit mapping. In conclusion, the activity of glutamatergic CLA projections to the mPFC is crucial to the ability to perform extra-dimension attentional shifts.

Disclosures: S. Mutel: None. **O. Gschwend:** None. **R. Salazar:** None. **C. Huber:** None. **R. Leone:** None. **J. Renfer:** None. **L. Fodoulian:** None. **I. Rodriguez:** None. **A. Carleton:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.16/ZZ17

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: Activity of basal forebrain neurons in a classical sustained attention task

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Abstract: The basal forebrain (BF) plays key roles in multiple brain functions, including sleep-wake regulation, attention and learning/memory. The BF consists of cholinergic, GABAergic, and glutamatergic neurons. Stimulation of BF cholinergic neurons enhances cortical processing and visual attention performance including the detection of sensory cues, in which projections from the horizontal diagonal band of Broca (HDB) to the prefrontal cortex are especially important. Less is known about potential involvement of BF GABAergic and glutamatergic neurons in attention.
To test whether neurons of the HDB indeed show activity patterns correlated with attention, we trained mice on the 5-choice serial reaction time task (5-CSRTT), which measures the ability of rodents to sustain spatial attention over a large number of trials. We developed an automated training system, in which mice freely alternated between their home cage and a training cage according to a fixed time schedule. During training, mice had to pay attention to detect light cues

and subsequently report to the illuminated port and nose-poke for water reward. We implemented both self-initiated and non-self-initiated versions of this task. To investigate the firing patterns of HDB neurons during attention; therefore we implanted tetrodes to the mouse HDB. To verify the placement of the implanted tetrodes immediately after the surgery we combined CT and MRI scans.
We found that the automated training greatly improved learning speed. Mice maintained an average accuracy over 80% during recording. A number of neurons in the HDB responded phasically to light cues but decreased their firing rates during nose-poke events when the trial was rewarded. These neurons showed a smaller cue-response in error trials with no response during nose poke. Another population of neurons responded exclusively to reward. Firing rate changes in the 'attention period' preceding cue presentation were less frequent. These data indicate that HDB neurons may have a more distinct role in learning; however, a specific role of cholinergic cells in sustained attention is yet to be tested.

Disclosures: D.G. Balazsfi: None. **E. Birtalan:** None. **B. Király:** None. **I. Horvath:** None. **D. Mathe:** None. **K. Szigeti:** None. **J. Sanders:** None. **B. Hangya:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.17/ZZ18

Topic: H.01. Animal Cognition and Behavior

Support: Alberta Gambling Research Institute
NSERC Discover Grant

Title: Task uncertainty encoded by the anterior cingulate cortex promotes feeder approach between operant trials

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Abstract: In previous studies we have characterized a form of approach behaviour in which rats made volitional orofacial contact with inactive feeders between trials of a self-paced, competitive 2-choice task termed 'Matching Pennies' (Gruber, 2018). This behaviour, termed extraneous feeder sampling (EFS), was never reinforced and therefore imposed opportunity and effort costs, yet persisted despite extensive training. The relative rate of EFS to operant responding increased with changes to the operant chamber, and also increased with devaluation of the reinforcement by pre-feeding. These data suggest that this behaviour is related to uncertainty. We hypothesized that the anterior cingulate cortex (ACC) promotes EFS because the ACC has been proposed to process information about uncertainty and exploration-related variables (Monosov, 2017). To

test this hypothesis, bilateral excitotoxic lesions of the ACC were performed in male Long Evans rats. Control rats received sham lesions. Lesions of the ACC resulted in no significant changes on Matching Pennies task performance compared to a sham group. However, differences emerged once a certain degree of uncertainty was introduced into the task. We first altered a single aspect of the operant chamber: the length of a barrier separating a nose-poke port from the feeders. We allowed rats to perform the task for 100 trials with their customary 13 cm barrier separating the nose-poke from the feeders. We then took the rats out of the chamber and replaced the barrier with a longer one, a shorter one, or one the same length. Rats were then placed back in the chamber and allowed to perform an additional 100 trials. The relative EFS rate increased for either novel barrier length as compared to the familiar one for both the ACC and sham groups. We then tested rats on the same task in a larger chamber in a different room. ACC lesioned rats performed more trials and had a lower relative EFS rate than then the control group rats. These data suggest that rats with ACC lesions were either less distracted by novel features of the unseen chamber/room or less uncertain about task contingencies.

Disclosures: S.H. Randolph: None. **T.C. Carrels:** None. **A.J. Gruber:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.18/ZZ19

Topic: H.01. Animal Cognition and Behavior

Support: Boehringer Ingelheim Pharmaceuticals Contract number:126676
NIH 5R01MH10263803

Title: Optogenetic investigation of the role of hypocretin in impulsivity

Authors: *S. M. TYREE[1], J. R. NICHOLSON[2], M. VON HEIMENDAHL[2], L. DE LECEA[1]
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Abstract: Hypocretin (Hcrt) neurons in the lateral hypothalamus are well-known to play a role in arousal and driving motivated behaviors, more recently, pharmacological studies have also suggested a role for Hcrt in impulsivity. To further investigate this, optogenetic methods have been used to study the role of the Hcrt circuit in behavioral inhibition via recording and manipulating Hcrt neuron activity during the Go/NoGo task. Mice were trained to discriminate between two audio cues and, based on the cue, either exhibit (“Go”) or inhibit (“NoGo”) nose-poking behavior in an operant chamber. Appropriate behaviors were rewarded with a 33% solution of sweetened condensed milk, inappropriate behavioral responses were neither punished nor rewarded. Hcrt-Cre mice received viral injections (recording study: GCamp6F; stimulation

study: ChR2) and fiber-optic implants into the lateral hypothalamus. After recovery, calcium recordings (from Hcrt neurons in GCamp6f-injected mice) were carried out throughout a ten-minute session of Go/NoGo trials to observe naturally occurring Hcrt activity. Additionally, behavior in the Go/NoGo task was observed during 40-minute sessions of Go/NoGo trials where mice received optogenetic stimulation (of Hcrt neurons in ChR2-injected mice) during specific period of Go/NoGo trials. Using these novel methods, we are able to show 1) changes in neural activity of Hcrt neurons over distinct trial periods within the Go/NoGo task (Precue period/Cue period/Reward period/Inter-trial interval); 2) differences in Hcrt activity in NoGo trials where behaviors must be inhibited compared to Go trials where nose-poking is appropriate; and 3) how manipulation of these Hcrt neurons can alter behavioral outcomes of impulsivity scores in the Go/NoGo tasks. These data strongly support a role for Lateral Hypothalamic neurons in behavioral inhibition and may lead to new therapeutic approaches for impulsive disorders.

Disclosures: S.M. Tyree: 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.; Boehringer Ingelheim Pharma GmbH & Co. KG. **J.R. Nicholson:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co.KG. **M. Von Heimendahl:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co.KG. **L. de Lecea:** 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.; Boehringer Ingelheim Pharma GmbH & Co. KG.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.19/ZZ20

Topic: H.01. Animal Cognition and Behavior

Title: The effects of guanfacine on two-choice reaction time task performance in rats

Authors: *Z. V. REDDING[1], K. E. SABOL[2]
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Abstract: *RATIONALE* Norepinephrine (NE) levels are critical to attentional control (Arnsten et al., 2005, J. of Clin Neurosci (67), 7-12). Prior studies in this lab found that the selective NE reuptake inhibitor, atomoxetine (ATX), reduced attentional lapses without affecting sensorimotor processing speed in rats performing the two-choice reaction time task (2CRTT). The present study explores the specific involvement of α-2 noradrenergic receptors using the selective

agonist, guanfacine. This drug is currently used to treat ADHD (Bidwell et al., 2010, Curr Psych Reports (12), 366-373). Reaction time is broken into initiation time (IT) and movement time (MT) to isolate attentional processes. IT is the time from stimulus presentation until rats first react to the stimulus. IT mode represents sensorimotor processing when rats are attentive. IT distribution skew (devmode; mean – mode) is thought to represent lapses in attention (Leth-Steensen et al., 2000, Acta Psychologica (104), 167-190; Sabol et al., 2003, Behav Pharm (7), 489-500). It is hypothesized that guanfacine will reduce attentional lapses (IT devmode) without affecting sensorimotor processing speed (IT mode). *METHODS* Twenty male Sprague-Dawley rats were tested in the 2CRTT. Rats nosepoked in a central aperture for a foreperiod that varies randomly between 0.3 and 6.0 sec. After the foreperiod, a stimulus light came on above an aperture to the left or right of the rat. The rat then removed its nose from the central aperture (IT) and entered the aperture underneath the illuminated light. A water drop was given for correct responses within an adjusting time criterion. Rats began new trials by entering the central aperture. Twice each week, guanfacine was administered thirty minutes before testing. Doses were assigned via the Latin square procedure and included saline, 0.01, 0.1, 0.3, and 1.0 mg/kg. Each rat received each drug dose two times. Data were analyzed with repeated measures ANOVA. *RESULTS* There was no effect of guanfacine on IT mode. Guanfacine reduced IT devmode at 0.1 and 0.3 mg/kg. *DISCUSSION* In our prior experiments, ATX reduced distribution skew (thought to represent attentional lapses) without affecting sensorimotor processing speed in attentive rats. Guanfacine administration revealed the same pattern of results, suggesting that α-2 receptor binding is responsible for the increased attentional control. The effect of guanfacine on distribution skew is consistent with guanfacine's role in the treatment of ADHD, supporting a translational function for this animal model of attentional lapses.

Disclosures: Z.V. Redding: None. **K.E. Sabol:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.20/ZZ21

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH104716

Title: Sexual dimorphism in noradrenergic regulation of attention

Authors: *E. DAUSTER, E. VAZEY
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Abstract: Norepinephrine (NE) signaling within cortical regions including the prefrontal cortex is critical for regulation of executive functions such as attention. This NE largely originates from

the brainstem nucleus: locus coeruleus (LC). In some species, females have been shown to have more LC neurons and more complex dendritic arborization, but functional consequences of this dimorphism are largely unknown. Our previous studies in male subjects suggest that increasing tonic LC activity drives inattentive behavior, therefore the present study investigates this effect in females. Using designer receptors exclusively activated by designer drugs (DREADDs), we specifically and reversibly manipulated activity of LC neurons in female rats. Behavioral responses were tested using an operant two-alternative forced choice (2AFC) paradigm, in which rats discriminate visual stimuli to press the appropriate response lever for a sucrose reward. Female Long Evans rats (n=23) were infused with AAV vectors containing either PRSx8-hM3Dq or PRSx8-mCherry to the LC before training on the 2AFC. An investigator blind to the genotype of the subjects carried out within-subject testing of LC activation using a latin-squared design across doses (0.1-1 mg/kg) of the DREADD activator clozapine-N-oxide. We found that LC upregulation with Gq-DREADDs in female subjects significantly reduces task engagement and accuracy while increasing distractibility and reaction time variability in the 2AFC task compared to vehicle injections and mCherry controls. This response phenotype is similar to that previously observed in males, however the dose-response relationship in females is shifted rightward and attentional measures are less severely disrupted than observed in males, indicating a functional dimorphism in response to LC upregulation between sexes. A major result of this study is an increased understanding of how attentional circuits work in both sexes.

Disclosures: E. Dauster: None. **E. Vazey:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.21/ZZ22

Topic: H.01. Animal Cognition and Behavior

Support: NIMH grant F32-MH106265
NIMH grant K99MH115082-01
NEI grant DP1EY024503
NEI grant R01EY011787
NARSAD award 19944
Burroughs Wellcome Fund, CASI 1015761
HHMI student research fellowship

Title: Distinct cortical ensembles process redundant and deviant sensory stimuli

Authors: *J. P. HAMM[1], Y. SHYMKIV[2], W. YANG[1], S. HAN[2], R. YUSTE[1]
[2]Biol. Sci., [1]Columbia Univ., New York, NY

Abstract: Cortical processing of sensory events is significantly influenced by context. For instance, repetitive or contextually redundant stimuli often elicit attenuated responses in primary visual cortex (V1), while unexpected or “deviant” stimuli elicit augmented responses. This contextual modulation of sensory processing is likely a fundamental function of neural circuits, yet a generalized understanding of how it is computed is still missing. Importantly, context processing is significantly altered in individuals with schizophrenia (SZ; e.g. reduced “mismatch negativity”), potentially relating to core pathophysiology and symptomatology. We measured neuronal activity in cortical volumes in V1 of awake mice using dual color and holographic two-photon calcium imaging to explore how local, intralaminar, and interregional circuits process deviant and redundant events. A visual “oddball” paradigm was employed wherein full-field square-wave stimuli of 2 possible orientations (e.g. 45 vs 135 degrees) were presented with varying regularity (88% redundant orientation; 12% deviant or “oddball” orientation). Responses in this paradigm were compared to a “standard” context wherein stimuli of 8 possible orientations were randomly presented. As we have described (Hamm and Yuste, 2016), robust stimulus-specific adaptation (i.e. reduced responses to redundant) and genuine deviance detection (i.e. enhanced responses to deviants) were observed at the population level, after averaging over all neurons.Interestingly, cluster analysis indicated the presence of 3 distinct groups of neurons: 40% showing a preference for standard contexts (“general adapting”), 40% showing a preference for deviant contexts (“deviance detectors”) and 20% lacking contextual modulation. Only the first two subgroups showed orientation selectivity. These context-specific subgroups of cells were present in layers 2-5 of cortex, although “deviance detectors” were twice as common in layer 2/3. By imaging the activity of axons originating from distal regions, we show that these context-driven preferences are i) absent in bottom-up inputs from dLGN thalamus, and ii) present in top-down projections from PFC (area Cg). Optogenetic suppression of PFC inputs to V1 disinhibited neuronal responses, affecting context processing at a gross level, but left subgroup preferences intact. Our results suggest that sensory cortical ensembles can independently code for contextual information, such as stimulus novelty. This underscores the relevance of ensembles in SZ pathophysiology, given that ensembles are altered in pharmacological and genetic mouse models of SZ (Hamm et al, 2017).

Disclosures: J.P. Hamm: None. **Y. Shymkiv:** None. **W. Yang:** None. **S. Han:** None. **R. Yuste:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.22/ZZ23

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5T32MH01990821

NIH Grant EY014924

Title: Dopaminergic modulation of attention-related neuronal activity in the macaque frontal eye field: Dependence on task difficulty

Authors: *A. L. MUELLER[1], T. MOORE[2]
[1]Stanford Univ., Stanford, CA; [2]Neurobio., Howard Hughes Med. Inst. - Stanford Univ., Stanford, CA

Abstract: Dopamine plays a key role in attention and attention-related disorders. The frontal eye field (FEF) is an area of the prefrontal cortex causally implicated in the control of visual spatial attention. We have previously demonstrated that small dose injections of a dopamine D1 receptor (D1R) antagonist into the FEF modulates visually driven signals in posterior visual cortex in a way that resembles attentional modulation. We now examine how local application of dopamine agonists and antagonists affects attention-related activity within the FEF. We trained two rhesus macaques on an attention task and then recorded from FEF neurons while testing the effects of iontophoretically-applied D1R agonists and antagonists on neuronal activity during behavior. In a single trial of the attention task, the monkey initially maintains fixation while holding down a lever. Next, two targets appear followed by a central cue indicating which target to attend to. After a delay, the targets are briefly blanked (50-300ms). After the blank, both targets reappear, with the cued target in either the same or a different orientation. The monkey reports a detected change in target orientation by releasing the lever and reports 'no change' by keeping the lever pressed. While the animal performed this task, we recorded from FEF neurons and used iontophoresis to locally apply either a D1R agonist (SKF81297) or a D1R antagonist (SCH23390) with currents of either 20nA or 50nA. We examine the visually-driven signals of FEF neurons during the period between cue presentation and target-blanking. We obtain a measure of attentional modulation by contrasting this activity between trials in which the receptive field stimulus is cued (attended) or not cued (unattended). We then examine the effect of dopamine agonists and antagonists on this attention-related activity, as well as on pre-cue activity. Thus far, we find significant, selective changes in attentional modulation during iontophoretic application both of D1R agonists and antagonists. In a further experiment, we vary the contrast of the cued targets: indicating in advance that the trial will be more or less difficult than previous trials. Thus far, we find that attention-related activity in the presence of D1R antagonists varies with task difficulty in individual neurons. Our results show that the attention-related activity of FEF neurons depends on D1Rs, and that and that this dependence can be shaped by task demands. These results demonstrate a role for dopamine, acting through D1Rs, in attentional modulation in the FEF and indicate a relationship between the variability of dopaminergic signals in the prefrontal cortex and behavior.

Disclosures: A.L. Mueller: None. **T. Moore:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.23/ZZ24

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP DGE 1148900
NIH NEI R01EY017699
NIH NIMH R01MH064043
NIH NIMH 1P50MH109429-01A1

Title: Effects of selective visual attention across the dorsal and ventral pulvinar

Authors: *R. LY[1], M. A. PINSK[1,2], S. KASTNER[1,2]
[1]Princeton Neurosci. Inst., [2]Dept. of Psychology, Princeton Univ., Princeton, NJ

Abstract: The pulvinar nucleus of the thalamus plays an important role in vision and attention. Lesions and reversible inactivation of the pulvinar lead to attentional impairments (Petersen et al., 1987, Desimone et al., 1990), and pulvinar neurons increase their firing rate during covert visual attention (Saalmann et al., 2012, Zhou et al., 2016). The pulvinar can be broadly split into dorsal and ventral subdivisions, which have different anatomical connectivity patterns. While the dorsal pulvinar connects with posterior parietal and frontal cortex among others, the ventral pulvinar connects strongly with early visual areas, e.g. V1 and V2. If the dorsal and ventral pulvinar are interconnected, attention signals from frontoparietal cortex could influence visual areas through the pulvinar. Few studies have characterized in detail the effects of attention on dorsal and ventral pulvinar, and no studies have established whether the subdivisions of the pulvinar are anatomically or functionally interconnected.
We recorded from hundreds of single and multi-units in dorsal and ventral pulvinar using linear microelectrode arrays in two macaque monkeys while the animals performed a spatial attention task. We found that neurons in the dorsal pulvinar, but not the ventral pulvinar, displayed elevated delay activity with attention. In addition, neurons in the ventral pulvinar, but not the dorsal pulvinar, showed attentional modulation of firing rate in response to a cued visual stimulus. Trial-wise variability of spike counts and spike-count correlations in the population were unaffected by attention in both subdivisions, which contrasts with commonly observed effects of attention across the cortex. Finally, we computed spike-field coherence and Granger-causality across subdivisions to investigate functional connectivity between pulvinar subdivisions. Altogether, these results provide a comprehensive understanding of the pulvinar and its subdivisions during selective visual attention.

Disclosures: R. Ly: None. **M.A. Pinsk:** None. **S. Kastner:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.24/ZZ25

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant RO1 EY017699
NIH Grant RO1 MH64043
NIH 21560-685 Silvio O. Conte Center

Title: Using deep learning to characterize cognitive population activity in the pulvinar

Authors: *F. ZHU[1], R. LY[3], S. KASTNER[3,4], C. PANDARINATH[2,5]
[1]Neurosci. Grad. Program, [2]Dept. of Neurosurg., Emory Univ., Atlanta, GA; [3]Princeton Neurosci. Inst., [4]Dept. of Psychology, Princeton Univ., Princeton, NJ; [5]Coulter Dept. of Biomed. Engin., Emory Univ. / Georgia Tech., Atlanta, GA

Abstract: Mounting evidence suggests that computation in many brain areas is performed through network-level phenomena, specifically, low-dimensional processes that underlie the activity of populations of neurons. Such processes have been shown to explain the often-puzzling responses of individual neurons, and to precisely relate neural activity to behavior on single trials. However, few studies have characterized such processes in the domain of cognition. Here we focus on the pulvinar, a higher-order nucleus of the thalamus, that has been shown to be engaged during visual selective attention. To characterize its activity, we used a recently developed deep learning method, Latent Factor Analysis via Dynamical Systems (LFADS), which attempts to uncover low-D structure underlying neural population activity on individual trials. We obtained spiking data from 348 multi-units in the pulvinar of a macaque monkey performing a selective visual attention task. Our first goal was to test whether low-D structure underlies population activity in the pulvinar, and our second goal was to characterize attentional effects on the firing activity of pulvinar neurons on single trials. If low-D structure does exist, then a given neuron's activity should be well-described by the activity of other recorded neurons in the population. We tested this idea using a generalized linear model, and found that the spiking activity (binned at 20 ms) of a given multi-unit could be predicted from the activity of other simultaneously recorded multi-units with much greater accuracy than chance ($p>0.0001$ for 92% of the recorded multi-units). We next tested whether LFADS could be used to uncover attentional effects from population activity. LFADS uses an artificial neural network to model observed population activity and to infer de-noised single-trial firing rates from neural spiking data. We found that LFADS inferred neural firing rates with 10-15 Hz oscillatory activity on single trials, which was not easily observed from the raw spiking activity of the neurons. In previous work, 8-15 Hz rhythmic spiking activity, typically phase-locked to oscillations in the

simultaneously recorded LFP, has been observed to correlate with changes in attentional state on a trial-averaged level. Future analysis will focus on relating these de-noised firing rates to behavioral outcomes (e.g., response time during visual attention tasks) on single trials.

Disclosures: F. Zhu: None. **R. Ly:** None. **S. Kastner:** None. **C. Pandarinath:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.25/ZZ26

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP DGE 1148900
NIH NEI R01EY017699
NIH NEI R21EY023565
NIH R01MH064043
NIH 21560685 Silvio O. Conte Center
PNI Innovation Award

Title: Distinguishing subdivisions of the pulvinar using functional response properties

Authors: *S. KASTNER, R. LY, M. A. PINSK
Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: The pulvinar nucleus of the thalamus plays an important role in vision and attention. Several parcellations of the pulvinar have been suggested (Stepniewska, 2004), based on cytoarchitecture, myeloarchitecture, neurochemistry, and receptive field (RF) maps. Except for the RF maps, these methods cannot be used to localize the pulvinar and its subdivisions in living animals; MRI atlases based on these methods need to be consulted. We can identify broad dorsal and ventral subdivisions of the pulvinar using T2-weighted MR images. However, because the pulvinar is deep and electrode tips are difficult to visualize, slight errors in depth measurements can lead to incorrect localization of the electrode. We present a method to distinguish dorsal and ventral pulvinar using neuronal and local field potential (LFP) responses to several tasks, and then we characterize differences in baseline activity, population coding, and attentional modulation across subdivisions.
We recorded from hundreds of sites across the pulvinar using linear arrays in two macaque monkeys. We consistently identified a set of sites with a strongly negative evoked LFP response to a 100 ms full-field white stimulus. These sites also have LFP response fields that correspond to RF maps reported from single-unit recordings in the ventral pulvinar. Therefore, we classify these sites as the ventral pulvinar. Sites in the ~1.5 mm above these sites often exhibit strong pre-saccadic modulation of firing rates as well as sustained suppression during attentive fixation,

consistent with a previous finding (Bender and Youakim, 2001). We classify these sites as the dorsal pulvinar.
We found differences in the latency of peri-saccadic activity, evoked LFP response shape, and baseline LFP power between dorsal and ventral pulvinar. In addition, selective visual attention acts differently on neurons in the two subdivisions. Neurons in dorsal pulvinar show elevated delay activity with attention, and neurons in ventral pulvinar show attentional modulation of firing rate in response to a cued visual stimulus. Altogether, these results can help guide neurophysiologists to target the pulvinar and its subdivisions and also improve our understanding of pulvinar function in vision, visuomotor behavior, and visual attention.

Disclosures: S. Kastner: None. **R. Ly:** None. **M.A. Pinsk:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.26/AAA1

Topic: H.01. Animal Cognition and Behavior

Support: NIMH 1P50MH109429-01A1 Silvio O. Conte Center
NIMH R01MH064043
NEI R01EY017699
NIH NEI R21EY023565
PNI Innovation Award

Title: Neural basis of attentional biasing guided by spatial association memories

Authors: *M. K. ERADATH[1], M. A. PINSK[1], S. KASTNER[1,2]
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Abstract: Attention and memory are two core cognitive processes in primates, resulting from computations across large-scale neural networks. The functional interactions between these two cognitive domains are evident in our everyday life. However, at the neural level, attention and memory have been mainly studied in isolation. In the present project, we explored the functional interactions between these two cognitive domains using simultaneous multisite electrophysiology from macaque monkeys. We used a spatial attention task in which monkeys detected a contrast change by directing covert attention to a spatial location based on either a local spatial cue indicating the possible location of the target after a variable delay period (exogenous cue trials) or based on the color of the central fixation spot, which indicated one of four potential spatial target locations (endogenous cue trials). We performed simultaneous recordings from area V4 of the ventral visual stream, lateral intra parietal (LIP) cortex of the dorsal attention network, entorhinal cortex (EC) of the medial temporal lobe association memory

system and dorso-lateral pulvinar, an area hypothesized to play an important role in regulating communication between cortical nodes during spatial attention. Previous studies have shown the emergence of behavioral rhythms (measured by hit rate) in similar tasks involving exogenous cue conditions, suggesting a rhythmic environmental sampling process. Here, monkeys showed similar behavioral oscillatory patterns during spatial attention, both in exogenous and endogenous cue conditions, indicating that a local stimulus-driven phase resetting is not required for setting up the attentional rhythms, rather it may be initiated by an attentional shift. Preliminary results of the neural data suggest differential roles of LIP and EC in processing exogenous and endogenous cue conditions. The role of pulvinar in regulating information flow from the ventral visual stream node V4 to EC and LIP appears to depend on the attentional demands associated specifically with to exogenous and endogenous cue conditions. Our work furthers an understanding of the functional interactions between attention and memory networks in the primate brain.

Disclosures: M.K. Eradath: None. **M.A. Pinsk:** None. **S. Kastner:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.27/AAA2

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG050518

Title: Effects of intranasal orexin A on attentional performance

Authors: *J. A. BURK, J. FELDMANN, E. MANESS, S. BLUMENTHAL
Psychological Sci., Col. of William and Mary, Williamsburg, VA

Abstract: Orexins are a class of neuropeptides that are associated with homeostatic functions, such as food intake, sexual behavior, and the sleep/wake cycle. Orexins also play a pivotal role in cognitive processes such as attention and memory. Orexinergic neurons project onto basal forebrain corticopetal cholinergic neurons, a neurotransmitter system that is necessary for normal attentional processing. Previous work in our lab showed that intracranial orexin A administration can attenuate attentional deficits following loss of basal forebrain corticopetal cholinergic neurons. In the present experiment, we tested the effects of intranasal administration of orexin A in FBNF1 hybrid rats (N = 12) on a visual attention task. This task required rats to discriminate between trials when a visual light was illuminated from trials when the light was not illuminated. Intranasal orexin A (100 nM) decreased accuracy in the visual sustained attention task, specifically on trials when the light was not illuminated. This task performance decline may be due to abnormally high stimulation of orexinergic receptors, which, in turn, led to over-excitation

of basal forebrain cholinergic neurons. This conclusion is consistent with the effects of other manipulations that abnormally elevate cortical acetylcholine.

Disclosures: J.A. Burk: None. **J. Feldmann:** None. **E. Maness:** None. **S. Blumenthal:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.28/AAA3

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG050518

Title: The effects of manipulating orexinergic neurotransmission on attentional performance in an NMDA receptor hypofunction model of schizophrenia

Authors: *E. B.-L. MANESS[1], S. A. BLUMENTHAL[2], J. R. FADEL[3], J. A. BURK[2]
[1]Applied Sci., [2]Psychological Sci., Col. of William and Mary, Williamsburg, VA; [3]Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Schizophrenia (SZ) is a psychiatric condition wherein those afflicted typically demonstrate a combination of positive symptoms, such as hallucinations and delusions, as well as negative symptoms, including alterations of processing that disrupt sociality, mood, and cognition. Aberrant attentional processing is thought to underlie several of the deficits in SZ. The NMDA receptor hypofunction model of SZ asserts that widespread failure of cortical inhibition - resulting from reduced NMDA receptor input to GABA interneurons - incites both the excessive subcortical excitation and hypofrontality that induce the positive and negative syndromes, respectively. Because the severity of negative and cognitive deficits more accurately predicts functional outcomes than does the prevalence of positive symptoms, pharmacotherapies which enhance attention, learning, and memory function for individuals with SZ are currently being explored. Orexin-A (OxA), a neuropeptide involved in wakefulness, appetitive drive, and incentive- and fear-linked behaviors, has also demonstrated cognitive-enhancing qualities in both neurotypical and pathological states. In the present experiments, we assessed the effects of OxA administration and orexin receptor blockade on attentional performance following administration of the NMDA receptor antagonist, dizocilpine (MK-801). Intranasal OxA administration decreased attentional accuracy following acute NMDA receptor blockade. Ongoing work is testing the effects of the dual orexin receptor antagonist filorexant (MK-6096) on attention following NMDA receptor blockade. The present results suggest that manipulations of orexinergic neurotransmission can alter attentional performance following NMDA receptor blockade in rats.

Disclosures: E.B. Maness: None. **S.A. Blumenthal:** None. **J.R. Fadel:** None. **J.A. Burk:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.29/AAA4

Topic: H.01. Animal Cognition and Behavior

Support: AG050518

Title: Effects of medial prefrontal cortical orexin-2 receptor blockade on attention

Authors: *S. A. BLUMENTHAL, A. TAPP, E. MANESS, J. BURK
Psychological Sci., Col. of William and Mary, Williamsburg, VA

Abstract: Orexin neurons project to a number of brain regions that are implicated in attentional performance, including to the medial prefrontal cortex (mPFC), a brain region that is critical for attention.In particular the right mPFC specifically has been found to be crucial for attention. Orexin receptor blockade in the basal forebrain impairs attentional performance, whereas orexin A administration can be beneficial under some conditions. However, the role of mPFC orexin receptors in attention has not been well-characterized. Based on the results from experiments assessing the effects of orexinergic manipulations in the basal forebrain, orexin receptor blockade was hypothesized to impair attentional performance, particularly in the right hemisphere. Two orexin receptor subtypes exist, orexin 1 and orexin 2 (Ox1R and Ox2R, respectively). While the role of Ox1Rs in attention has been examined through in several studies, the contribution of Ox2Rs has not been assessed in such detail. The present experiment examined the effects on attentional performance of Ox2R blockage, via an Ox2R antagonist, (TCS-OX2-29), in the left and or right mPFC separately. Rats were trained in a two-lever sustained attention task that required discrimination between visual signal and no signal trials. Rats had guide cannula implanted into either the left or right mPFC and, after recovery and re-establishing baseline performance, TCS-OX2-29 was intracranially administered (0nM, 1nM, 10nM, 20nM). Consistent with our hypothesis, higher TCS-OX2-29 doses disrupted attentional performance. However, attention was enhanced at the lowest TCS-OX2-29 dose. We speculate that mild antagonism of Ox2Rs may increase receptor sensitivity for subsequent orexin transmission, leading to improvements in attention.

Disclosures: S.A. Blumenthal: None. **A. Tapp:** None. **E. Maness:** None. **J. Burk:** None.

Poster

238. Mechanisms of Attention

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 238.30/AAA5

Topic: H.01. Animal Cognition and Behavior

Support: NIH grants EY007023
NIH grants NS090473
NSERC postdoctoral grant

Title: Active control of arousal by a locus coeruleus GABAergic circuit

Authors: *V. BRETON-PROVENCHER[1], M. SUR[2]
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Abstract: Arousal and novelty responses linked to locus coeruleus noradrenergic (LC-NA) activity affect cognitive performance. However, the mechanisms that control modes of LC-NA activity remain unknown. Here, we reveal a local population of GABAergic neurons (LC-GABA) capable of modulating LC-NA activity and arousal. Monosynaptic retrograde virus tracing shows that inputs to LC-GABA and LC-NA neurons arise from similar regions, though a few regions provide differential inputs to one subtype over the other. Extracellular targeted recordings to LC-NA and LC-GABA populations demonstrate two modes of LC-GABA responses whereby spiking is either correlated or broadly anti-correlated with LC-NA responses, reflecting anatomically similar and functionally coincident inputs, or differential and non-coincident inputs, to LC-NA and LC-GABA neurons. Optogenetic modulation of the two populations shows that coincident inputs control the gain of phasic LC-NA mediated novelty responses, while non-coincident inputs, such as from the prefrontal cortex to LC, alter overall levels of LC-NA responses without affecting response gain. These findings demonstrate distinct modes by which an inhibitory LC circuit regulates the gain and tone of arousal in the brain.

Disclosures: V. Breton-Provencher: None. **M. Sur:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.01/AAA6

Topic: H.01. Animal Cognition and Behavior

Support: 5T32EY007143-23

Title: A circuit dissection of reward timing in primary visual cortex

Authors: *K. J. MONK, S. ALLARD, M. G. HUSSAIN SHULER
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Abstract: Primary sensory cortex has historically been studied as a low-level feature detector, but has recently been implicated in many functions typically attributed to higher-level cognition. For instance, after an animal learns that a light predicts water at a fixed delay, neurons in primary visual cortex (V1) produce "reward timing" activity (i.e., neural activity that represents the time between the light and the water). Experimental manipulations localized to this area implicate V1 as both a site of learning as well as a site of producing this interval activity (as opposed to reporting this timing information from some other region *via* feedback/feedforward input). However, the mechanisms by which V1 circuitry produces reward timing is unknown. A formal model proposes how this timing information can be produced within V1 using a simple connection rule resulting in a broad distribution of inhibitory feedback across a population of excitatory cells. In previous studies, it has been shown that the activity of different interneuron subtypes (e.g., those expressing parvalbumin (PV), somatostatin (SOM), and vasointestinal polypeptide (VIP)) play unique roles in modulating ongoing excitatory cell activity during stimulus representation within V1. Yet, it is not clear what role/s, if any, these populations play in the representation of time. The model described above has formal predictions regarding the role of inhibitory elements which we test with mice exclusively expressing channelrhodopsin in different interneuron populations. Consistent with these predictions, we find that PV+ and SOM+ interneurons have a stereotyped activity pattern during the delay interval. Furthermore, we find that optogenetic activation of PV+, but not SOM+ nor VIP+, interneurons shortens the network representation of time. To assess the behavioral significance of PV+ interneuron activation within V1, we train mice on a novel action timing task. By combining computational modeling, *in vivo* electrophysiology, and optogenetic manipulations we dissect the circuit mechanism by which V1 produces a representation of time.

Disclosures: K.J. Monk: None. **S. Allard:** None. **M.G. Hussain Shuler:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.02/AAA7

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant F31 NS106737
NIH Grant T32 NS007421
NIH Grant R01 NS100849

Title: D1 and D2 striatal neurons contribute to time-based decision-making

Authors: *B. J. DECORTE, Y. KIM, N. NARAYANAN
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Abstract: Time-based decision-making is critical for daily functioning and is heavily impaired in neurodegenerative diseases that affect the striatum (e.g., Parkinson's disease, Huntington's disease, etc.). We conducted two studies to explore the striatum's role in this deficit. Dopamine tunes striatal output by modulating distinct pools of medium spiny neurons (MSNs) that express either D1- or D2-type dopamine receptors. Therefore, we first investigated how striatal dopamine mediates time-based decision-making via D1 and D2 receptors. Specifically, we trained rodents on an operant task in which they were presented with a houselight and had to start responding just before and stop responding just 6 seconds elapsed. During testing, we infused either a D1 antagonist (SCH-23390) or a D2 antagonist (Sulpiride) into the striatum. Blocking striatal D2 receptors delayed the decision to both start and stop responding, whereas D1 blockade selectively delayed the decision to stop responding. These results suggested that D1- and D2-MSNs play dissociable roles in guiding decisions based on time. To explore this, we used electrophysiology and optogenetics to assess how D1 and D2 MSNs fired around the decision to start and stop responding. Specifically, we recorded from striatal neurons while D1 and D2-cre mice, expressing cre-inducible channelrhodopsin, performed the task. We identified D1 and D2-MSNs in our population by evaluating which neurons responded to laser stimulation. A subset of striatal neurons showed transient activation or suppression selectively around the decision to start or stop responding. Furthermore, population activity began to predict when a decision would be executed several seconds prior to the moment at which the decision actually occurred. Finally, D1-MSNs were more likely to encode the decision to stop responding, whereas D2-MSNs typically encoded start and/or stop decisions. However, no differences in time-coding between the two subtypes were apparent. Collectively, these results suggest that the striatum both mediates both time-keeping and decision-making, with D1 and D2-MSNs playing differential roles in the latter process. These results give important insight into the cognitive deficits caused by striatal dysfunction; a common symptom of neurodegenerative disease.

Disclosures: B.J. Decorte: None. **Y. Kim:** None. **N. Narayanan:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.03/AAA8

Topic: H.01. Animal Cognition and Behavior

Support: MH065561
MH073057

Title: Dissociation between monoaminergic medications within the prelimbic cortex during timing behavior

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Abstract: Dopaminergic and noradrenergic agonists are used to improve cognitive functioning, performance, and working memory, particularly for the treatment of patients with attentional disorders. Among the processes impaired by distracters, and whose dysregulation is documented in affective disorders, is the ability to time in the seconds-to-minutes range, i.e., interval timing. Previously we have shown that the presentation of emotional distracters during a peak-interval timing task results in delayed timing behavior (Matthews et al. 2012, Front Integr Neurosci 6: 111). Delays in timing behavior may suggest that attentional and working memory resources are diverted away from the primary timing task and used to process a distracting stimulus, as proposed by the Relative Time Sharing (RTS) model (Buhusi & Meck 2009, Phil Trans R Soc B 364: 1875-1885). According to the RTS model, a pool of attentional resources is allocated to all mental tasks a subject is currently performing. If a distracter is presented, timing precision is delayed. Here we aimed to investigate the role of specific neurotransmitters within the prelimbic cortex (PrL), which had been previously identified as a structure that was involved in interval timing behavior as well as the relative sharing of attentional resources that are reallocated following emotional distracter presentations (Matthews et al. 2012). Because in Matthews et al. 2012 the drug used was a dopamine and norepinephrine reuptake inhibitor, we intended to further distinguish between the attentional effects of dopamine and norepinephrine reuptake. Our experimental setup allowed us to discriminate if either drug shifted attentional resources back to the primary timing task or if either drug differentially worked with emotional distracters. We hypothesized that either vanoxerine or atomoxetine would decrease time delay following the presentation of emotional distracters. We further hypothesized there would be a differential effect between the two medications. Our results indicated a discriminable effect between vanoxerine and atomoxetine within the prelimbic cortex. While it does not appear that vanoxerine significantly altered working memory, atomoxetine significantly decreased the time delay following the presentation of novel and emotional pre-exposed distracters, $F(2,32)=3.30$, $p<0.05$. Results are discussed in relation to the brain circuits involved in dopamine and norepinephrine, as well as the pharmacological management of affective disorders.

Disclosures: A.R. Matthews: None. **M. Buhusi:** None. **C.V. Buhusi:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.04/AAA9

Topic: H.01. Animal Cognition and Behavior

Support: CREST (no. JPMJCR13W1)
KAKENHI (no. 17H06036)

Title: Embedding-based decoding model for spike activity data

Authors: *K. WATANABE, T. FUKAI
Riken Ctr. For Brain Sci., Wako, Japan

Abstract: Accumulating evidence suggests that information processing in the brain relies on the sequential activation of a neurons ensemble or cell assembly. However, the ability of the existing techniques (e.g., template matching, PCA and ICA) to detect cell assemblies is still severely limited. Here, we propose a novel method to extract repeated spatiotemporal activity patterns of a neuronal population. Our method uses an embedding technique, in which population activity data into a high-dimensional vector representation. This enables us to extract the repeated activation of cell assemblies and discuss their relationships to behavior. We tested the capability of our method using artificial data. Then, we apply the method to population neural data recorded simultaneously from the amygdala and hippocampus of behaving rats (https://crcns.org/data-sets/hc/hc-14). The data was previously recorded to show coincident firing of hippocampal and amygdala neurons during the consolidation of fear memory (Girardeau, Inema & Buzsáki, Nat Neurosci, 2017). Our method further reveals the presence of spike sequences of amygdala neurons and their relationships to animal's behavior and hippocampal activity. We thank Joshua Johansen for directing our attention to this interesting problem and Gabrielle Girardeau and György Buzsáki for making their data available online. This work was partly supported by the Brain/MINDS project and the RIKEN Junior Research Associate Program.

Disclosures: K. Watanabe: None. **T. Fukai:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.05/AAA10

Topic: H.01. Animal Cognition and Behavior

Support: CONACYT Grant 236836
CONACYT Grant 196
PAPIIT Grant IN202317

Title: Neuronal activity cascades in the premotor cortex of Rhesus monkeys underlie periodic state trajectories during rhythmic tapping

Authors: *J. A. GAMEZ, G. MENDOZA, L. PRADO, A. BETANCOURT, H. MERCHANT
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Abstract: Rhythmic timing is a fundamental element of human musical cognition. Recently, we showed that Rhesus monkeys are able to generate predictive isochronous rhythmic taps as observed in humans. However, the neuronal population code behind the generation of rhythmic tapping is practically unknown. Hence, we recorded the multiple single unit extracellular activity in the medial premotor cortex (MPC) of two monkeys performing an isochronous tapping task (ST) in synchrony with a visual metronome. We found that neural MPC populations showed a progressive pattern of activation, generating neuronal cascades that are repeated cyclically for each produced interval and that show two key properties: the number of neurons involved in each evolving activation patterns, as well as the duration of neural activation periods increased as a function of the target interval. In addition, we found that MPC neurons show a strong periodic pattern that becomes evident when its activity is projected into a lower dimensional state space. Interestingly, different tempos are encoded by circular trajectories of different radii, whose variability follows the scalar property. The neural state trajectories can predict the duration of the produced intervals in ST on a trial by trial basis. These oscillatory dynamics are not explained by the repetitive motor actions performed by the monkey. Finally, simulations of neural cascades revealed a tight relation between the number of neurons and the duration of their activation periods in the evolving pattern, the properties of the neural state trajectories, and the rhythmic tapping behavior of monkeys. Thus, our results support the notion that rhythmic behaviors are encoded by the dynamic state of MPC neural populations.

Disclosures: J.A. Gamez: None. **G. Mendoza:** None. **L. Prado:** None. **A. Betancourt:** None. **H. Merchant:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.06/AAA11

Topic: H.01. Animal Cognition and Behavior

Support: NIH R15DA039405

Title: Temporal dynamics of anticipatory negative contrast

Authors: D. J. MCGOVERN[1], *M. S. MATELL[2]
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Abstract: Anticipatory negative contrast is a phenomenon in which the experienced value of a good is diminished because a higher valued good is anticipated in the future, and is seen in rodents anticipating concentrated sucrose solutions (Flaherty 1996) as well as drugs of abuse (Grigson, 2008). Specifically, voluntary consumption of a low-concentration sucrose solution (8%), as well as the length of lick clusters, a proxy for 'liking' (Dwyer 2012), are decreased when rats anticipate access to a better reward (32% sucrose solution). In the present work, we asked whether this diminishment in value reflects the expected interval until the higher quality reward is available.In this procedure Sprague-Dawley rats (n=20) were given access to the low concentration sucrose solution for 3 minutes, and consumption and licking microstructure were recorded. Half the rats continued receiving the low concentration solution for another 3 minutes (the low-low group), whereas the other half of rats were instead given 3 minutes of access to the high concentration solution (the low-high group). In both groups, onset of a tone cue indicated availability of the solutions, and a houselight was presented during the second 3 minute period, to minimize "checking behavior" for the concentration change in the rats in the low-high group. The total number of licks made, as well as the number and length of lick clusters, and the interval between clusters were analyzed, focusing on the changes in these statistics as a function of time until the high concentration solution became available. Our results demonstrate that lick number (i.e., consumption), and lick cluster length ('liking'), decline more rapidly during the first 3-minute interval in the low-high group than the low-low group (Time x group interaction $p<0.001$ and $p<0.05$, respectively). These results indicate that temporal expectations are an important factor in hedonic evaluation, and suggest that neural investigations into reward processing and associated dysfunction (i.e., addiction - Berridge, 2009) will profit from considering these temporal dynamics.

Disclosures: D.J. McGovern: None. **M.S. Matell:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.07/AAA12

Topic: H.01. Animal Cognition and Behavior

Support: Human Frontier Science Program http://www.hfsp.org; project RGP0015/2013
European Research Council advanced grant CONCEPT (http://erc.europa.eu; project 294498).

Title: Direct modulation of the perceived passage of time through optogenetic activation of somatosensory cortex

Authors: *A. FASSIHI[1,2], S. REINARTZ[2], F. PULECCHI[2], A. TOSO[2], M. GIGANTE[2], M. E. DIAMOND[2]
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Abstract: In humans and in rats, duration of a vibration influences its perceived intensity: longer duration feels stronger, shorter feels weaker. In this study, we first show that when rats judge vibration duration, vibration amplitude influences its perceived duration. Second, we ask by targeted optogenetic manipulation whether the amplitude-dependent bias in the perceived passage of time originates within barrel cortex. Vibrations were normally distributed velocity noise, each stimulus defined by mean speed (sp) and duration (T). One group of rats learned to compare the mean speeds of vibration pairs (sp1 versus sp2), while another group learned to compare the durations of vibration pairs (T1 versus T2). Psychometric curves, where choice was plotted as a function of the difference between the paired stimuli, verify that rats "duration rats" judged T1 versus T2 (while showing a bias based on sp1 versus sp2) whereas "intensity rats" judged sp1 versus sp2 (while showing a bias based on T1 versus T2). We injected AAV5-CaMKIIa-hChR2(H134R)-EYFP in barrel cortex of the "duration rats". After 4-6 weeks, an optical fiber accompanied by an array of moveable tungsten electrodes was inserted at the centers of injection sites (barrel cortex, D3-D4) to simultaneously record neuronal activity and deliver illumination. In 2/3 of duration comparison trials, the speeds of the two vibrations were equal while either Stimulus1 or Stimulus2 was paired with light stimulation. In the remaining trials, stimulus speed, as well as duration, were manipulated as a control to ensure that the animal did not alter strategy due to the optical stimulation. Tactile stimuli paired with optogenetic activation in barrel cortex were perceived as greater in duration in all rats tested (n = 4). To disentangle this effect from possible visual cues or distraction, we introduced control sessions where a light source, similar in strength and wavelength, was placed externally. The rats showed no bias related to external light during tactile stimulus presentation, confirming that the behavioral effect of barrel cortex stimulation was likely due to a light-evoked increase in spiking.

Stimulation of barrel cortex opposite to the barrel field excited by the vibration also increased the perceived stimulus duration. These findings suggest that the vibration amplitude-dependent shift in the perceived passage of time originates in a signal processed within barrel cortex. Time perception appears to involve the accumulation of activity from sensory cortex, and the "accumulator" integrates input bilaterally.

Disclosures: A. Fassihi: None. **S. Reinartz:** None. **F. Pulecchi:** None. **A. Toso:** None. **M. Gigante:** None. **M.E. Diamond:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.08/AAA13

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI (21300125, 25280051, 26119519,16H01510)

Title: The peak pattern in the peak interval procedure shifts rightward by the administration of NMDA antagonist in rats

Authors: *S. SAKATA[1], M. HATTORI[2]
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Abstract: Timing and time perception are fundamental to survival and goal approaching in all animals. It is known that animals have some special timing ability of intervals. However, neural mechanisms of time perception are still unknown. The purpose of this study is to investigate the effects of NMDA antagonist on timing behavior. Firstly, using six male rats of Wistar strain, approximately 3 month-old at the beginning of the experiment, we examined psychological expectation of the interval timing in laboratory experimental settings with the peak-interval (PI) procedure. Interval-timing refers to time estimation in the second-to-minutes range. In the PI procedure, rats were trained on a fixed interval schedule to press lever for food after a specified interval (30 seconds in this experiment) as signaled by a certain stimulus. The rats received reinforcement only for desirable response. Though with some individual variations, the distribution of the lever press responses eventually showed an apparent peak in the vicinity of 30 seconds. Secondly, after 30 sessions of trainings, NMDA antagonist was administered directly into the septum region of the brain via microinjection. As a result, the peak time shifted rightward and lever press responses increased. This result of this study suggests that the comparison between the rats administered with NMDA antagonist, NMDA agonist, dopamine agonist and antagonist may clarify neural mechanisms of the interval timing. All experimental procedures were conducted in accordance with protocols approved by the Hiroshima University Animal Care Committee.

Disclosures: S. Sakata: None. **M. Hattori:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.09/AAA14

Topic: H.01. Animal Cognition and Behavior

Support: Simons Foundation SCGB 350397
NIH Grant 1R01MH101297
McKnight Foundation

Title: A neuronal representation of elapsed time in the medial entorhinal cortex during immobility

Authors: *J. G. HEYS, D. A. DOMBECK
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Abstract: The hippocampus and entorhinal cortex are thought to be necessary for encoding episodic memories (i.e. memories of specific personal experiences that occur in a spatial-temporal context). In support of this idea, neurons in the hippocampus and medial entorhinal cortex (MEC) fire selectively as function of animal position within an environment (O'keefe and Dostrovsky 1971; Hafting et al. 2005), and are thought to encode spatial aspects of episodic memories. While the vast majority of studies in MEC have focused on neural representations of space, it is unclear if or how MEC supports temporal aspects of episodic memory. Moreover, nearly all studies of MEC focus on neural activity during periods of locomotion, leaving open the question of how MEC may support neural representations of time during periods of animal immobility. To answer these questions we developed a "Door-Stop" (DS) task for head-fixed mice in virtual reality that combines both a locomotion dependent, spatial navigation phase, and an immobile timing phase. We then performed cellular resolution functional imaging in MEC during the DS task. During the immobile timing phase, we found many individual neurons that fired at regular, fixed delay times from the moment that the animal stopped to wait at the door. Across the population of these simultaneously recorded temporal coding neurons in MEC, we found that different cells fire selectively at all phases spanning the temporal interval, and therefore provide a neural representation that could be used to encode the entire wait time interval. A comparison of the physical location of the somata of MEC neurons reveals that temporal coding neurons are spatially clustered in MEC compared to spatial encoding neurons, which were active during locomotion in the DS task, and compared to all active cells identified in the imaging field. Furthermore, we found that temporal encoding cells and spatial encoding cells exhibit a predisposition for encoding either time or space, respectively, when animals were switched between different environments. Finally, we found that the temporal coding neurons

exhibit fully formed temporal representations from the first moments of exploration in a novel environment, suggesting that the MEC elapsed time-encoding sub-network does not require learning to form temporal representations. Our findings provide new insight into the functional domains of MEC and demonstrates the likely existence of different sub-circuits that encode either time during animal immobility or space during animal locomotion.

Disclosures: J.G. Heys: None. **D.A. Dombeck:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.10/AAA15

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH105174
NIH Grant R01MH097084
Jane Coffin Childs Memorial Fund Postdoctoral Fellowship

Title: Coordination of hippocampal-cortical activity during transient coherent theta oscillations

Authors: *J. Y. YU[1,2], L. M. FRANK[3,2,4]
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Abstract: The presence of coherent oscillations across brain structures is thought to reflect inter-region activity coordination and information exchange. Coherent oscillations in the 6-12 Hz theta band are seen in rat hippocampus and prefrontal cortex (PFC), and are thought to signal the coordination of information that supports memory and decision making. These oscillations are observed continuously in the hippocampus during spatial exploration. However, theta oscillations in prefrontal cortex occur in brief bouts. How continuous hippocampal and transient prefrontal theta oscillations coordinate information between the two brain regions remains unclear. We identified transient coherent theta oscillations across hippocampus and prefrontal cortex. These periods of high coherence lasted approximately 1s and often occurred as rats approached choice points in a foraging task. To determine whether the structure of prefrontal cortex activity is altered during these transient coherence bouts, we examined the relationship between PFC gamma oscillations and hippocampal theta. We found evidence for phase-amplitude coupling of low (25-55Hz) and high (80-120Hz) prefrontal cortical gamma oscillations to hippocampal theta phase. We further observed that this phase amplitude coupling changes with increased hippocampal-cortical theta coherence. Our results suggest the presence of

distinct and transient periods of hippocampal-prefrontal activity coordination during ongoing behavior.

Disclosures: J.Y. Yu: None. **L.M. Frank:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.11/AAA16

Topic: H.01. Animal Cognition and Behavior

Support: R01MH090188
5F30MH097356-02
Howard Hughes Medical Institute

Title: Continuous sub-second alternation between alternative neural representations

Authors: *K. KAY[1,2], J. E. CHUNG[1], M. SOSA[1], J. SCHOR[1], M. KARLSSON[1], M. C. LARKIN[1], D. F. LIU[1], L. M. FRANK[1,2]
[1]UCSF, San Francisco, CA; [2]Howard Hughes Med. Inst., San Francisco, CA

Abstract: The ability to represent alternative scenarios is essential to a range of cognitive functions. Crucially, it has been argued that in natural biological settings, neural representation of alternatives operates at the sub-second timescale. Indeed recent work indicates that single scenarios are represented in ~100 ms in the hippocampus, a brain structure vital to cognition. Yet it has remained unknown whether the hippocampus (or the brain more generally) can consistently represent alternative scenarios this quickly. Here we report that the hippocampus can represent alternative scenarios many times a second. In navigating rats, we found that hippocampal neural activity represents mutually exclusive spatial experiences in continuous alternation at up to 16 Hz. This representation was moreover paced by the internally generated ~8 Hz theta rhythm and often occurred in the absence of overt deliberative behavior. These findings suggest that cognitive functions dependent on representation of alternatives are expressed at the sub-second timescale.

Disclosures: K. Kay: None. **J.E. Chung:** None. **M. Sosa:** None. **J. Schor:** None. **M. Karlsson:** None. **M.C. Larkin:** None. **D.F. Liu:** None. **L.M. Frank:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.12/AAA17

Topic: H.01. Animal Cognition and Behavior

Support: National Science Foundation Graduate Research Fellowship
NRSA Predoctoral Fellowship Award No.1F31AG057150
Genentech Foundation Fellowship
George and Judy Marcus Discovery Fellowship
NIA R01 Grant No. RF1AG047655
NIA R01 Grant No. RF1AG055421
NIA R01 Grant No. R01AG055682

Title: Apolipoprotein E4-induced hippocampal network activity deficits correlate with learning and memory impairments

Authors: *E. A. JONES[1,2], A. K. GILLESPIE[3], S. YOON[1], L. M. FRANK[3], Y. HUANG[1,4,2]
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Abstract: Alzheimer's disease is characterized by progressive cognitive decline, yet our ability to measure disease progression at functional level in animal models is limited. To address this, we built upon our previous finding that aged female apoE4 knock in (KI) mice show deficits in two hippocampal network signatures of learning and memory: reduced abundance of sharp wave ripples (SWR), the local field potential signature of place cell replay which are critical for memory consolidation, and reduced SWR-associated slow gamma power, which coordinates this replay across regions and hemispheres. We investigated whether these network deficits correlate with spatial learning and memory deficits. Our findings suggest that SWR abundance correlates with learning early in water maze in apoE4-KI mice, while SWR-associated slow gamma power correlates with memory during probe trials in apoE4-KI mice. We then measured progression of these network phenotypes by recording from mice every 3 months over aging and determined how well they predicted future learning and memory impairment. Preliminary results suggest that the onset of SWR-associated slow gamma power loss corresponds with the onset of GABAergic interneuron loss, and that this slow gamma power loss at early ages could predict memory impairment at later ages. These results provide evidence that SWR-associated slow gamma power could be used as a functional biomarker at the network-level to monitor in mouse models the progression of AD symptoms over aging or the success of therapeutic interventions.

Disclosures: E.A. Jones: None. **A.K. Gillespie:** None. **S. Yoon:** None. **L.M. Frank:** None. **Y. Huang:** F. Consulting Fees (e.g., advisory boards); E-Scape Bio, Inc..

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.13/AAA18

Topic: H.01. Animal Cognition and Behavior

Title: Behavioral sequences predict elapsed time in the peak-interval procedure

Authors: *E. PETTER, W. H. MECK
Duke Univ., Durham, NC

Abstract: We sought to investigate behavioral strategies mice use in timing intervals in the multi-seconds range. To do this we trained five mice on a discrete-trial fixed-interval (FI) procedure. This procedure requires mice to press a lever after a fixed amount of time since signal onset in order to receive a reward. We used continuous behavioral tracking and classification, in order to assess potential behavioral sequences during interval timing. Importantly, behavioral classification was unsupervised, eliminating observer bias. Mice were filmed over consecutive sessions in order to assess how the temporal control of behavior was acquired. We observed that the structure of behavior changed as temporal precision improved during acquisition. Specifically, the probabilities of transitioning among different behaviors became more stereotyped, so that there was a greater probability of selecting a smaller subset of behavioral states. These behavioral states are supportive of temporal processing such that an increase in transition probabilities correlates with the temporal precision displayed in the FI procedure. We also observed that individual mice develop unique behavioral sequences, as opposed to reinforcement standardizing the same behaviors across mice. A multi-class support vector machine was used to classify individual time bins during the FI, based solely upon behavioral states. These classifications were better than chance, and showed improved performance for well-trained mice. While these results indicate that behavioral sequences emerge during interval timing, they don’t establish their necessity as disruption of the sequences doesn’t force a similar disruption in timing accuracy and precision.

Disclosures: E. Petter: None. **W.H. Meck:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.14/AAA19

Topic: H.01. Animal Cognition and Behavior

Title: Mediodorsal thalamus projections to the prelimbic cortex are important for proper supra-second timing behavior

Authors: *N. A. LUSK, W. H. MECK
Psychology & Neurosci., Duke Univ., Durham, NC

Abstract: Multiple lines of evidence have demonstrated the importance of the reciprocal connections between the medial prefrontal cortex (mPFC) and mediodorsal thalamus (MD) in goal directed behavior, task acquisition, and maintenance of working memory over supra-second delays. While a growing number of studies have demonstrated correlations between neural activity within the mPFC and interval timing, there is substantially less work examining how MD afferents may contribute to the mPFC's ability to support the temporal control of behavior. Though, previous lesion work provides compelling evidence for the importance for the MD in timing (e.g., Yu, Gupta, & Yin, 2010) the contributions of this thalamo-cortical pathway to interval timing is unclear. Here we implement pharmacological and optogenetic techniques in order to investigate the role of the MD and its projections to the mPFC in the ability to time supra-second durations. Muscimol injections into the MD disrupted timing behavior in a head-fixed timing procedure using a 10-s target duration. Moreover, the effects of optical inhibition of MD projections terminating in the prelimbic cortex (PL) was also examined in mice trained on a peak interval operant timing procedure using a 30-s target duration. Video monitoring allowed for the tracking of behavior across the time course of the experimental session. In line with the muscimol infusions, optical stimulation lead to disruption of timing behavior. Importantly, behavioral recordings did not show a significant change in total body movement across conditions, making alterations in behavioral patterns an unlikely explanation for the current results. Taken together, these results provide some of the first evidence for the importance of the MD-mPFC pathway in interval timing, validating previous theoretical frameworks such as the striatal beat-frequency model of interval timing in which thalamo-cortical connections play a central role in sustaining timing dynamics within the cortex (e.g., Lusk, Petter, MacDonald, & Meck, 2016; Merchant, Harrington, & Meck, 2013).

Disclosures: N.A. Lusk: None. **W.H. Meck:** None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.15/AAA20

Topic: H.01. Animal Cognition and Behavior

Title: Investigating the role of circadian clock in animal development and learning behavior

Authors: *C.-Y. CHANG
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Abstract: Circadian clock cued by light-dark cycle is important in regulating many cellular functions and animal behaviors, including cognitive ability. Previous studies have already shown that changes of external cues, e.g., constant light (LL), constant darkness (DD) and light/dark cycle switch (L/D CS), deeply affect animal's circadian rhythm. Though mounting studies have suggested that animal's biological clock can be adjustable to adopt changes of external cue accordingly, the underlying mechanism and the effect on the animal's behaviors still remain poorly understood. Currently, *in vivo*, study demonstrated that early experience on the disruption of L/D cycle has profound effect on the animal's learning behavior. In my study, my preliminary data has confirmed the flexibility of circadian rhythm in our animal model. The new circadian pattern can gradually develop to adopt a new L/D cycle after animal experienced L/D CS. Surprisingly, learning damage could be observed in the animals under the condition of LL and DD and L/D CS, but only L/D CS induced learning deficit could be recovered once new circadian pattern is adopted. To further research, even after a new L/D C was adopted and the learning damage was reversed, however, learning deficit could be observed again when early L/D SC experienced animal is aged. On the other hand, when flies experience LL and DD and L/D CS from lava stage, adult's learning impairment can be found on all of those phenotypes, delayed development only appears under the condition of LL. In conclusion, our study develops a novel framework for studying the circadian clock in the developmental stages, manipulating the progression of adults' growth and learning performance.

Disclosures: C. Chang: None.

Poster

239. Cortical and Hippocampal Circuits: Timing and Temporal Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 239.16/AAA21

Topic: H.01. Animal Cognition and Behavior

Support: RFBR 16-04-01545 A

Title: Distinct contextual memory engrams can be bound together in mice within intermediate and long-term time intervals

Authors: *K. M. SAIDOV[1], A. A. TIUNOVA[2], O. I. IVASHKINA[1,3], K. A. TOROPOVA[1,3], N. S. VOROBYEVA[1,2], K. V. ANOKHIN[1,2,3]
[1]Dept. of Neurosci., Natl. Res. Ctr. Kurchatov Inst., Moskva, Russian Federation; [2]P. K. Anokhin Inst. of Normal Physiol., Moskva, Russian Federation; [3]Lomonosov Moscow State Univ., Moskva, Russian Federation

Abstract: Recent experimental evidence suggest that memories acquired within few hours can be linked together. We investigated whether contextual memories can be bound when separated by different time intervals in contextual fear conditioning model in mice. Mice were allowed to explore a new context A and after 5 min, 30 min, 2 h, 5 h or 1, 3, 7, 30 or 120 days were exposed to a new context B, where they received a footshock. A separate group of mice initially received a footshock in the context B and 72 h later was allowed to explored the context A. 72 h after the training all mice were tested in the contexts A, B and the novel context C with intervals 24 h between the tests. A delay from 5 h to 30 days between the trainings resulted in mouse freezing in a neutral context along with the footshock context during the tests. This did not occur with 5 min - 2 h and 120 d intervals, and also when mice were initially trained in the footshock context first. After testing mice that were trained in the two contexts with 5 min or 24 h intervals, we investigated overlap in populations of neurons of both engrams in the hippocampus, amygdala and cortex using the c-fos catFISH cellular imaging. An overlap during retrieval was higher with the 24 h delay than with the 5 min delay in CA1 and CA3, dentate gyrus, lateral amygdala and basolateral amygdala. We propose that shared populations of neurons in the hippocampus and amygdala allow the binding and associated recall of contextual memories.

Disclosures: K.M. Saidov: None. **A.A. Tiunova:** None. **O.I. Ivashkina:** None. **K.A. Toropova:** None. **N.S. Vorobyeva:** None. **K.V. Anokhin:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.01/AAA22

Topic: H.01. Animal Cognition and Behavior

Support: NIDA RO1 DA013951
NIAAA T32 AA007474

NIDA 2T32 DA007288-26

Title: The abused inhalant toluene impairs risk/reward decision making in Sprague-Dawley rats independent of mPFC CB1R signalling

Authors: *K. M. BRAUNSCHEIDEL[1], M. P. OKAS[1], S. B. FLORESCO[2], J. J. WOODWARD[1]
[1]Neurosci., Med. Univ. of South Carolina Dept. of Neurosciences, Charleston, SC; [2]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Volatile organic solvents like toluene cause intoxication and changes in brain function similar to those produced by classic drugs of abuse. These include alterations in the signaling properties of neurons within the medial prefrontal cortex (mPFC), a region responsible for top-down control of complex behaviors. For example, we previously demonstrated that, in brain slices containing the mPFC, acutely applied toluene caused a long-lasting, endocannabinoid-dependent depression in glutamatergic synaptic transmission. The consequence of this effect is unknown, but would be expected to disrupt behaviors that require an intact mPFC. To test the hypothesis that toluene alters mPFC-dependent behavior via enhanced endocannabinoid signaling, we used the rodent model of risk/reward decision making, probabilistic discounting (PD). Sprague-Dawley rats were trained to lever press for a reward (20% sweetened condensed milk): one lever delivered a small, certain reward (30 µl, 100% of the time) while a second lever delivered a large, uncertain reward (90 µl, reinforcement probability fluctuates from 100% to 6.25% or vice versa). Following stable responding, rats were placed in a toluene vapor chamber, exposed to abuse-level concentrations of toluene (6000 ppm or 10500 ppm) for 15 minutes, and then returned to their home cage for 30 minutes before PD testing. Interestingly, under conditions where reinforcement probability *decreased*, rats dramatically *increased* risky lever selection following toluene treatment. Conversely, when reinforcement probability *increased*, toluene exposed rats showed *decreased* risky lever selection. Separate cohorts of animals were then trained and implanted with a bilateral guide cannula directed at the mPFC. One group was microinfused with vehicle or the CB1R antagonist AM251 (5 or 50 ng) using a within-subject, counter-balanced design. Another group was microinfused with vehicle or AM251 and exposed to vapor chambers to generate three treatments: Vehicle + Air, Vehicle + 10500 ppm toluene, AM251 + 10500 ppm toluene. Results from these studies suggest that blocking CB1R signaling in the mPFC does not disrupt PD, nor mitigate the effects of toluene on flexible risk/reward decision making. However, CB1 antagonism does depress sensitivity to positive reinforcement as reflected in a reduction in win/stay strategy. Follow-up studies using the CB1R agonist WIN-55,212-2 are investigating the effect of enhanced mPFC CB1R activity on PD. In summary, toluene drastically impairs probabilistic discounting in a manner suggestive of mPFC dysfunction, but independent of mPFC CB1R signaling.

Disclosures: K.M. Braunscheidel: None. **M.P. Okas:** None. **S.B. Floresco:** None. **J.J. Woodward:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.02/AAA23

Topic: H.01. Animal Cognition and Behavior

Support: DA017960

Title: Methylphenidate enhances specific dimensions of cognitive performance in a rodent strategy shifting assay of cognitive flexibility

Authors: C. P. KNAPP[1], O. G. KUPONIYI[1], S. B. FLORESCO[2], B. D. WATERHOUSE[1], *R. L. NAVARRA[1]
[1]Cell Biol. and Neurosci., Rowan Univ. Sch. of Med., Stratford, NJ; [2]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Executive functions represent a branch of higher order cognitive processes that include attention, behavioral inhibition, working memory, and cognitive flexibility. Cognitive flexibility requires reasoning and problem solving in order to shift behavioral strategies in response to changing environmental demands. Impairment of cognitive flexibility is common to neuropsychiatric disorders, such as ADHD. ADHD patients perform significantly worse than unaffected individuals in tasks requiring cognitive flexibility, especially when a particular task grows in difficulty. Disruption of executive function in ADHD is associated with improper regulation of catecholamine transmitters, dopamine (DA) and norepinephrine (NE), functioning within the prefrontal cortex (PFC). Drugs that enhance DA and NE within the PFC are the first line of treatment for patients with ADHD, but the specific dimensions of executive function that receive the most benefit from treatment with these agents have not been identified. Methylphenidate (MPH) is a pro-cognitive agent and ADHD medication that increases concentrations of DA and NE through inhibition of their respective reuptake transporters. In the present study, we utilized an automated operant strategy shifting task to investigate the effects of MPH on different components of cognitive flexibility and performance including strategy shifting, reversal learning, and processing speed. Rats learned one of two initial rules, either press the lever on a specific side of the chamber (i.e. egocentric response - left or right) or press the lever indicated by a visual cue. Following acquisition of the initial rule, rats were required adapt to a new strategy either by changing the rule across dimensions (egocentric vs visual cue) or reversal learning within a dimension. During initial learning, rats required more trials to acquire the visual cue vs response rule. MPH improved the retrieval of the visual cue strategy 24 hours following initial acquisition. MPH also reduced overall choice latencies during retrieval, reversal learning, and strategy shifting tests, indicating enhanced processing speed. The effect of MPH on choice latencies were driven primarily by reducing reaction times on correct trials.

These results begin to elucidate the potential for MPH to improve performance and behavioral efficiency within the operant strategy shifting task of cognitive flexibility. Further characterization of the mechanisms by which MPH improves performance across cognitive dimensions could lead to better understanding of behavioral parameters to investigate when considering treatment options for cognitive dysfunction.

Disclosures: C.P. Knapp: None. **O.G. Kuponiyi:** None. **S.B. Floresco:** None. **B.D. Waterhouse:** None. **R.L. Navarra:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.03/AAA24

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Medial orbitofrontal cortex involvement in extinction and cue-induced reinstatement of instrumental reward-seeking behaviour

Authors: *S. B. FLORESCO, N. E. SYMONDS, N. L. JENNI
Univ. British Columbia, Vancouver, BC, Canada

Abstract: The medial subregion of the orbitofrontal cortex (mOFC) is thought to play an important role in value-based decision-making, as lesioning or inactivating this cortical region results in the adoption of choice strategies based more on observable (rather than previously learned) information. Despite this, its role in mediating basic instrumental and Pavlovian reward-seeking behaviour is not entirely understood. The present series of experiments examined the role of the mOFC in (1) extinction and (2) cue-induced reinstatement of food-seeking behaviour, as well as (3) Pavlovian conditioned responding for reward. For experiments 1 and 2, rats were trained to lever press for a sucrose reward, contingent with the delivery of a tone and light cue. They then underwent extinction, followed by a reinstatement test where lever press produced the previously reward-paired cues alone. Intra-mOFC infusions of either saline or GABA agonists (to temporarily inactivate neural activity) were given prior to the first day of extinction, or the reinstatement test day in different cohorts of rats. (1) Inactivation of mOFC improved extinction performance (fewer lever presses) on the first day of instrumental extinction. However, on subsequent, drug free days, rats that received mOFC inactivation displayed retarded rates of extinction learning, making more active lever presses than the control group on extinction day 3&4. (2) mOFC inactivation prior to reinstatement induced differential effects on cue-induced reinstatement that were dependent upon baseline performance. “Reinstater” rats that displayed robust responding under control conditions showed no reinstatement after mOFC inactivation. In

contrast, for “non-reinstater” rats that showed little responding during reinstatement tests under control conditions, mOFC inactivation robustly increased reinstatement, suggesting perhaps that individual differences in reinstatement may be supported by differences in mOFC mediated representations of expected value. (3) Results pertaining to the involvement of the mOFC in Pavlovian conditioned responding will be discussed. These findings have important implications for understanding how the mOFC governs adaptive reward processing, and how dysfunction within this region may contribute to pathological patterns of reward seeking.

Disclosures: S.B. Floresco: None. **N.E. Symonds:** None. **N.L. Jenni:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.04/AAA25

Topic: H.01. Animal Cognition and Behavior

Support: CIHR

Title: Mediation of cue-guided risk/reward decision making by basolateral amygdala-nucleus accumbens circuitry

Authors: *M. VAN HOLSTEIN[1], P. MACLEOD[2], S. B. FLORESCO[2]
[1]Psychology, Univ. of British Columbia, Vancouver, BC, Canada; [2]Univ. British Columbia, Vancouver, BC, Canada

Abstract: We often face decisions requiring a choice between options that vary in terms of reward magnitude and uncertainty. In some situations, the probabilities of different outcomes can be inferred from different cues. For example, an experienced Blackjack player knows the odds of winning a hand are larger when the dealer is showing a “6” card compared to an “ace”. Studies with humans have revealed that - the nucleus accumbens (NAc) and amygdala are recruited during decision making under risk when participants are presented with explicit cues that inform them about the probabilities of winning a gamble. Preclinical studies with rodents have provided insight in the neural basis of risk/reward decision making, however, many of these studies have used tasks where choice is guided by internally-generated information, identifying a role for basolateral amygdala (BLA)-NAc shell circuitry in guiding probabilistic discounting. Yet, how these regions may contribute to decision making guided by external discriminative stimuli has not been explored. To bridge this gap between assays in humans and rats we developed an assay we have colloquially termed the “Blackjack” task. Using this task, we assessed the roles of the NAc shell-BLA circuitry in cue-guided risky decision making when animals are presented with a choice between a small/certain (1 pellet) and a large/risky (4 pellet) reward option. Crucially, in this task, the odds of obtaining the large reward vary unpredictably, and are explicitly signaled

by discriminative auditory cues. Prior to a choice trial, one of two tones informs the rat that the odds of obtaining the larger reward is either 12.5% (poor odds) or 50% (good odds). Under control conditions, well-trained rats selected the large reward option more often when the odds were good vs. poor (~75% vs. 20%). Bilateral inactivation of the BLA increased risky choice on poor odds trials, in a manner similar to inactivation of the NAc shell (Floresco et al., 2018, J Neurosci). However, the role of these regions was distinct in that inactivation of the BLA was accompanied by pronounced alterations in how rewarded or non-rewarded choices influenced choice selection on subsequent trials, whereas inactivation of the shell only reduced sensitivity to non-rewarded outcomes. Furthermore, preliminary results indicate that disconnection between the BLA and NAc shell induce a similar profile in choice to bilateral inactivation of either structure alone. These findings point to a key role for BLA-NAc circuitry in guiding cue-guided risk/reward decision making to bias action selection away from options that are unlikely to yield rewards.

Disclosures: M. Van Holstein: None. **P. MacLeod:** None. **S.B. Floresco:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.05/AAA26

Topic: H.01. Animal Cognition and Behavior

Support: CIHR MOP 133579

Title: Optogenetic suppression of medial prefrontal cortical activity during action selection and action outcomes differentially biases risky choice

Authors: *D. A. BERCOVICI, O. PRINCZ-LEBEL, S. B. FLORESCO
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Decision-making often requires weighing costs and benefits associated with different options that vary in terms of reward magnitude and uncertainty. Previous studies animals have used long-lasting inactivations of the prelimbic (PL) region of the medial prefrontal cortex to identify a key role for this region in updating choice biases in response to changes in reward contingencies and biases choice towards more profitable options when the reward probabilities change. However, it is unclear how choices are shaped by discrete periods of activity in the PL that occur at different points of the decision process (e.g.; prior to choices or when their outcomes are realized). To address this, we used optogenetic suppression of neural activity to investigate how temporally-specific phasic neural activity within the PL during different phases of the decision process influences choice. Rats received intra-PL infusions of AAV encoding the inhibitory opsin eArchT and were well-trained on a probabilistic discounting task, where they

chose between a smaller/certain reward and a larger reward delivered in a probabilistic manner, with the odds of obtaining the larger reward changing over a session (50-12.5%). During testing, discrete ~5 s pulses of light were delivered via optic fibers into the PL to suppress activity around the time of specific task events; during periods “prior to choice” or after different “choice outcomes”. Preliminary results suggest that suppressing PL activity prior to choice biases choice away from their more preferred option, most prominently during the high, 50% probability block, suggesting that prior to choice selection, PL activity promotes actions directed towards uncertain yet more profitable outcomes. In contrast, inhibition following non-rewarded risky choices increased preference for the risky option during the low, 12.5% probability block, indicating that when action outcomes are realized, activity in the PL encodes information about non-rewarded actions to update optimal choice-strategies based on reward delivery probability. These findings provide novel insight into how discrete patterns of firing within the PL convey contrasting types of information that guide flexible decision making in situations involving reward uncertainty.

Disclosures: D.A. Bercovici: None. **O. Princz-Lebel:** None. **S.B. Floresco:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.06/BBB1

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

Title: Prelimbic cortex selectively promotes active avoidance during an active/inhibitory avoidance task

Authors: *G. CAPUZZO[1], S. B. FLORESCO[2]
[1]Psychology, [2]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Potentially aversive situations often require flexible allocation of action selection to avoiding punishment. For example, some situations may require an organism to make a response to actively avoid negative outcomes, whereas others may require behavioural suppression to ensure safety. Failure to coordinate behaviour discrimination in real-life conflicting situations can lead to aversive consequences because of improper inhibition of motor output when action is needed or, vice versa, when defensive actions are performed instead of withheld. Disruption of appropriate functioning in avoidance behaviours can lead to improper action selection and increase in negative outcomes seen in disorders such as substance abuse, anxiety and depression. Previous work by our group has shown that different regions of the nucleus accumbens are involved in regulation of avoidance behaviours assessed with an active/inhibitory avoidance task,

with distinct roles in inhibiting behaviour and motivating action to avoid punishment. In the present study, we investigated the contribution of a main input to the nucleus accumbens, the prelimibic region (PL) of the medial prefrontal cortex, to regulating flexible instrumental avoidance. Male Long Evans rats were trained on a variation of a Go/No-Go task that required them to discriminate between two auditory cues presented pseudorandomly that indicated whether a mild footshock could be avoided by using an active or inhibitory avoidance strategy. Each trial began with presentation of one of the two cues and insertion of a lever. Active avoidance trials required rats to press a lever within 15s of cue/lever presentation to avoid a shock. Inhibitory avoidance trails required animals to withhold a press during presentation of another auditory cue. In well-trained rats, PL inactivation induced a marked reduction in the proportion of active avoidance responses. In contrast, during inhibitory avoidance trials, PL inactivation had no effect on performance. These results suggest a role for the PL cortex goal-directed action in aversively motivated behaviours as separate from inhibition of punished actions, and adds a link in the neural network of avoidance processing to help further our understanding of how conditioned instrumental behaviours are processed by cortical and striatal regions. Furthermore, these findings may provide insight into how prefrontal cortical dysfunction may relate to pathological avoidance behaviors that may occur in neuropsychiatric disorders.

Disclosures: G. Capuzzo: None. **S.B. Floresco:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.07/BBB2

Topic: H.01. Animal Cognition and Behavior

Support: CIHR MOP 133579

Title: Alterations in different aspects of risk/reward decision-making induced by excessive corticotropin-releasing factor activity

Authors: *C. A. BRYCE, A. J. ADALBERT, M. M. CLAES, S. B. FLORESCO
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Depression is a stress-related disorder characterized by a debilitating constellation of affective and cognitive symptoms. Though the etiology of depression is currently unknown, depressed patients show potentiated corticotropin-releasing factor (CRF) levels. Along with affective symptoms, depression also causes substantial cognitive impairments, including alterations in risk/reward decision-making. Previous work by our group has shown that excessive CRF alters effort-related decision-making, reducing preference to work harder to obtain larger rewards in a manner similar to that observed in depressed patients. In the present study, we

assessed how increasing CRF activity alters choice behavior when rewards are uncertain. In so doing, we looked at two forms of risk/reward decision-making guided either by internally-generated information or by external cues. To this end, we trained separate squads of male rats on a probabilistic discounting task and external cue-guided "blackjack" task. The probabilistic discounting task required rats to choose between two response options; a small/certain option and a large/risky option that delivered a large reward with ascending (6.25-100%) or descending (100-6.25%) odds, requiring animals to keep track of changing reward probabilities. In the Blackjack task, rats choose between a small/certain option or a large/risky option. On different trials, distinct auditory cues signalled if the odds of obtaining reward were good (50%) or poor (12.5%). Intraventricular infusions of CRF (1 or 3 μg) did not affect choice on the probabilistic discounting task, but did increase trial omissions more prominently when delivery of the large reward was uncertain. In comparison, CRF infusion (3μg) altered choice on the Blackjack task in a manner dependent on baseline risk preference. In rats that were risk-preferring, CRF selectively reduced risky choice on good odds trials, when the risky option had greater utility. However, these treatments did not affect choice in risk-averse rats. Interestingly, one hour of restraint stress either reduced or increased choice of the large risky reward during trials in which the odds were most uncertain when risk/reward contingencies were internally represented or guided by external cues, respectively. Together these results reveal the complex effects of CRF on various aspects of cognition, some of which mirror those in depression. Specifically, increased CRF activity may selectively disrupt effective reward-related decision-making when guided by external stimuli that inform the likelihood of obtaining reward.

Disclosures: C.A. Bryce: None. **A.J. Adalbert:** None. **M.M. Claes:** None. **S.B. Floresco:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.08/BBB3

Topic: H.01. Animal Cognition and Behavior

Support: CIHR MOP 133579

Title: Neural correlates of risk/reward decision making in the medial prefrontal cortex and basolateral amygdala

Authors: *E. Ö. EINARSSON[1], R. FAYYAZI[2], J. K. SEAMANS[2], S. B. FLORESCO[3]
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Psychiatry, UBC, Vancouver, BC, Canada; [3]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Impairments in cost-benefit decision making are central to the pathophysiology of several psychiatric disorders. In experimental settings, these abnormalities are characterized by poor performance on probabilistic decision making tasks involving choices between certain but small rewards, and uncertain larger rewards.The basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) are two reciprocally connected regions that contribute differently to risk/reward decision making, with the BLA supporting reward value representation, and the mPFC monitoring changes in reward contingencies to modify decision biases. Moreover, mPFC-dependent modifications in decision biases are enacted via mPFC descending pathways to the BLA. However, it is not clear how neurons in the mPFC and BLA encode information regarding choice behavior and outcomes during decision making. Here, we examined firing of mPFC and BLA neurons during key task events (e.g. pre-choice, after rewarded/non-rewarded choice outcomes) in a probabilistic discounting task. To this end, we recorded multi-unit activity simultaneously from both regions using multi-tetrode arrays during performance of a task where rats chose between a small/certain reward and a large/risky reward, with risky reward probabilities changing over blocks of free-choice trials from 70% to 10%. Preliminary observations suggest that neurons in both regions are sensitive to changes in large/risky reward probability and the direction of choice, modifying their activity to key task events in a tonic and phasic manner. In addition, neurons in both regions were sensitive to different types of outcomes (large vs small vs no reward), suggesting activity in these regions may encode decision outcomes to update value representations and guide subsequent action selection.

Disclosures: E.Ö. Einarsson: None. **R. Fayyazi:** None. **J.K. Seamans:** None. **S.B. Floresco:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.09/BBB4

Topic: H.01. Animal Cognition and Behavior

Support: CIHR MOP 133579

Title: Medial orbitofrontal projections to the nucleus accumbens and basolateral amygdala differentially influence efficient risk/reward decision-making

Authors: *N. L. JENNI, Y. LI, S. B. FLORESCO
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Optimal choice in situations involving reward uncertainty relies on choice strategies that access representations of learned contingencies rather than on any immediately observed outcome. The medial subregion of the orbitofrontal cortex (mOFC) is thought to play a key role

in this process. Previous work by our group has found inactivating the mOFC increases choice of larger, probabilistic rewards, by increasing win-stay behaviour - reflecting the adoption of a strategy based on immediate reward feedback, rather than what had been learnt regarding changes in profitability of the risky option over time. However, it remains unclear the subcortical regions through which the mOFC interacts with to support its role in risk/reward decision-making. To address this, rats were well trained on a probabilistic discounting task where they choose between a small/certain (1 pellet) and a large/uncertain 4 pellet option, the odds for which decrease systematically across 5 blocks of trials (100-6.25%). In an initial experiment, an asymmetrical pharmacological disconnection was used to temporarily disrupt the transfer of information from mOFC◊nucleus accumbens (NAc). We then attempted to replicate this experiment using a chemogenetic approach. In these experiments, a cre-dependent DIO-hM4D(Gi)-DREADD was infused into the mOFC and a retrograde rgAAV-CRE into the NAc or the basolateral amygdala (BLA) in separate groups of rats to exclusively express the Gi-DREADD within mOFC neurons that projected to either the NAc or BLA. Pharmacological disconnection of mOFC-NAc circuits reduced choice of the risky option in the 100% trial block, and increased responding in the 12.5 and 6.25% trial blocks indicating that activity within this pathway is important for optimizing choice. Preliminary data show a dose dependent effect of CNO (1 or 3 mg/kg) relative to vehicle treatments in the mOFC◊NAc group that mimicked the alterations in choice induced by pharmacological disconnections - albeit to a seemingly smaller extent. For rats expressing the Gi-DREADD in mOFC◊BLA projection neurons, CNO (1 or 3 mg/kg) dose-dependently increased risky choice in later blocks of trials when it was no longer advantageous, which could reflect an inability to update or access a previously learnt value representation of the risky option. In contrast, CNO had no effect relative to vehicle treatment in rats treated with mCherry virus controls. Together, these preliminary studies implicate mOFC-subcortical circuits in optimal choice on the probabilistic discounting task, and support existing literature on the role of the mOFC in value-based decision-making.

Disclosures: N.L. Jenni: None. **Y. Li:** None. **S.B. Floresco:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.10/BBB5

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant PJT-149004

Title: Chemogenetic modulation of the dopaminergic nigrostriatal pathway shifts risky decision-making patterns in rats

Authors: *B. A. HATHAWAY[1], M. M. SILVEIRA[1], M. TREMBLAY[2], C. A. WINSTANLEY[1]
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Abstract: It is well-established that risky decision making is critically involved in the development and maintenance of addiction. Reward-concurrent cues may mediate this relationship, as previous results have indicated such stimuli enhance risk preference and may potentiate cocaine intake in rats. Despite extensive addiction research implicating the dorsal striatum in compulsive drug seeking, the role that dorsal striatal dopaminergic activity plays in the maintenance of risk preference driven by win-associated cues remains unclear. Accordingly, the present studies examined the effects of both acute and chronic inhibition or excitation of the dopaminergic nigrostriatal pathway on risky decision-making profiles in rats. Female TH:Cre rats (n = 47) and transgene negative litter mates (n = 44) were trained on the cued version of the rat gambling task (rGT), a rodent analogue of the human Iowa Gambling Task, to assess cue-enhanced decision making. This task was designed such that the optimal strategy for earning sugar pellets over time is to favor options paired with lower per-trial gains, as these are associated with a higher probability of winning and shorter time-out penalties. Consistently selecting the high-risk, high-reward options ultimately results in longer and more frequent time-out penalties, and therefore less reward overall. Adding salient reward-paired cues to this task results in a substantial proportion of rats exhibiting a risk-preferring choice profile. To assess nigrostriatal involvement in the cued rGT (crGT), inhibitory DREADD (designer receptor exclusively activated by a designer drug) hM4D(Gi) or excitatory DREADD hM3D(Gq) was infused into the substantia nigra prior to task training. After a statistically stable baseline was reached, rats were given an acute clozapine-N-oxide (CNO) challenge, followed by a chronic injection period in which CNO was given twice daily for 14 days. crGT performance was assessed while CNO was on board. While acute CNO administration did not affect choice, chronic administration shifted risk preference in a manner dependent on the rats' previously established decision-making profiles. These results provide evidence for the involvement of the dopaminergic nigrostriatal pathway in the maintenance of risky decision making, and therefore shed light on its role in the development and maintenance of addiction.

Disclosures: B.A. Hathaway: None. **M.M. Silveira:** None. **M. Tremblay:** None. **C.A. Winstanley:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.11/BBB6

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Open Operating Grant

Title: Cues enhance the pro-addicitive power of motor impulsivity

Authors: *T. HYNES[1], J.-M. N. FERLAND[2], C. WINSTANLEY[1]
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Abstract: The audiovisual cues featured in human gambling are thought to enhance the addictive potential of play. Our group has modeled this phenomenon in rats using the cued rat gambling task (crGT), a variant of our original rat gambling task (rGT). In the crGT, audiovisual cues are presented with each win, and compared to the rGT, animals become more risky and some exhibit greater motor impulsivity. The cues associated with drug use likewise become powerful incentive stimuli, capable of evoking within individuals a greater desire for the drug, thereby facilitating the transition to addiction. Given the high comorbidity between drug addiction and gambling disorder, we primarily wondered whether cue-induced risky choice and impulsivity would impact the self-administration of cocaine. We also asked if cocaine self-administration modulated the ongoing expression of these pro-addictive traits.
We trained two groups of male Long-Evans rats to stability in either the rGT (n=16) or crGT (n=16) before implanting them with jugular catheters and allowing them to self-administer cocaine (FR1; 0.75 mg/kg/inf) for 10 days. Concurrent rGT/crGT testing was run prior to each self-administration session.
Rats trained in the crGT were significantly riskier and more impulsive than those trained in the rGT. For rats trained in the crGT, baseline impulsivity was positively correlated with cocaine seeking, whereas no correlation was observed in the rGT group. These findings suggest that repeated exposure to reward cues may make individuals more impulsive as well as potentiate the pro-addictive power of trait impulsivity.
Both groups exhibited reductions in state impulsivity following cocaine self-administration; this is consistent with the therapeutic efficacy of psychostimulants against disorders of impulse control and may support elements of the self-medication hypothesis of addiction. Cocaine-induced decreases in impulsivity were not associated with ongoing decreases in cocaine seeking, which remained tightly coupled to baseline impulsivity throughout the self-administration phase of testing.
While risky decision making was not associated with increased cocaine seeking/taking, a history of self-administration did cause an increase in risky choice in rats already risky at baseline. As individuals become risker, they become more prone to maladaptive cost/benefit decision making. It is therefore possible that risky decision making does not directly influence the acquisition of drug use, but rather influences the propensity of individuals to compulsively consume (i.e., in the face of aversive consequences) – a facet of addiction which we will explore in future studies.

Disclosures: T. Hynes: None. **J.N. Ferland:** None. **C. Winstanley:** A. Employment/Salary (full or part-time):; Michael Smith Foundation. F. Consulting Fees (e.g., advisory boards); Shire Pharmaceutical.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.12/BBB7

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant - PJT-148631

Title: acute down regulation of mesolimbic dopamine on a rat gambling model

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Abstract: Behavioral research indicates that impaired decision making, response inhibition, and impulsiveness may be responsible for the uncontrolled, compulsive behavior in those with gambling disorders (GD). Lesions or inactivations of the Nucleus Accumbens (NAc) impair probabilistic decision making. The NAc has been deemed a “corticolimbic” interface, due to its critical role in integrating inputs from the affective corticostriatal loop. This system is biased by mesolimbic dopamine (DA), which is therefore suited to gate and integrate inputs to the NAc, regulating NAc firing. It may be appropriate to view behavioral impacts of this system as a dysregulation of input to the NAc.Using an animal model of the Iowa Gambling Task, the cued rat Gambling Task (crGT), we will elucidate the processes influencing decision making and how such processes may be disrupted in GD. Pilot data indicates that chronic down-regulation of DA release in the NAc improves decision making for subjects on the rGT; regulation of DA release from the VTA may bias subjects to make fewer risky choices. I will follow up this finding by acutely downregulating DA in the VTA and NAC.Male transgenic rats expressing cre-recombinase in cells containing tyrosine hydroxylase will be used to target DA of the mesocorticolimbic system. hM4Di-DREADD will be infused into the Ventral Tegmental Area (VTA), which can be activated by systemic administration of Clozapine-N-Oxide (CNO) to inhibit DA release. Kappa Opioid Receptor DREADD will be infused into the NAc shell, which can be activated by systemic administration of salvinorin B (SalB), to downregulate DA receptors. Animals will undergo operant training on the crGT until they reach baseline stability. They will then undergo acute drug challenges on the crGT in a Latin-square design. Doses of CNO will be administered at 1 mg/kg via intraperitoneal injection at 0 mg/kg, 0.3 mg/kg, 1 mg/kg, and 3mg/kg dissolved in 6% DMSO and 9% sterile saline. SalB will be administered at 2 mg/kg via subcutaneous injection at 0 mg/kg, 7.5 mg/kg, 15 mg/kg, in a vehicle of 100% DMSO.We hypothesize that acute downregulation of DA within the VTA and NAc shell will improve decision making in a dose dependent manner. Repeated measures ANOVA,

demonstrated that SalB improved decision making on the cRGT (dose x transgene: F2, 24 = 4.694, p = .014). Dysregulation of decision making ability appears to potentiate addictive behavior. To understand potential interventions for GD, it is valuable to consider this as a decision-making disorder; understanding the influence of DA from the VTA to NAc could provide insight into the neurobiological mechanism underlying the behavioral dysregulation seen in GD.

Disclosures: C.D. Hounjet: None. **J.N. Ferland:** None. **M. Silveira:** None. **C.A. Winstanley:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.13/BBB8

Topic: H.01. Animal Cognition and Behavior

Support: NSERC RGPIN-2017-05006

Title: Investigating the pathway between anterior cingulate cortex and basolateral amygdala on a rodent cognitive effort task

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Abstract: On a day to day basis, humans must routinely decide how to allocate their cognitive resources so as to obtain lucrative outcomes. While such processes may seem trivial, the consequences of not appropriately allocating cognitive effort can be quite severe. Indeed, reduced willingness to exert effort is observed in a wide range of psychiatric disorders including depression and schizophrenia, which can be debilitating to patients and detrimental to treatment outcomes. To probe the neural regions regulating decision-making with cognitive effort costs, we have developed an animal model of effort-based decision making, known as the rodent cognitive effort task (rCET). In the rCET, animals choose between hard or easy options varying in attentional demand and potential reward. Successful completion of the hard trial, which involves detection of a brief visuospatial light stimulus (duration = 0.2 s) results in receipt of twice the amount of sugar pellets compared to the easy trial (stimulus duration = 1 s). Previously we have demonstrated that the anterior cingulate cortex (ACC) and basolateral amygdala (BLA) regulate willingness to exert cognitive effort. Specifically, bilateral ACC inactivations decrease effortful, high reward choice (HR), while inactivations of the BLA bias rats away from their preferred option at baseline. However, it is unknown how these areas might interact to guide cognitively effortful choice. In the present investigation, thirty-seven male Long-Evans rats were trained on

the rCET and the role of ACC-BLA signaling was probed. This was achieved by performing a functional disconnection, in which unilateral inactivation of ACC was paired with unilateral BLA inactivation in the contralateral hemisphere. Ipsilateral pathway inactivations, as well as single unilateral inactivations of the ACC and BLA were also conducted. Contralateral inactivations decreased effortful choice in a subset of subjects initially preferring the HR option ("workers"), but did not affect measures of attention. Subsequent experiments revealed that unilateral BLA inactivation similarly reduces effortful choice in "worker" rats, suggesting that the effects observed following BLA-ACC disconnection are likely explained by disrupted unilateral BLA signaling. In contrast, ipsilateral inactivations affected measures of attentional performance, effects which could not be accounted for by unilateral inactivation of either area alone. Together, these data suggest that disrupting BLA activity unilaterally can have marked effects on willingness to exert cognitive effort, but that perturbing ACC/BLA signaling can affect attentional ability.

Disclosures: L. Mortazavi: None. **M.M. Silveira:** None. **C.A. Winstanley:** Other; Shire.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.14/BBB9

Topic: H.01. Animal Cognition and Behavior

Support: Parkinson Society Canada 2016-1072

Title: A novel GPR52 agonist, BD442618, attenuates ropinirole-induced increases in preference for uncertain outcomes in rats

Authors: *B. RUSSELL[1], M. TREMBLAY[2], M. M. BARRUS[1], S. HOBSON[3], A. J. GROTTICK[4], C. A. WINSTANLEY[5]
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Abstract: Selective dopamine $D_{2/3}$ agonists, such as ropinirole (ROP), effectively treat the motor symptoms of Parkinson's Disease (PD), and unlike L-DOPA, do not cause problematic dyskinesias after prolonged use. Thus, $D_{2/3}$ agonists can be an attractive alternative to L-DOPA for the long-term management of PD. However, $D_{2/3}$ agonists induce impulse control and gambling disorders in a substantial minority of patients, raising concern over the use of these agents. Adjunctive medications that could be safely administered with $D_{2/3}$ agonists and prevent the development of such psychiatric side-effects would therefore be highly desirable. GPR52 is a Gs-coupled g-protein coupled receptor (GPCR) enriched in D_2-receptor expressing neurons of

the striatum. Activation of GPR52 has been demonstrated to attenuate behaviours associated with increased striatal dopamine release without altering basal function. We have shown previously that ROP increases preference for uncertain outcomes on a rodent test of gambling-like decision making known as the rat betting task (rBT). This task measures preference for certain versus uncertain rewarding outcomes of equal utility. Although most rats maintain a constant preference for the uncertain outcome regardless of the amount at stake, some rats increase their preference for guaranteed rewards as the wager-size increases, even though the relative expected value of the two options remains constant. The choice strategy of these wager-sensitive rats may be considered mathematically non-normative, and such irrational decision-making patterns have been linked to the manifestation and severity of problem gambling. The degree of wager-sensitivity has been associated with the density of $D_{2/3}$ receptors in the dorsal striatum. We therefore hypothesised that a GPR52 agonist may attenuate the ability of ROP to promote choice of uncertain outcomes in wager-sensitive rats. Healthy male rats performed the rBT prior to implantation of an osmotic pump that delivered either ROP (5 mg/kg/day) or saline for 28 days. After pump implantation, rats received a daily injection of either vehicle or the GPR52 agonist BD442618 (BD). The dose of BD increased incrementally throughout the experiment, such that rats received 0.3 mg/kg of BD for the first 12 days, 1 mg/kg for the next 8 days, and 3 mg/kg for the remaining 8 days. We found that ROP robustly increased choice of the uncertain option, and that 3 mg/kg BD significantly reduced this effect in wager-sensitive rats. In conclusion, BD may be effective at reducing ROP-induced increases in risky decision-making in those vulnerable to iatrogenic gambling disorder.

Disclosures: B. Russell: None. **M. Tremblay:** None. **M.M. Barrus:** None. **S. Hobson:** Other; CNS Disease Research, Boehringer Ingelheim Pharma GmbH & Co KG. **A.J. Grottick:** Other; CNS Drug Discovery, Beacon Discovery Inc.. **C.A. Winstanley:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.15/BBB10

Topic: H.01. Animal Cognition and Behavior

Support: NSERC RGPIN-2017-05006

Title: Investigating orbitofrontal cortex contributions to decision making involving cognitive effort costs

Authors: *M. SILVEIRA[1], S. WITTEKINDT[1], C. A. WINSTANLEY[2]
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Abstract: Organisms must frequently evaluate the amount of effort that must be invested in pursuit of future rewards. Research in the area of cost/benefit decision-making supports dissociable roles for ventral and dorsal cortical areas in decision making, in which lesions or inactivations of the anterior cingulate cortex (ACC) affect valuations of physical effort, while similar manipulations to the orbital frontal regions do not affect effort allocation but selectively affect decisions involving other costs. This distinction is largely based on the physical effort that discounts lucrative outcomes, but a growing literature has emphasized the cognitive effort costs representative of the decisions individuals face in modern societies. Akin to the physical effort literature, we previously demonstrated a causal role for the ACC in the processes by which rodents decide how to allocate attentional effort for lucrative outcomes, but the role of the orbital frontal regions has never been causally investigated. Indeed, the tendency to consider effort as a unitary construct may mask distinct cortical substrates regulating cognitive versus physical effort allocation. To address this, 24 female Long-Evans rats were trained on the rodent Cognitive Effort Task (rCET) and performance was assessed following temporary inactivation of the lateral orbitofrontal cortices (LOFC). The rCET is an adapted version of the standard 5-CSRTT, in which rats can decide at trial outset whether to detect an easy (1 s) or hard (0.2s) visual stimulus across five possible locations, and where successful completion of easy or hard trials results in one or two sugar pellets, respectively. Inactivations of the LOFC did not affect rats' willingness to exert cognitive effort for larger rewards, and did not affect the attentional ability required to complete difficult, high reward trials. However, inactivations selectively increased choice omissions, and in keeping with previous literature, increased impulsive action. These effects can be contrasted with previous work on the rCET, in which inactivation of medial and dorsal cortical areas simultaneously affect willingness to exert cognitive effort as well as ability. Indeed, the current work suggests that cognitive deficits induced by cortical perturbation are not necessarily accompanied by shifts in effort allocation. More generally, this work provides further support for a dorsal/ventral divide in decision-making, with dorsal prefrontal regions recruited when decision costs are incurred on the individual (e.g. physical, cognitive effort), and orbitofrontal cortices involved when costs are inherent to the outcome itself (e.g. delay, risk).

Disclosures: M. Silveira: None. **S. Wittekindt:** None. **C.A. Winstanley:** F. Consulting Fees (e.g., advisory boards); Shire.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.16/BBB11

Topic: H.01. Animal Cognition and Behavior

Support: Research Center Program of Institute for Basic Science (IBS-R002-G1)

National Research Foundation Grant (NRF-2016- Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program (South Korea)

Title: Differential coding of reward and movement information in the striatal direct and indirect pathways

Authors: *J. SHIN[1], D. KIM[2], M. JUNG[1]
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Abstract: To better understand striatal neural processes underlying reward-based learning and movement control, we examined the responses of D1 and D2 medium spiny neurons (MSNs) in the -dorsomedial striatum of mice performing a probabilistic Pavlovian conditioning task. These neurons, which are components of the direct and indirect pathways, respectively, showed diverse arrays of reward- and tongue movement-related activity, but with quantitative differences. D1 and D2 MSNs tended to increase and decrease activity as a function of reward value, respectively, suggesting striatal value representation by relative activity levels between D1 and D2 MSNs. D1 MSNs increased activity more strongly than D2 MSNs in association with lick offset, suggesting the involvement of D1 MSNs in suppressing licking behavior. In addition, rapid responses to negative outcome and previous reward signals were stronger among D2 than D1 MSNs, suggesting stronger contributions of D2 MSNs to outcome-dependent behavioral adjustment. These findings provide new insights into striatal neural circuit operations underlying reward-based learning and movement control.

Disclosures: J. Shin: None. **D. Kim:** None. **M. Jung:** None.

Poster

240. Animal Cognition and Behavior: Decision Making: Corticolimbic Circuits

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 240.17/BBB12

Topic: H.01. Animal Cognition and Behavior

Support: Institute for Basic Science Grant (IBS-R002-G1)
National Research Foundation Grant (NRF-2014-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program)
National Research Foundation Grant (NRF-2016-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program)

Title: Different contributions of somatostatin- and parvalbumin-expressing neurons to flexible representation of task variables in rodent prefrontal cortex

Authors: *H. JEONG[1,3], D. KIM[2,3], M. JUNG[1,2,3]
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Technol., Daejeon, Korea, Republic of; [3]Ctr. for Synaptic Brain Dysfunctions, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Neurons in the prefrontal cortex (PFC) are selectively responsive to variables that are relevant to a task at hand. To investigate how different interneuron subtypes contribute to such flexible representation of task variables, we examined discharge characteristics and inactivation effects of somatostatin (SOM)- and parvalbumin (PV)-expressing neurons in the mouse medial PFC during a probabilistic classical conditioning task. SOM neurons showed strong cue-related activity predicting an upcoming reward or punishment, and its inactivation suppressed cue-related, but not outcome-related, activity of nearby pyramidal neurons. By contrast, PV neurons showed strong outcome- and cue-related responses after outcome delivery, and its inactivation suppressed both cue- and outcome-dependent responses of pyramidal neurons after, but not before, trial outcome. In addition, inactivation of PV, but not SOM, neurons delayed reversal of cue-related responses in neighboring pyramidal neurons when cue-outcome contingency was reversed. These results suggest different contributions of SOM and PV neurons to maintaining significant sensory information and evaluating trial outcome in reference to expected outcome.

Disclosures: H. Jeong: None. **D. Kim:** None. **M. Jung:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.01/BBB13

Topic: H.01. Animal Cognition and Behavior

Support: Barncancerfonden
Sven-Olof Jansons livsverk
Linnea & Josef Carlssons stiftelse

Title: A rodent model of cognitive deficits induced by radiation to the growing brain

Authors: S. BARRIENTOS[1], J. SJÖBOM[1], *P. PETERSSON[1,2]
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Abstract: Progressive cognitive decline is a chronic side-effect of radiotherapy in brain cancer patients, especially in those treated during childhood. Major cognitive disabilities after cranial radiation arise from damage to, among other structures, the prefrontal cortex (PFC) and the hippocampus, whose connectivity is thought to be critical for different memory functions. To investigate how early age radiation-induced injury to these circuits affects memory performance in adulthood, we have here developed and initially evaluates, a model in which 21 days-old rat pups (n=60) received cranial radiation to either the whole brain or focused on the PFC or

hippocampus. After two months, both irradiated and sham treated rats were tested in a novel object recognition (NOR) task and in an object location recognition (OLR) task. In this initial behavioral screen, no significant effects were observed between radiation groups in the NOR task, while the OLR task indicated differences between irradiated groups and sham controls. Thus, suggesting that cranial radiation does not impair recognition memory for objects *per se* but for object-place associations. To investigate the functional shortcomings in the PFC-hippocampus circuits of the adult brain following early age cranial radiation in further detail we next used large-scale multisite neurophysiological recordings while the animals were challenged to solve a delayed non-match to sample task in a T-maze. In particular, functional connectivity in the PFC-hippocampus circuits under high working-memory demands were analyzed with respect to neuronal synchronization and correlated with behavioral performance in the task.
Taken together, we here present a rodent model that allows us to apply both behavioral and neurophysiological experimental approaches to study cognitive dysfunction of the irradiated brain. A better understanding of the mechanisms that underlie the cognitive decline in cancer patients following radiotherapy will be an important first step towards improving the existing procedures and rehabilitation efforts.

Disclosures: S. Barrientos: None. **J. Sjöbom:** None. **P. Petersson:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.02/BBB14

Topic: H.01. Animal Cognition and Behavior

Support: Japan Society for the Promotion of Science, KAKENHI, Grant Numbers 17H02088

Title: The effects of embolism induced by varied particle number of microsphere on motor and cognitive functions and parkinsonism

Authors: *N. HIMI[1], N. OKABE[1], E. M. NAKAMURA[1], H. TAKAHASHI[2], N. HAYASHI[1], I. SAKAMOTO[1], T. KOGA[2], Y. YOSHIMI[3], O. MIYAMOTO[1]
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Abstract: [Introduction] The cerebrovascular embolism (CE) could induce multiple microinfarction, resulting in cognitive dysfunction like the vascular dementia (VD). However, the suitable animal model representing multiple microinfarction is not established in VD and vascular parkinsonism. In this study, we proposed the novel rat CE model that exhibit VD-like memory dysfunction induced by microsphere (MS) administration. We have the relationship between MS particle number and various outputs including histological and behavioral

changes.[Methods] CE were induced by MS (from 2,500 to 4,000 particles) injection into right internal carotid artery of rats with measurement of cerebral blood flow (CBF). The pathological output including motor functions (physical deficit score and rotarod) and cognitive functions (Morris water maze) were observed. Moreover, the effect of MS on progression of parkinsonism was also studied using 6-hydroxydopamine model rats. The progression of parkinsonism was evaluated by apomorphine-induced rotation and density of tyrosine hydroxylase (TH) positive neurons in substantia nigra (SN).[Results**]** MS injection dose-dependently aggravated the motor functions (score and rotarod) and the memory function (MWM), decreased CBF in both hippocampus and cortex, and exacerbated PD like symptoms (turning behavior and loss of TH positive neurons at SN). Especially, the injection of 3,000 particles of MS decreased in CBF (76.2 ± 6.7 % to control) at hippocampus and induced memory dysfunction without motor dysfunction. Therefore, 3,000 particles of MS injected rat would be more appropriate as a VD model.
[Conclusion] MS injection dose-dependently induced memory and motor dysfunction, and accelerated the progression of PD.

Disclosures: N. Himi: None. **N. Okabe:** None. **E.M. Nakamura:** None. **H. Takahashi:** None. **N. Hayashi:** None. **I. Sakamoto:** None. **T. Koga:** None. **Y. Yoshimi:** None. **O. Miyamoto:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.03/CCC1

Topic: H.01. Animal Cognition and Behavior

Support: SABA Innovative Student Dissertation Grant
NIGMS T32 GM081741
WVU Department of Psychology

Title: Differential effects of d-amphetamine and atomoxetine on risk-based decision making of Lewis and Fischer 344 rats

Authors: *J. OZGA, C. VONDER HAAR, K. G. ANDERSON
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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is associated with deficits in risk-based decision making, in which individuals with ADHD tend to make riskier choices as compared to control participants. Risk-based decision-making is assessed commonly by using probabilistic-discounting procedures. One common treatment for ADHD, *d*-amphetamine, increases risk-taking of rats on these procedures while atomoxetine, an alternative ADHD

medication, has produced mixed effects. Results from previous studies with rats may result from genetic or neurochemical factors. Lewis (LEW) and Fischer 344 (F344) rats have neurochemical differences that may be relevant to risk-based decision-making and how drugs affect such behavior. Thus, the purpose of the current study was to evaluate dose-dependent effects of *d*-amphetamine and atomoxetine on probabilistic discounting of LEW and F344. Male LEW and F344 chose between one food pellet delivered 100% of the time and three food pellets delivered following decreasing probabilities of delivery (i.e., 100%, 66.7%, 33.3%, 16.5%, and 8.25%). Following establishment of stable baseline choice, saline, *d*-amphetamine (0.1 - 1.8 mg/kg), and atomoxetine (0.1 - 7.8 mg/kg) were tested acutely. Following a three-week "wash-out" period, rats were sacrificed by live decapitation and brains were punched for the following tissue sections: locus coeruleus, hippocampus, frontal cortex, and striatum. Subsequently, Western Blot was used to quantify dopamine and norepinephrine transporter densities in these regions. LEW and F344 did not differ in choice at baseline. *d*-Amphetamine increased risky choice for both rat strains at low-to-moderate doses, although it did so at a lower dose (0.1 and 0.3 mg/kg) for F344 as compared to LEW (0.3 mg/kg only). At high doses (1.0 and 1.8 mg/kg), *d*-amphetamine produced an overall disruption in choice patterns, increased frequency of omitted trials, and reduced reinforcer magnitude sensitivity. Atomoxetine had no effect on any outcome measures for either rat strain. Although LEW and F344 differ on tasks assessing motor and choice impulsivity, with LEW being the more impulsive of the two, the present results suggest that LEW and F344 do not differ in global measures of risk-based decision-making. Effects of *d*-AMP on risk-based decision may be biology-dependent and given the absence of effects, atomoxetine may be an attractive alternative to stimulant medications for ADHD.

Disclosures: J. Ozga: A. Employment/Salary (full or part-time):; West Virginia University. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Society for the Advancement of Behavior Analysis Innovative Student Dissertation Grant. **C. Vonder Haar:** None. **K.G. Anderson:** A. Employment/Salary (full or part-time):; West Virginia University.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.04/CCC2

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01MH099660
NIH R01DC015776
NIH R21HD053114
NIH U54HD090260

Title: Tbx1 is a 22q11.2 gene that affects cognition, dendritic spine density and D2 receptor in the medial prefrontal cortex in mice

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Abstract: Hemizygous deletion of human chromosome 22q11.2 is associated with elevated rates of intellectual disability (ID), schizophrenia and autism spectrum disorder (ASD). However, how more than 40 protein-coding 22q11.2 genes contribute to diverse neuropsychiatric disorders is still poorly understood. *Tbx1* is one of the candidate 22q11.2 driver genes. There are cases of *TBX1* mutations associated with ASD and ID in humans, but those carriers also have other gene mutations and variants. In mice, *Tbx1* heterozygosity alone alters neonatal social communication, adult social cognition and working memory. To further delineate the degree to which Tbx1 contributes to developmental neuropsychiatric disorders, we examined dimensions of these mental illnesses in mice. We tested behavioral dimensions in the attentional set shifting (wild-type (WT), n=7; heterozygous (HT), n=6), acoustic prepulse inhibition (WT, n=20; HT, n=28), non-acoustic prepulse inhibition (WT, n=29; HT, n=42), working memory in the T-maze (WT, n=13; HT, n=13) and reference memory in the Morris water maze (WT, n=14; HT, n=14) at 2 months of age. We used qRT-PCR to examine mRNA levels of dopamine receptor subtypes in the medial prefrontal cortex (mPFC) and tyrosine hydroxylase (TH), a synthetic enzyme of dopamine, in the midbrain of congenic *Tbx1* heterozygous (n=8) and wild-type (n=8) littermates at 2 months of age. Moreover, we applied Cre plasmid (1 μg/μl) and loxP-STOP-GFP plasmid (1μg/μl) by *in utero* electroporation at E15.5 to induce *Tbx1* heterozygosity in layers 2/3 neurons in the mPFC of $Tbx1^{flox/+}$ mice, and evaluated the density of dendritic spines at postnatal days 21-23 (n=19 dendrites in 11 sections of three WT mice; n=62 dendrites in 13 sections of four HT mice). Our data show that *Tbx1* heterozygosity reduced levels of cognitive flexibility in the attentional set shifting, sensorimotor gating in acoustic prepulse inhibition, working memory in the T-maze and acquisition of hippocampus-dependent reference memory in the Morris water maze (all $P<0.05$); no detectable effect was seen in non-acoustic prepulse inhibition, maintenance of hippocampal-dependent reference memory, or striatum-dependent reference memory. In the mPFC of *Tbx1* heterozygous mice, D2 (but not D1 or D5) receptor mRNA was selectively reduced (all $P<0.05$) without a concomitant change in mRNA levels of TH. The density of dendritic spines was increased after cell-specific induction of *Tbx1* heterozygosity in layers 2/3 neurons in the mPFC ($p<0.01$). Our data identify the effects of *Tbx1* heterozygosity on a select set of cognitive, neuronal and synaptic dimensions relevant to developmental neuropsychiatric disorders.

Disclosures: T. Hiramoto: None. **S. Enomoto:** None. **T. Takahashi:** None. **T. Izumi:** None. **G. Kang:** None. **S. Tanaka:** None. **K. Okumura:** None. **D. Ikawa:** None. **K. Ye:** None. **A. Hishimoto:** None. **K. Tanigaki:** None. **H. Ohba:** None. **B. Morrow:** None. **R. Sharp:** None. **M. Geyer:** None. **M. Makinodan:** None. **T. Yoshikawa:** None. **S. Okabe:** None. **N. Hiroi:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.05/CCC3

Topic: H.01. Animal Cognition and Behavior

Support: Top talent, Donders Centre for Medical Neuroscience
NWO VICI 453-04-002
Investissements d'Avenir ANR-10-IAIHU-06
ANR-11-INBS-0011 (NeurATRIS)
Dutch Top Institute Pharma T5-209

Title: Neurobiological basis of prefrontal cognitive dysfunction in a rat model for schizophrenia

Authors: *D. MAAS[1,2], V. EIJSINK[3], J. VAN HULTEN[3], L. PAVLIDI[3], M. VLASSOPOULOU[3], P. DE WEERD[4], J. R. HOMBERG[5], A. VALLÈS[3,4], B. NAIT-OUMESMAR[6], G. MARTENS[3]
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Abstract: Cognitive dysfunction is implicated in multiple psychiatric disorders, including schizophrenia (SZ), and thought to arise from prefrontal cortex (PFC) dysfunction. Here we found PFC-dependent cognitive impairment in a rat model for SZ and revealed the neurobiological sequence of events causing this impairment. The APO-SUS rat line, which is selectively bred based on hyperactivity upon apomorphine injection, shows without genetic or pharmacological intervention similarities with SZ patients on behavioural, endocrinological and neurobiological level. In this rat line, we revealed, using transcriptomic analysis, decreased expression of genes related to the metabolism of the antioxidant glutathione in the medial (m)PFC. Levels of glutathione itself were also found to be significantly lower in the mPFC of the APO-SUS rats. Oligodendrocyte progenitor cells (OPCs) are extremely vulnerable to oxidative stress caused by decreased levels of glutathione, and we indeed identified a reduced proliferation and differentiation of OPCs in the APO-SUS mPFC. This was accompanied by a decrease in

myelinated axon number and caliber, but no active demyelination was observed, indicating neurodevelopmental hypomyelination. Furthermore, the expression patterns of glutathione-related genes were altered from birth onwards, while myelin-related gene expression was decreased only from post-natal day 28 onwards. We conclude that oxidative stress leads to defective OPC maturation and hypomyelination, contributing to prefrontal cognitive dysfunction in SZ, a finding with relevance for other psychiatric disorders.

Disclosures: D. Maas: None. **V. Eijsink:** None. **J. van Hulten:** None. **L. Pavlidi:** None. **M. Vlassopoulou:** None. **P. De Weerd:** None. **J.R. Homberg:** None. **A. Vallès:** None. **B. Nait-Oumesmar:** None. **G. Martens:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.06/CCC4

Topic: H.01. Animal Cognition and Behavior

Title: Prior cocaine self-administration disrupts reward prediction error signaling by rat dopamine neurons

Authors: *Y. K. TAKAHASHI, T. A. STALNAKER, Y. MARRERO-GARCIA, R. M. RADA, G. SCHOENBAUM
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Abstract: Midbrain dopamine neurons have been shown repeatedly to signal errors in reward prediction. We have previously shown that inputs from orbitofrontal cortex and ventral striatum contribute critically to the computation of reward prediction errors by dopamine neurons in rat ventral tegmental area (VTA). Since prior use of cocaine causes changes in processing of expected outcomes in orbitofrontal cortex and ventral striatum, cocaine may thereby affect dopaminergic error signaling. Here we tested this hypothesis by recording from putative dopamine neurons in VTA from rats after self-administration of either cocaine or sucrose. Recordings were made in a simple odor-guided choice task, which we have used previously to demonstrate prediction error signals in rat dopamine neurons. In this task, different odor cues signal that a sucrose reward is available in one of two nearby fluid wells. During recording, we independently manipulated the timing or size of reward across blocks of trials to induce both positive and negative reward prediction errors. Consistent with our prior work in this task, dopamine neurons in control rats (sucrose-experienced or naïve) exhibited robust error signals; activity in both single units and across the population showed a phasic increase to an unexpected reward and this firing declined with learning. After learning, the same neurons also suppressed firing upon omission of an expected reward and showed phasic activity to the predictive cues that differed according to their value. By contrast, dopamine neurons recorded in rats that had

self-administered cocaine failed to suppress firing when an expected reward was omitted. In addition, these neurons also exhibited lower amplitude and imprecisely timed increase in firing on delivery of an unexpected reward and failed to show changes in firing to reward predictive odor cues. These results are similar to the effects of orbitofrontal and, to a lesser extent, ventral striatal lesions on dopaminergic error signaling. Thus, they provide a mechanism where by drug-induced effects on the processing of expected outcomes in prefrontal and striatal regions may disrupt learning.

Disclosures: Y.K. Takahashi: None. **T.A. Stalnaker:** None. **Y. Marrero-Garcia:** None. **R.M. Rada:** None. **G. Schoenbaum:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.07/CCC5

Topic: H.01. Animal Cognition and Behavior

Support: NHMRC-ARC Dementia Research Development Fellowship

Title: Clinically relevant attention phenotypes in the R451C Neuroligin 3 mouse model of autism spectrum disorder

Authors: *E. L. BURROWS, C. MAY, T. HILL, J. LETSCHERT, A. J. HANNAN
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Abstract: Autism Spectrum Disorder (ASD) is characterized by social communication impairments and repetitive and restrictive behavior. One of the earliest identifiable features of ASD is altered attention, which may underlie the development of these core traits. Mice expressing the ASD-associated R451C mutation in the gene coding for the synaptic adhesion protein Neuroligin-3 (NL3) exhibit impaired reciprocal social interactions as well as repetitive and restrictive behaviors. Attention has not been scrutinized in this mouse model. Attention was assessed in $NL3^{R451C}$ mice using two well-established tasks in automated touchscreen chambers. In the 5-choice serial reaction task (5CSRT), rodents were trained to attend to touchscreen stimuli that appear in any one of 5 locations. In the continuous-performance test (CPT), animals were required to discriminate, and identify a visual target pattern over multiple distractor stimuli. In both tasks, $NL3^{R451C}$ mice displayed enhanced ability to attend to stimuli when task-load was low, but a reduced attentional ability when task difficulty was increased. NL3 mice also displayed high distractibility leading to reduced task participation and fewer impulsive responses. Although attentional deficits are frequently reported in clinical autism, this is the first time an ASD-associated gene mutation has been demonstrated to cause an attentional phenotype. The verification of these specific behavioral differences relevant to the symptoms of ASD further

advances the translational validity of the $NL3^{R451C}$ mouse and provides a model for future study into the causes and treatment of ASD and its co-morbid complications

Disclosures: C. May: None. **T. Hill:** None. **J. Letschert:** None. **A.J. Hannan:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.08/CCC6

Topic: H.01. Animal Cognition and Behavior

Title: Impaired learning performance and decreased hippocampal c-Fos expression in the spontaneously hypertensive (SHR) rat following exposure to an altered light-dark cycle

Authors: *S. S. JACKVONY[1], S. TRAN[1], K. ELISMAN[1], P. CACKOVIC[1], A. F. SCHROEDER[2], E. ANDERSON[1], I. LAMPTEY[1], V. DUSZAK[1], J. A. SCHROEDER[1]
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Abstract: The Spontaneously Hypertensive Rat (SHR) has been defended as having face, construct and predictive validity as an animal model of attention deficit hyperactivity disorder (ADHD). In addition to developing inattentiveness and hyperactivity at 3-4 weeks of age, SHR rats display impaired performance on a variety of learning and memory tasks. Methylphenidate has been shown to be effective in attenuating ADHD-like behavior and improving spatial learning and memory performance in SHR rats. The shift in circadian rhythms during adolescence combined with the demands of typical academic scheduling, particularly school start times, means that sleep time is often compromised in teen students. It is clear that a shortened sleep cycle can significantly impact performance on attentional tasks, especially in children diagnosed with ADHD. This study examined the effects of a chronic (3 week) shortened light cycle (8 hr light/16 hr dark or 6 hr light/18 hr dark) on spatial and object recognition learning performance in SHR and Sprague Dawley rats. While there was no difference in Morris Water maze performance between strains, SHR rats displayed impairments in the Novel Object Recognition task. Methylphenidate administration during learning acquisition did not affect learning performance in either strain. Immunohistochemical measurement of hippocampal c-Fos expression revealed that SHR rats had significantly fewer c-Fos positive cells compared to Sprague Dawleys. These results further validate the SHR model of ADHD and add to the understanding of the effects of a shortened sleep cycle on attention and learning.

Disclosures: S.S. Jackvony: None. **S. Tran:** None. **K. Elisman:** None. **P. Cackovic:** None. **A.F. Schroeder:** None. **E. Anderson:** None. **I. Lamptey:** None. **V. Duszak:** None. **J.A. Schroeder:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.09/CCC7

Topic: H.01. Animal Cognition and Behavior

Support: BrainsCAN Accelerator Program
Weston Brain Institute

Title: Assessing cognitive dysfunction in the M83 alpha-synuclein mouse model of Parkinson's disease using automated touchscreen tasks

Authors: R. FRANCO, I. PINEDA, J. JOVIANO-SANTOS, M. COWAN, S. KOUCHEHBAGH, J. RYLLET, T. BUSSEY, L. SAKSIDA, V. PRADO, M. PRADO, *F. H. BERALDO
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Abstract: Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder after Alzheimer's disease. PD was initially characterized as a motor disease; however, cognitive impairment has become increasingly recognized as an import component of PD physiopathology. In fact, deficits in executive function and other aspects of cognition such as memory, attention and cognitive flexibility occur in 50-60% of PD patients, even before the onset of classical motor symptoms. Alpha-synuclein (α-syn) is a major player in PD and individuals with increased α-syn gene copy numbers or PD-related mutations present cognitive alterations. However, robust and comprehensive assessment of executive function in PD α-synucleinopathy mouse models is lacking. In this study, we used the automated and translatable touchscreen technology to determine executive function in the α-syn PD mouse model M83. It has been reported that Homozygous (HOM) M83 mice show α-syn pathology at 7 months and motor impairments at 10 months of age. We evaluated potential early motor impairments and observed that HOM M83 mice (5 months of age) presented increased locomotor activity compared to control mice, but no major differences were observed in wire hang and grip strength when compared to controls. Attention and cognitive flexibility were also assessed in M83 mice in the Five Choice Serial Reaction Time Task (5-CRSTT) and Pairwise Visual Discrimination (PVD) and reversal tasks. At 5-6 months of age HOM mice did not show any attention deficits in the 5-CRSTT. Interestingly, in PVD M83 HOM mice, 5-6 months of age, could learn the task but were impaired in the reversal learning suggesting that these mice present deficits in cognitive flexibility. This work provides an initial assessment of executive function in a mouse model of PD. These results and the evaluation of other mouse models of neurodegenerative diseases in touchscreen tasks will be deposited into an open-access database allowing for storage, searching and re-analysis of touchscreen data. Ultimately, the comparison of high-level of cognition

amongst different PD mouse models and other mouse models of neurodegeneration may provide a combination of tests for early evaluation of therapeutic approaches to improve specific cognitive deficits in neurodegenerative diseases.

Disclosures: R. Franco: None. **I. Pineda:** None. **J. Joviano-Santos:** None. **M. Cowan:** None. **S. Kouchehbagh:** None. **J. Ryllet:** None. **T. Bussey:** None. **L. Saksida:** None. **V. Prado:** None. **M. Prado:** None. **F.H. Beraldo:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.10/CCC8

Topic: H.01. Animal Cognition and Behavior

Support: APU Faculty Research Council Grant

Title: Executive functions in agenesis of the corpus callosum: Spatial working memory and sustained attention in the BTBR inbred mouse strain

Authors: F.-W. M. HSU, B. HERD, *L. A. MARTIN
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Abstract: Agenesis of the corpus callosum (AgCC) is a rare congenital condition characterized by the complete or partial absence of the corpus callosum. The goal of our study was to examine executive functioning in mice with AgCC. We compared the BTBR T+tf/J (BTBR) strain with AgCC to the C57BL/6J (B6) strain with an intact corpus callosum. Spatial working memory was assessed utilizing a delayed matching-to-position (DMTP) task, and sustained attention was tested with an operant task requiring mice to distinguish between signal and nonsignal stimuli. Both tasks required operant conditioning and discrimination between learned associations with two retractable levers. In the DMTP task, mice were trained to press one of two levers to receive liquid reinforcement, followed by a variable time delay, and then a choice phase between the two levers to receive the reinforcement. In the sustained attention operant task, the mice had to press the left lever following a signal event (a variable flash of light) and the right lever following a nonsignal event to receive a food reward. AgCC was confirmed via histological analysis. Interestingly, a subset of BTBR mice could not learn the associations which may be linked to variable loss of the hippocampal commissure. We found that both the BTBR and B6 groups demonstrated a predictable decline in performance as the time delays increased, but no significant differences in choice accuracy were found between the two strains on the DMTP task. We also found a predictable increase in accuracy as the length of stimulus light increased for both strains, but no significant differences in the level of function between the two strains on the

sustained attention task. Overall, the results from the DMTP and sustained attention tasks indicate that complex executive functions may not be impacted by AgCC.

Disclosures: F.M. Hsu: None. **B. Herd:** None. **L.A. Martin:** None.

Poster

241. Animal Cognition and Behavior: Executive Function: Models of Disorders

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 241.11/CCC9

Topic: H.01. Animal Cognition and Behavior

Support: UHD HIP Grant
UHD ORCA Grant

Title: A new user-friendly open-source fly tracker to study attention deficient hyperactivity disorders in *Drosophila melanogaster*

Authors: T. MCKENZIE, S. GUTIERREZ, J. GONZALEZ, *Y. KANG
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Abstract: Alterations in animal locomotive behaviors are important landmarks to study psychiatric disorders like Attention Deficit Hyperactivity Disorders (ADHD). These locomotive behaviors can be captured with video tracking software ranging from commercially available Ethovision to Ctrack, an open source software which requires Mathlab. In our lab, we have developed a user friendly Graphic User Interface (GUI) tracking algorithm to analyze single fly movements with behavioral outputs, using computer vision. We then applied this tool to study several locomotive phenotypes such as travel distance, velocity, wall preference in an open arena in the following ways. 1) We were able to validate the tool by comparing the behaviors of wild type and ADHD mutant flies from our software and those from Ethovision. 2) We explored the possible link between diet and ADHD and found that flies developed hyperactivities when bred on high sugar/low yeast diets, but not on high sugar/high yeast or low sugar/low yeast diet. Flies fed on the same diet right after hatching did not develop the same locomotive phenotypes and the phenotype was not affected by mutations in *DAT1*, encoding for the dopamine transporter involved in modulating the level of dopamine in neurons. Therefore, the hyperactivity effect by the high sugar diet was probably developmental rather than modulation of neural activities by high sugar, consistent with human studies which suggested epigenetic modification caused by prenatal diets are associated with ADHD. Taken together, we have established a new user-friendly and open source tool to study ADHD in flies and this tool can be suitable for both research and educational purposes.

Disclosures: T. McKenzie: None. **S. Gutierrez:** None. **J. Gonzalez:** None. **Y. Kang:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.01/CCC10

Topic: H.01. Animal Cognition and Behavior

Support: Grants-in-Aid Scientific Research on Innovative Areas (Y.I., JP26112005)
the Supported Program for the Strategic Research Foundation at Private Universities (M.K., Y.S., Y.I.) from MEXT
Brain/MINDS (M.K, Y.S., Y.I.) from AMED
JST-CREST (JPMJCR1751)

Title: Reactive inhibition correlates with only trial-based but not block-based proactive inhibition

Authors: *J. YOSHIDA, S. SOMA, Y. SAKAI, Y. ISOMURA
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Abstract: In our daily life, we inhibit our behavior according to situations (behavioral inhibition). It is known that we utilize various types of behavioral inhibition. Reactive inhibition is stopping a reaction according to the present external signal. Proactive inhibition is retarding reaction start depended on the circumstance changes. Some of previous studies suggest possibilities that these different types of behavioral inhibition share the same neuronal mechanism, however, no single theory has not been accepted. As the first step to approach the issue, we conducted stop-signal task for head-restrained rats by using a spout-lever and examined behavioral correlation among the multiple behavioral inhibition (64 sessions in nine male Long-Evans rats). In our stop-signal task, rats had to respond to a go cue as quickly as possible (go trial). On the other hand, they did not have to respond if a stop cue followed the go cue (stop trial). The task alternated between a block of only go trials (G-block) and a block of go and stop trials (GS-block). By measuring the spout-lever movement after stop cue presentation, we directly evaluated reactive inhibition performance in the stop trials. Besides, we observed block- and trial-based proactive inhibition as delay of reaction time in go trials. The former was found in long-term circumstance changes of comparison between go trials in G- and GS-block. On the other hand, the latter was observed in shorter-term circumstance changes of comparison between go trials following go and stop trials. We tested behavioral correlation among the three types of inhibition. In the beginning, we checked about the two proactive inhibition. They did not show any correlation (Pearson's correlation, $r = 0.086$, $p = 0.499$) even though their inhibition styles of retarding reaction start are very similar. Subsequently, we confirmed correlation between reactive and proactive inhibition. Reactive inhibition significantly correlated with trial-based proactive inhibition ($r = -0.328$, $p = 0.008$), however, did not correlate with block-based

proactive inhibition (r = -0.010, p = 0.935). Our data suggests that reactive and trial-based proactive inhibition may share the similar neuronal mechanism, but block-based proactive inhibition may be regulated by a unique neuronal mechanism.

Disclosures: J. Yoshida: None. **S. Soma:** None. **Y. Sakai:** None. **Y. Isomura:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.02/CCC11

Topic: H.01. Animal Cognition and Behavior

Support: FEDER through the Competitiveness Factors Operational Programme (COMPETE)
Foundation for Science and Technology (FCT), project POCI-01-0145-FEDER-007038
Foundation for Science and Technology (FCT), project PTDC/NEU-SCC/5301/2014
Foundation for Science and Technology (FCT), grant SFRH/BD/52291/2013
Foundation for Science and Technology (FCT), grant SFRH/BD/109111/2015
Foundation for Science and Technology (FCT), grant PDE/BDE/113602/2015
Foundation for Science and Technology (FCT), grant SFRH/BPD/80118/2011

Title: Prefrontal-striatal functional encoding of impulsivity - A brief (3 seconds) history of brain time

Authors: *M. ESTEVES[1,2], A. M. CUNHA[1,2], J. REIS[1,2], A. ALMEIDA[1,2], N. SOUSA[1,2], H. LEITE-ALMEIDA[1,2]
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Abstract: Impulsivity is an adaptive response allowing fast reaction to stimuli. However, its dysregulation is associated with disorders such as substance abuse or attention deficit/hyperactivity disorder (ADHD). Several prefrontal and subcortical areas are known to play a relevant role in response inhibition. How these areas interact across the temporal window preceding the execution of timed vs premature actions is yet to be described.
We have therefore assessed local field potentials (LFPs) bilaterally in frontal and striatal areas: prelimbic and orbital prefrontal (OPF) cortices, caudate and nucleus accumbens (NAcc) during performance of the Variable Delay-to-Signal (VDS) task. During training, the animals learn that nosepoking in an orifice while its light is on is considered a timed response and is rewarded with a sugar pellet, while nosepokes performed within the 3 s delay before the light turning on are considered premature and punished with a timeout. The number of premature responses at the end of training is associated with action impulsivity.

We determined that all these regions play a role in behavioral inhibition at specific time frames up to 3 seconds before the response (timed or premature). Three to 2 seconds before a nosepoke, all left regions, as well as the right NAcc, associate with the type of response (i.e. show different activation before a timed or a premature response). Interaction of this left lateralized network with the right hemisphere then culminates with differential activation of the right OPFC immediately before the response.
In conclusion, brain activity in the studied network is markedly different in the temporal window preceding timed and premature responses. Evidence of behavioral (dis)inhibition can be found up to 3 seconds before the actual response and evolves in a time- and hemisphere-specific fashion.

Disclosures: M. Esteves: None. **A.M. Cunha:** None. **J. Reis:** None. **A. Almeida:** None. **N. Sousa:** None. **H. Leite-Almeida:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.03/CCC12

Topic: H.01. Animal Cognition and Behavior

Support: NIH R21MH110678

Title: Prefrontal dopamine D2 signaling controls aggressive behaviors in mice

Authors: *B. XING, N. MACK, W.-J. GAO
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Abstract: Prefrontal cortex (PFC) has been recognized as a critical brain region executing top-down control of social behaviors such as aggression. However, the mechinisms of this regulation are unknown. Here, we found a role for dopamine D2 receptor (DRD2)-expressing neurons in the mPFC in the aggressive behaviors. Compared with the mice exhibiting normal social interaction in resident-intruder test, DRD2 signaling is upregulated in the PFC from the aggressive mice. Repeated exposure to social stimuli increases c-fos induction in the DRD2-expressing cells but not DRD1-expressing cells in the mPFC from aggressive mice. Interesingly, blockade of DRD2-expressing neuronal activity by inhibitory DREADD increases aggressive behaviors without affecting anxiety levels and locomotor activity, whereas optogenetic activation of these neurons suppresses aggressive bursts and reduces the intensity of aggressive behaviors, but does not change the duration of the aggressive bursts. We also evlaluate the effect of prefrontal DRD2 inhition in three-chamber test, habituation-dishabituation test and tube test to assess the social motivation, social recognition and social hierarchy, respectively. Moreover, optogenetic activiation of prefronal-central amygdala (CeA) prejections is sufficient to swich

“aggressive” mouse to “social” mouse, recapitulating the effects of mPFC DRD2 activation. These results suggest that the prefrontal D2 signaling regulate intermales aggression through connections with amygdala.
Supported by NIH R21MH110678 to W. J. Gao

Disclosures: B. Xing: None. **N. Mack:** None. **W. Gao:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.04/CCC13

Topic: H.01. Animal Cognition and Behavior

Support: Bumpus Foundation Fellowship
NIH grant R01NS106822

Title: Causal role for the subthalamic nucleus in interrupting cognition

Authors: *J. HESTON[1], M. BAQAI[2], N. BAVAFA[2], A. R. ARON[3], T. S. HNASKO[4]
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Abstract: Activity in the subthalamic nucleus (STN) increases inhibitory output from the basal ganglia and has long been hypothesized to have an anti-kinetic function, suppressing both ongoing and incipient behaviors. Indeed, much literature is consistent with a central role for the STN in interrupting action by suppressing motor commands in response to stop signals or unexpected events (UE). Recent evidence from human studies further suggests that unexpected events also recruit STN to interrupt cognition, thereby freeing animals to attend to new information. However, there has been no causal evidence demonstrating that STN activity is capable of interrupting cognitive function. Here we address this using optogenetics to activate or inhibit mouse STN during a cognitive task. We develop a delayed match to position task that requires mice to hold an action plan across a variable delay period and show that performance in this task decays with increasing delay length. Brief optogenetic activation of the STN during this delay impairs performance, providing evidence that STN activity is sufficient to decrement performance on a cognitive assay of working memory and goal maintenance. Finally, to test the necessity of STN activity in interrupting cognition we introduce a UE during the delay. Similar to ChR2-activation of the STN, introduction of a UE impairs performance in this task, and we test whether inhibiting the STN during UE presentation mitigates this effect.

Disclosures: J. Heston: None. **M. Baqai:** None. **N. Bavafa:** None. **A.R. Aron:** None. **T.S. Hnasko:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.05/CCC14

Topic: H.01. Animal Cognition and Behavior

Title: Serotonin 5HT1A activation causes strong biphasic effects in a model of waiting impulsivity in rats

Authors: *M. L. GROFT[1], P. R. NICKLAS[1], N. J. PISTORY[1], P. J. MCLAUGHLIN[2]
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Abstract: The serotonin $5HT_{1A}$ receptor exists both as an inhibitory autoreceptor in raphe nuclei, and also postsynaptically in various cortical regions. Activation of the autoreceptor reduces serotonergic tone, because this receptor provides potassium-dependent inhibitory feedback. This population of $5HT_{1A}$ may be relevant in anxiety, and in the efficacy of antidepressants. In contrast, postsynaptic $5HT_{1A}$ are highly expressed in cortex, amygdala, and hippocampus. These may mediate impulsivity and are abnormally expressed in suicide attempters. While the $5HT_{1A}$ receptor has been studied in animal models of impulsivity, this distribution would indicate a biphasic dose-response curve in impulsive-like behavior, with greater impulsivity reflecting decreased serotonergic tone, mediated by autoreceptor activity. This would be followed by a performance improvement, as a function of dose. We characterized effects of systemic administration of $5HT_{1A}$ ligands on the paced Variable Consecutive Number with Discriminative Stimulus (VCN-S_D) task in male rats. This task was developed to model waiting impulsivity without possible cognitive confounds. Animals initiated chains of responses on one operant lever, which retracted after each press, until a criterion was reached that varied between trials. A tone (S_D) indicated that reinforcement was available via a single response on another lever. Premature responding reset the chain at zero. The main performance measure was percentage of completed chains. Due to the S_D and variable criteria, the VCN-S_D is not dependent upon working memory, timing, or counting processes, and is not sensitive to the anticholinergic drug scopolamine. The $5HT_{1A}$ agonist 8-OH-DPAT impaired accuracy at the lowest dose (0.0125 mg/kg), but higher doses improved performance. In fact, the highest dose tested (0.1 mg/kg) produced perfect performance in all animals (Exp. 1). In contrast with previous research, the antagonist WAY 100,635 had no effect per se (Exp. 2), but reversed effects of 8-OH-DPAT (Exp. 3). These results help reconcile disparate findings about the $5HT_{1A}$ receptor and impulsivity. Future work is needed to elucidate the interaction of impulsivity and anxiety over a wide dose range of drugs that target this receptor.

Disclosures: M.L. Groft: None. **P.R. Nicklas:** None. **N.J. Pistory:** None. **P.J. McLaughlin:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.06/DDD1

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIMH R21 R21MH109953
NARSAD/NIMHD 2G12MD007592
NIH/NIMHD-RCMI 5G12MD007592

Title: Genetic factors for inhibitory control and impulsivity

Authors: *S. J. HINOJOS, P. R. SABANDAL, A. MERINO, R. UMAROVA, K.-A. HAN
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Abstract: The capacity to inhibit impulsive actions is critical for goal-oriented behaviors and survival in humans and animals. It is influenced by aging, genetics and environment. Dysfunctional inhibitory control is associated with multiple brain disorders including insomnia, attention deficit-hyperactivity disorder, and Alzheimer's and Parkinson's diseases. However, the factors and mechanisms for inhibitory control remain poorly understood. To investigate this, we developed a version of the Go/No-Go test to measure response inhibition and impulsivity in *Drosophila*. We used genetic approaches and found that the dopamine-D1-cAMP pathway is critical for impulsivity. In addition, we conducted unbiased genetic screens for the genes interacting with the dopamine system for inhibitory control. One of the novel genes that we identified is *scully*, a fly homolog of the Alzheimer's Disease-associated gene 17-β-hydroxysteroid dehydrogenase 10 (HSD17β10). The progress of this study will be presented. The finding of the study may offer novel insights into the impulsivity-associated brain disorders. This work was supported by the NIH/NIMH R21 R21MH109953, Brain & Behavior Research Foundation NARSAD and NIMHD 2G12MD007592 grants.

Disclosures: S.J. Hinojos: None. **P.R. Sabandal:** None. **A. Merino:** None. **R. Umarova:** None. **K. Han:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.07/DDD2

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIMH R21 R21MH109953
NARSAD and NNIMHD 2G12MD007592

Title: Aberrant sleep affects inhibitory control

Authors: *E. SALDES, A. ARZOLA, Jr, P. R. SABANDAL, K.-A. HAN
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Abstract: Sleep is an essential physiological process and plays crucial roles in attention, decision making, learning and memory. Previous studies have demonstrated that sleep deprivation increases error rates in subjects performing the Go/No-Go test, indicating the important role of sleep in inhibitory control. However, the underlying neural and cellular mechanisms remain unclear. Our study aims to clarify how sleep affects inhibitory control. To address this, we investigated inhibitory control using a Go/No-Go test in *Drosophila melanogaster*. We manipulated fly sleep genetically or pharmacologically. In the genetic approach, we used the fly mutants with abnormal sleep including the dopamine transporter mutant *fumin* and the potassium channel mutants *Shaker* and *Hyperkinetic*. As a complementary approach, we examined the wild-type flies fed with different doses of caffeine that disrupts sleep. Both genetic and pharmacological manipulations led to impaired inhibitory control, supporting the notion that abnormal sleep causes impulsivity. The progress in this study will be presented. Our study may offer novel insights into the mechanisms by which sleep alters inhibitory control that is important for goal-oriented behaviors and survival. Supported by the NIH/NIMH R21 R21MH109953, Brain & Behavior Research Foundation NARSAD and NNIMHD 2G12MD007592 grants.

Disclosures: E. Saldes: None. **A. Arzola:** None. **P.R. Sabandal:** None. **K. Han:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.08/DDD3

Topic: H.01. Animal Cognition and Behavior

Title: Different subtypes of impulsivity are preferably expressed in rat during re-acquisition of reward or to acute cocaine depending on when exposed to a gambling task

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Abstract: Impulsivity is highly associated with the development of a number of psychiatric disorders, including addictions. In behavioral approach, the subtypes of impulsivity can be divided as impulsive action and impulsive choice in large. Rodent version of the gambling task (rGT) allows us to measure both impulsive action and choice in rat. In the present study, we examined how different starting time of exposure to a gambling task, continued and 3 weeks delayed after pre-training, differentially influences two different subtypes of impulsivity in rGT performances. Rats were trained in a touch screen chamber to learn the relationships between 4 different light signals on the window of the screen and accompanied reward outcomes or punishments set up with different magnitudes and probabilities. Depending upon their stabilized pattern of preference upon free choice, rats were categorized as risk-averse or risk-seeking group. While passing through a series of experimental scheme, including extinction, re-acquisition, and acute cocaine injection, rats were re-tested for their premature response during inter-time interval and for their choice preference toward 4 different windows in rGT. Interestingly, rats exposed continuously compared with those delayed to gambling task showed increased impulsive action especially during re-acquisition period. On the contrary, rats exposed delayed compared with those continued to gambling task showed increased impulsive choice after acute cocaine injection, but these results are only appeared in a sub-group pre-categorized as high impulsive and risk-averse group. These results suggest that different aspect of impulsivity can be differentially expressed in the process of decision-making, and influenced by the time when exposed to a gambling task.

Disclosures: J. Han: None. **B. Cho:** None. **M. Kwak:** None. **W. Kim:** None. **J. Kim:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.09/DDD4

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Senior Investigator Award to TWR: 104631/Z/14/Z
Lundbeck Foundation international postdoc grant for MEH: R182-2014-2810 and R210-2015-2982

Title: Dissociable roles of rat medial and lateral orbitofrontal cortex in visual reversal learning; GABAergic, glutamatergic and serotonergic modulation

Authors: *M. E.-S. HERVIG[1,2], L. FIDDIAN[1], T. BOŽIč[1], L. PIILGAARD[1], J. ALSIÖ[1], T. W. ROBBINS[1]
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Abstract: Background: Deficits in reversal learning, the ability to suppress prepotent associations and exhibit flexible behaviour on contingency changes, are observed in several neuropsychiatric disorders including schizophrenia, eating disorders and obsessive-compulsive disorder. Much work indicates that reversal learning is modulated by serotonin and mediated by a neurocircuitry involving the orbitofrontal cortex (OFC) as shown across species. There are indications that 5-HT2A and 5-HT2C receptors play important roles in mediating reversal learning, but their regional roles remain unknown.
Aims: To define the role of lateral and medial OFC (lOFC and mOFC) and subregion-specific 5-HT2A and 5-HT2C receptors in visual reversal learning in rats.
Methods: Male Lister Hooded rats were trained in a touchscreen serial visual reversal task. We tested the effects of intra-mOFC and intra-lOFC microinfusions of baclofen/muscimol (1mM/side; inducing inactivation), dihydrokainic acid (0.5 or 1.0 μg/side; inducing overactivation) as well as 5-HT2A (M100 907) and 5-HT2C (SB 242084) receptor antagonists (1.0 or 3.0 μg/side) on performance in this task. We performed within-subject analyses of performance measures including perseverative errors, omissions and latencies.
Results: lOFC inactivation increased early errors (i.e. perseverative errors), whereas mOFC inactivation reduced early errors. mOFC overactivation also reduced early errors. Investigation of the effect of lOFC overactivation is in progress. We have previously shown that Intra-lOFC SB 242084 reduces early errors (Alsiö et al. 2015) and here we saw indication that intra-lOFC M100 907 may increase early errors. In the mOFC, we saw no effects of 5-HT2A and 5-HT2C antagonism.
Conclusion: We show that inactivating the lOFC and mOFC causes opposite effects on perseveration in reversal learning, and that, as opposed to intra-lOFC 5-HT2C blockade (Alsiö et al. 2015), intra-lOFC 5-HT2A antagonism may impair reversal learning. Overall, we show, for the first time, that both the mOFC and lOFC play important, yet dissociable, roles in visual reversal learning.

Disclosures: M.E. Hervig: None. **L. Fiddian:** None. **T. Božič:** None. **L. Piilgaard:** None. **J. Alsiö:** None. **T.W. Robbins:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.10/DDD5

Topic: H.01. Animal Cognition and Behavior

Title: Neural dynamics of selective inhibition in the dorsal premotor cortex of non-human primates

Authors: *F. GIARROCCO[1,2], P. PANI[1], M. GIAMUNDO[1], F. FABBRINI[1], E. BRUNAMONTI[1], S. FERRAINA[1]
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Abstract: The ability to selectively suppress actions in response to the environment changes is extremely relevant for both cognitive and executive aspects and it is an essential for adaptive and goal-oriented behaviour. Despite their relevance, the neural dynamics underpinning this behaviour are still poorly investigated.To directly tackle this issue, we recorded multi-unit activity (MUA) from 96 channels Utah arrays in the dorsal premotor cortex (PMd) of two male rhesus monkeys (Macaca mulatta) trained in a modified version of a reaching countermanding task (CMT). In this version, three different kinds of trials were randomly presented: on 60% of trials (no-signal trials) monkeys were instructed to reach a peripheral target as quickly as possible after a go signal presentation. On 40% of trials one out of two signals could follow the go signal after a variable and unpredictable delay (stop signal delay, SSD). One signal was the stop signal (stop signal trials, 20%) and monkeys were instructed to withhold their response. The SSD during signal trials was adjusted based on the performance following a tracking procedure. The other signal was the ignore signal (stop ignore signal trials, 20%) and monkeys were instructed to respond as they do during no-signal trials. We found that monkeys differently adapted their behaviour across sessions using two strategies for selective stopping. In the Independent Discriminate then Stop (IDTS) strategy monkeys first discriminated the signal, then decided to stop (or not). Differently, in the Stop then Discriminate (STD) strategy monkeys first inhibited the response whenever a signal occurred, then discriminated the signal and restarted a response on stop ignore trials. We found that MUA showed different dynamics related to the behavioral strategies. When monkeys adopted the IDTS strategy, MUA showed different pattern between trials when a movement was made (stop ignore signal and no-signal trials) and trials when the movement was withheld (correct stop signal trials). Differently, when monkeys adopted the STD, MUA showed the same pattern on stop ignore signal and stop signal trials, for about 180-200 ms after the signal. Following this period MUA activity in stop ignore signal trials modulated as in no-signal trials up to movement generation. These results show the presence of strong neural correlates of selective inhibition in the PMd of non-human primates.

Disclosures: F. Giarrocco: None. **P. Pani:** None. **M. Giamundo:** None. **F. Fabbrini:** None. **E. Brunamonti:** None. **S. Ferraina:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.11/DDD6

Topic: H.01. Animal Cognition and Behavior

Support: NIH , "Functions of ERK/MAPK signaling in GABAergic circuit development"

Title: Acquisition and Maintenance of fixed-minimum interval performance is impaired in cortical GABAergic neuron deficient mice

Authors: *T. A. GUPTA[1], C. W. DANIELS[1], D. INGUITO[1], A. COURY[1], K. NISHIMURA[2], F. SANABRIA[1], J. NEWBERN[2]
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Abstract: Gain-of-function mutations of the ERK/MAPK cascade in GABAergic interneurons induces a decrease in the number of cortical GABAergic neurons. This mutation, which models the RASopathy Noonan Syndrome, is associated with potential deficits in response inhibition capacity, related to those observed in Attention Deficit Hyperactivity Disorder. GABAergic deficient mice and healthy controls were trained in a Fixed-Minimum Interval (FMI) schedule of reinforcement, wherein the interval between a nose-poke and a head entry into a food trough define an inter-response time (IRT). IRTs longer than a criterion waiting requirement (0.5 s, 2 s, 4 s, 8 s) were reinforced. Mutant mice took longer to adjust their IRTs to each waiting requirement and produced more variable IRTs, indicated by increased coefficients of quartile variation. Accordingly, acquisition of the waiting requirements differed between controls and mutants, such that controls reached asymptotic performance more rapidly. Thus, GABAergic interneurons are involved in the acquisition and maintenance of response-withholding performance, potentially reflecting a key role in response inhibition capacity.

Disclosures: T.A. Gupta: None. **C.W. Daniels:** None. **D. Inguito:** None. **A. Coury:** None. **K. Nishimura:** None. **F. Sanabria:** None. **J. Newbern:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.12/DDD7

Topic: H.01. Animal Cognition and Behavior

Title: Sex differences in early risk assessment but not impulsive choice revealed by within-subjects assessment of delay discounting and probability discounting in mice

Authors: *N. M. GRISSOM[1], J. LESCHISIN[2], J. JEONG[2], E. GASPARINI[2]
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Abstract: In addition to deficits in social function, individuals affected by autism spectrum disorders (ASD) often demonstrate abnormalities in motivated behavior and decision making. Autism spectrum disorders are highly sex- and gender-biased, affecting males:females at a 4:1 ratio. These findings raise the question of whether sex-linked differences in the neurobiology of decision making may be connected to increased male vulnerability to autism. We investigated whether there are baseline sex differences in how male and female mice decide to distribute their actions over conditions of delayed reward (delay discounting) versus uncertain reward (probability discounting or risky decision making). Tasks were tested within subjects to allow direct comparison of delay and probability preference within individuals, and tested over multiple sessions to determine if impulsive choice behavior shifted over time with increased experience with each task. As expected, the length of delay significantly affected tendency to choose the larger reward. However, no significant differences were found between sexes in delay discounting, regardless of delay order presentation (ascending or descending delay). This similarity suggests that baseline differences in motivation and ability to assess reward values are minimal between sexes. The same mice were then shifted to a probability discounting paradigm to determine whether a willingness to take risk may affect the way mice evaluate reward value and decide between choices. Curiously, males were shown to be more likely to prefer the uncertain large reward significantly more frequently compared to females in session one of testing. However, this effect was only observed when the probability schedule was new to the animals, at a time of maximum uncertainty. As animals learned the relative probabilities of earning the large reward with increasing experience with the task, preference for risk was no different between males and females. We are currently comparing demand functions across time and across tasks to determine whether choice behavior is stable within an individual, as there were substantial individual differences in discounting within each sex. These data suggest that motivation for rewards and the ability to balance known costs with reward outcome does not differ between sexes, but behavior when learning about uncertain options does differ between sexes.

Disclosures: N.M. Grissom: None. **J. Leschisin:** None. **J. Jeong:** None. **E. Gasparini:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.13/DDD8

Topic: H.01. Animal Cognition and Behavior

Support: PHS research grants AA024571
DA041674
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Influence of medial prefrontal subregion inactivation on action control using a variable ratio go/no-go task

Authors: *J. P. CABALLERO[1], D. E. MOORMAN[2]
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Abstract: The rodent medial prefrontal cortex is important for execution and inhibition of reward seeking, with the prelimbic (PL) thought to guide execution of goal-directed behavior and IL thought to inhibit goal-directed, and promote habitual, behaviors. Differential regulation of action by mPFC subregions is frequently tested in a temporally staggered manner, such as using reward seeking and extinction, as in previous work by our group and others. However, tasks like the go/no-go or stop signal reaction time tasks probe action execution and inhibition in the same session, obviating the need for learning-associated changes in behavior, which occur during extinction. To better understand how mPFC networks regulate action control, we are performing chemogenetic manipulation of PL and IL during a variable ratio go/no-go task in which probability of go vs. no-go is changed across sessions. The rationale for this task design variant is to probe the impact of expectation bias (e.g., 80%/20% go vs. 80%/20% no-go) on behavioral performance and mPFC control. To characterize mPFC function during this task, male Long-Evans rats receive an infusion of a virus to express the inhibitory DREADD hM4Di in either the PL or IL. Rats are then trained on a go/no-go task. In go trials, a lever extends and an auditory/visual cue signals that the rat should press the lever in order to obtain 0.1mL of 15% sucrose. In no-go trials, a lever extends and a different visual cue signals that rats should not press the lever in order to receive sucrose. After training, rats are tested on different response ratios (100/0, 80/20, 50/50, and 20/80) on separate days. On testing days, rats receive either clozapine-N-oxide (CNO) or vehicle, in a counterbalanced order. Rats are perfused after their final day of testing and immunohistochemistry is performed to label for virus expression and c-fos in the PL and IL and related brain structures. Preliminary findings reveal that DREADDs were selectively expressed in either PL (n=4) or IL (n=2). Rats with PL DREADD inactivation

during 100/0 ratio task performance substantially increased their proportion of well entries (n=3/4 rats). This is in accordance with our previous study in which pharmacological inactivation of dorsal mPFC increased reward seeking. DREADD inactivation of IL slightly increased the proportion of omissions (i.e., decreased go lever pressing). Additional rats are currently being tested and c-fos staining is being analyzed. This behavioral paradigm, combined with selective PL/IL DREADD inactivation will significantly advance our understanding of the prefrontal control of response execution and inhibition.

Disclosures: J.P. Caballero: None. **D.E. Moorman:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.14/DDD9

Topic: H.01. Animal Cognition and Behavior

Support: NIDA R21 DA041903
R00 DA033878
T32 DA007244
UNC CFAR P30 AI50410
R01 DA032933
K05 DA021696

Title: Cannabinoidreceptor type 1 upregulation in the infralimbic cortex of female tat transgenicmice following ten months of tat expression and testing for inhibitory controldeficits using the Go/No-Go task

Authors: *I. R. JACOBS[1], D. J. HERMES[1], A. G. ANTONUCCI[1], A. B. FERGUSSON[1], K. L. LEGGETTE[1], N. R. MISEO[1], A. M. PROCA[1], C. B. RUSSELL[1], C. MANJARRES[1], K. MACKIE[2], A. H. LICHTMAN[3], B. M. IGNATOWSKA-JANKOWSKA[4], S. FITTING[1]
[1]Dept. of Psychology and Neurosci., Univ. of North Carolina - Chapel Hill, Chapel Hill, NC; [2]Psychol & Brain Sci., Indiana Univ. Bloomington Dept. of Psychological and Brain Sci., Bloomington, IN; [3]Pharmacol. and Toxicology, Virginia Commonwealth Univ., Richmond, VA; [4]Neuronal Rhythms in Movement Unit, Okinawa Inst. of Sci. and Technol., Onna-son, Kunigami, Okinawa, Japan

Abstract: HIV-1 associated neurocognitive disorder (HAND) is characterized by mild deficits in cognitive and behavioral abilities such as attention, impulsivity and inhibitory control. An HIV-1 viral protein, the transactivator of transcription (Tat), is thought to cause synaptodendritic injury through excitotoxic Ca^{2+} and Na^{+} influx from upregulated NMDA and AMPA receptors. Tat's effects largely affect the fronto-striatal-thalamo-cortical (FSTC) circuit which is responsible for

regulating attention, impulsivity and inhibitory control. The present study is focused on assessing inhibitory control deficits in a Tat transgenic mouse model after prolonged Tat expression. This transgenic model utilizes a slow release of Tat under the control of a tetracycline on system to study deficits induced by Tat expression. To assess inhibitory control deficits, a Go/No-Go task was administered. In the Go/No-Go task, mice are required to perform different behaviors for two different stimulus arrangements. In the Go arrangement, mice perform a nose poke for a sugar pellet reinforcer and in the No-Go arrangement the mice are required to withhold their nose poke response to receive reinforcement. Fourteen animals were trained on this task and $P_{inhibition}$ scores were gathered as an index of inhibitory control. $P_{inhibition}$ calculates the number of correct omissions on No-Go trials while remaining sensitive to the number of incorrect omissions on Go trials. Following testing, animals were sacrificed and perfused in preparation for immunohistochemistry. Brain slices from the prefrontal cortex were then stained for cannabinoid receptor type 1 (CB1R). Images from the prelimbic and infralimbic cortex were then put through ImageJ to quantify the average intensity of the stain per pixel as a way to quantify CB1R expression throughout these two regions. Testing from the Go/No-Go task revealed a main effect of sex. Specifically, female Tat(+) animals showed significantly less inhibitory control than male Tat(+) animals, while Tat(-) animals did not differ. Furthermore, female Tat(+) mice showed significantly higher CB1R expression in the infralimbic cortex than any other group. Previous *in vitro* research in our lab has found CB1R to be neuroprotective against Tat, so it is possible that Tat resulted in synaptodendritic damage in female mice and the upregulation of CB1R represents a compensatory response to that injury.

Disclosures: I.R. Jacobs: None. **D.J. Hermes:** None. **A.G. Antonucci:** None. **A.B. Fergusson:** None. **K.L. Leggette:** None. **N.R. Miseo:** None. **A.M. Proca:** None. **C.B. Russell:** None. **C. Manjarres:** None. **K. Mackie:** None. **A.H. Lichtman:** None. **B.M. Ignatowska-Jankowska:** None. **S. Fitting:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.15/DDD10

Topic: H.01. Animal Cognition and Behavior

Support: NIDA R21 DA041903
R00 DA033878
T32 DA007244
UNC CFAR P30 AI50410
R01 DA032933
K05 DA021696

Title: Time dependent inhibitory control deficits in tat transgenic mice using the Go/No-Go task and cannabanoid receptor antagonists

Authors: *A. M. PROCA[1], I. R. JACOBS[1], D. J. HERMES[1], A. G. ANTONUCCI[1], A. B. FERGUSON[1], K. L. LEGGETTE[1], N. R. MISEO[1], C. B. RUSSELL[1], C. MANJARRES[1], A. H. LICHTMAN[2], B. M. IGNATOWSKA-JANKOWSKA[3], S. FITTING[1]
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Abstract: HIV-1 associated neurocognitive disorder (HAND) symptoms include mild deficits in attention, impulsivity, and inhibitory control. These symptoms are thought to be the result of synaptodendritic injury and the resulting loss of neuronal interconnections due to exposure to the transactivator of transcription (Tat), a viral protein produced by HIV-1. Tat's effects stem from excitotoxic Ca^{2+} and Na^{+} influx into the affected neuron and primarily impact the fronto-striatal-thalamo-cortical (FSTC) circuit, which is responsible for regulating attention and inhibitory control. Previous research in our lab has shown cannabinoid receptor type 1 (CB1R) to be neuroprotective against the damage precipitated by Tat. The effects of Tat in the brain can be studied using the Tat transgenic mouse which is characterized by a slow release of brain-specific Tat under the control of a tetracycline on system. Research with this transgenic line has shown time dependent effects on hippocampal-dependent memory with longer Tat exposure resulting in greater deficits. We used the Go/No-Go (GNG) task to study deficits in impulsivity and inhibitory control in the Tat mice. Mice were trained to perform different behaviors in two stimulus arrangements. In the Go arrangement, the mouse was required to perform a behavior for a sugar pellet reinforcer; in the No-Go arrangement, the mouse omitted the behavior from the Go arrangement for reinforcement. Two cohorts of mice were trained and tested after two weeks and ten months of Tat expression. At test, inhibitory control can be captured in a measure called $P_{inhibition}$. Testing at ten months revealed a main effect of sex on $P_{inhibition}$ with females demonstrating significantly less inhibitory control than males. Specifically Tat(+) females showed significantly lower inhibitory control than Tat(+) males with no significant differences between Tat(-) males and females. Additionally, there was a main effect of sex on measures of impulsivity with females performing less premature responses than males. Tests after two weeks revealed no significant differences; following these null results, CB1R and cannabinoid receptor type 2 (CB2R) were antagonized in an attempt to induce dose-dependent deficits in inhibitory control. Results still showed no significant differences after CB1R, CB2R, or CB1R and CB2R antagonism. It is possible that after only two weeks of Tat expression, protein levels were not high enough to produce deficits on their own and thus antagonizing CB receptors did not noticeably modulate Tat induced damage.

Disclosures: I.R. Jacobs: None. **D.J. Hermes:** None. **A.G. Antonucci:** None. **A.B. Ferguson:** None. **K.L. Leggette:** None. **N.R. Miseo:** None. **C.B. Russell:** None. **C. Manjarres:** None. **A.H. Lichtman:** None. **B.M. Ignatowska-Jankowska:** None. **S. Fitting:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.16/DDD11

Topic: H.01. Animal Cognition and Behavior

Support: MnDRIVE Postdoctoral Neuromodulation Fellowship - University of Minnesota (MTP)
MQ Fellows Award (PER)

Title: Parvalbumin-positive interneurons in the nucleus accumbens inhibit impulsive behavior of mice

Authors: *M. T. PISANSKY, E. M. LEFEVRE, B. H. TRIEU, P. E. ROTHWELL
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Abstract: Impulsive behavior characterizes various psychiatric disorders, including drug addiction. The nucleus accumbens (NAc), a forebrain region classically implicated in reward, is central to the neural circuitry mediating impulsivity. Within the NAc, primary projecting medium spiny neurons (MSNs) receive feed-forward inhibition from parvalbumin-positive (PV+) interneurons. To investigate the role of PV+ interneurons on impulsive behavior we virally expressed within the NAc core of PV-Cre+ mice: (1) the calcium indicator GCaMP6m to monitor in vivo activity using fiber photometry; (2) the Gi-coupled hM4D DREADD receptor to inhibit these neurons using systemic CNO administration; (3) excitatory opsins to optogenetically activate these neurons using light. Impulsive behavior was measured using the five-choice serial reaction time (5-CSRT) task, in which a mouse withholds an operant response until it can be directed to a location indicated by a brief visual cue. Premature responses, defined as those occurring prior to the onset of the visual cue, are an index of impulsivity. Fiber photometry revealed that decreased PV+ interneuron activity precedes impulsive responses. Chemogenetically inhibiting PV+ interneurons increased premature responses without altering response latencies or open field locomotor activity. Conversely, preliminary data suggest that optogenetic activation of PV+ interneurons reduced impulsive behavior. These experiments indicate that PV+ interneuron activity shapes the selection and timing of behavioral responses, most likely through feed-forward inhibition of MSN activity and striatal output.

Disclosures: M.T. Pisansky: None. **E.M. Lefevre:** None. **B.H. Trieu:** None. **P.E. Rothwell:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.17/DDD12

Topic: H.01. Animal Cognition and Behavior

Support: MQ Fellows Award (2016)
MnDRIVE

Title: Cell type-specific chemogenetic inhibition of mouse nucleus accumbens medium spiny neurons alters attention in the 5 choice serial reaction time task

Authors: *D. W. LEIPOLD[1,2], P. E. ROTHWELL[2]
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Abstract: Deficits in cognitive processes are associated with a wide range of neuropsychiatric conditions. Understanding how these cognitive processes are normally implemented will aid in the development of treatments to ameliorate such deficits. Two important cognitive processes - attention and impulse control - can be indexed in mice using the 5 choice serial reaction time task (5CSRTT), an operant task that requires animals to withhold responses to a visual cue presented randomly at one of five locations for a period of time. During each trial animals can either respond correctly, prematurely, incorrectly at a different location, or omit a response. Premature responses represent a measure of impulsivity, and incorrect/omission trials reflect lapses in attention. Lesion studies of the nucleus accumbens (NAc) and striatum have indicated their importance for attention and impulsivity in the 5CSRTT, but we know little about how specific cell types contribute to these effects. Medium Spiny Neurons (MSNs) account for 95% of the cells in this region, further subdivided by their expression of either D1- or D2- dopamine receptors. We virally expressed the inhibitory Designer Receptor Exclusively Activated by Designer Drugs (DREADDs), hM4D(Gi) in into D1- or A2a-MSNs by injecting into D1-Cre or D2-Cre mice respectively. Wild-type littermates not expressing Cre were used as controls, and administration of clozapine-N-oxide (CNO, 2 mg/kg) had no behavioral effects in control mice. However, chemogenetic inhibition of D1-MSNs increased omissions in the 5CSRTT in both male and female transgenic mice, implying a deficit in attention. Preliminary data suggests that chemogenetic inhibition of D2-MSNs decreases omissions while increasing correct responding in both male and female mice. Response latencies were not changed, suggesting these effects are not due to general changes in movement. Considering the divergent behavioral patterns of the inhibition of MSN subtypes on attention, this study highlights the importance of manipulations that leverage cellular specificity in studies of corticostriatal contributions to attention and impulse control.

Disclosures: D.W. Leipold: None. **P.E. Rothwell:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.18/DDD13

Topic: H.01. Animal Cognition and Behavior

Title: Delay discounting of punishment during economic decision-making

Authors: *A. VONGPHRACHANH[1], D. B. GABRIEL[2], N. W. SIMON[2]
[2]Psychology, [1]Univ. of Memphis, Memphis, TN

Abstract: Addiction is characterized by ongoing substance abuse despite physical, financial, and social consequences. Critically, these negative outcomes are often delayed relative to immediate drug reinforcement, resulting in myopic decision-making that fails to appropriately respond to consequences. Discounting of delayed outcomes has been well studied in human and animal models, but these protocols primarily measure preference for immediate over delayed rewards. Systematic discounting of delayed consequences, which is associated with substance abuse, remains largely unexplored. To address this gap in the literature, we have developed the Delayed Punishment Decision-making Task (DPDT). In this task, rats choose between a small, single pellet reward and a large, three pellet reward accompanied by a mild foot shock (.35 mA). As the task progresses, a delay precedes the shock that is systematically enhanced with each 12 trial block (0s, 4s, 8s, 12s, 16s), followed by a final block in which the shock and delay are no longer present. For this study, we trained male (n=10) and female (n=10) Long Evans rats in the DPDT. Initially, rats engaged in two forced choice trials in which levers associated with a small, safe reward and large reward accompanied by a foot shock are extended to establish the difference in reward magnitudes. Next, rats chose their preferred lever for 10 free choice trials. After they showed >75% preference for the large reward throughout the session, foot shock amplitude was gradually increased by .5 mA increments, starting from 1.0 mA until reaching an amplitude of .35 mA. Upon reaching this shock level, subjects trained for an additional 15 consecutive sessions. We observed that rats discounted the negative value of delayed punishment, as indicated by a significant increase in choice of the large, punished reward as delay preceding the shock increased. These data were stable across the final five days of training, as indicated by a lack of block x session interaction. There was no significant difference in latency to choose the small vs large reward. Furthermore, there was no significant correlation between body weight and preference for the large reward. This preliminary study demonstrated that the ability of punishment to reduce reward preference is attenuated if punishment is delayed. Further experimentation will explore sex differences in punishment discounting, as well as the influence of acute and extended exposure to drugs of abuse. Development of the DPDT is the first step toward understanding the neural mechanisms underlying reduced valuation of delayed punishment, as well as how this process becomes pathological in substance abuse.

Disclosures: A. Vongphrachanh: None. **D.B. Gabriel:** None. **N.W. Simon:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.19/DDD14

Topic: H.01. Animal Cognition and Behavior

Title: Dopaminergic influences on a novel task measuring preference for probabilistic vs. effortful rewards in rats

Authors: *D. B. GABRIEL[1], A. VONGPHRACHANH[2], N. W. SIMON[1]
[1]Psychology, [2]Univ. of Memphis, Memphis, TN

Abstract: Economic decision-making is the process by which one reward is chosen over another based on each reward's relative value. Understanding the biological underpinnings of economic decisions is a key step in identifying causal factors for suboptimal decision-making, such as pathological gambling. Rodent models measure economic decision-making by offering subjects a choice between a small reward and a large one associated with a discounting factor that decreases preference for that reward. Common discounting factors include probability of reward omission and greater effort required for reward delivery. These tasks have successfully parsed apart much of the underlying neurobiology of multiple forms of economic decision-making. However, real-world decisions are typically more complicated than these simplified models, often involving the assessment and comparison between different discounting factors. To model this, we developed an "effort vs probability task" (EvP) in which rats were offered a choice between rewards of equal magnitude accompanied by different discounting factors. The probabilistic reward consisted of a 25% probability of delivery fixed throughout the session, whereas the effortful reward increased effort required throughout the session (1, 5, 10, and 20 actions). We observed an increased preference for the probabilistic reward as effort requirements increased, quantified by a significant effect of block. Stable performance was achieved after 30 sessions, quantified by no effect of day in a repeated-measures ANOVA over the last five sessions of training.
We then measured the effects of D1 and D2 antagonists on the EvP. We found that both D1 and D2 blockade increased preference for the probabilistic reward over the effortful option. D1 blockade during the EvP resulted in dose-dependent effects, with only the highest dose (.03) significantly increasing choice of the probabilistic reward. D2 blockade of increased preference for the probabilistic reward across all doses. There were no effects on locomotion or response latency by either drug, although high (.05) and medium (.03) doses of the D2 antagonist significantly increased trial omissions. Overall, these data suggest that dopamine receptor blockade biases decision-making toward uncertain rewards and away from high effort options.

Disclosures: D.B. Gabriel: None. **A. Vongphrachanh:** None. **N.W. Simon:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.20/DDD15

Topic: H.01. Animal Cognition and Behavior

Support: Faculty Research Grant (University of Memphis)
Brain Behavior Research Foundation Young Investigator Grant

Title: Risky decision-making predicts dopamine release dynamics in nucleus accumbens

Authors: *A. WOODS[1], T. FREELS[4], D. B. GABRIEL[2], H. JOYNER[2], S. MORRISON[2], D. B. LESTER[3], N. W. SIMON[2]
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Abstract: Excessive risk taking in the face of punishment is expressed across several forms of psychopathology. In particular, substance abuse is characterized by ongoing drug seeking despite the risk of social, financial, and physical consequences. Thus, elucidating the neural mechanisms underlying risky decision-making may have utility for identifying vulnerability to substance abuse disorders. The risky decision-making task (RDT) measures risk taking in a rat model by assessing preference between a small, safe reward and a large reward accompanied by a systematically increasing risk of punishment (mild foot shock). On average, rats shift preference away from the risky reward as the probability of punishment increases. However, the RDT reliably reveals substantial variability in performance, including a subpopulation of "risk takers" with a consistent preference for risky rewards even with high risk of consequences. To determine the neurobiological factors that are comorbid with risk-taking, we characterized rats in RDT, then used Fixed Potential Amperometry to measure the relationship between evoked dopamine release in the nucleus accumbens (NAC) and risk preference. We observed that risk preference was correlated with dopamine release in the NAC evoked by medial forebrain bundle stimulation, and that rats characterized as "risk-takers" demonstrated significantly greater evoked dopamine efflux than the rest of the population. Risk-takers also showed enhanced dopamine half-life in response to nomifensine, a dopamine reuptake inhibitor. These results were in contrast with delay discounting performance, which did not predict any NAC dopamine parameters. These data suggest that the risk-taking phenotype is likely related to dopamine release dynamics in the NAC. Furthermore, baseline risk-based decision-making is more closely associated with NAC dopamine sensitivity than delay based decision-making.

Disclosures: A. Woods: None. **T. Freels:** None. **D.B. Gabriel:** None. **H. Joyner:** None. **S. Morrison:** None. **D.B. Lester:** None. **N.W. Simon:** None.

Poster

242. Animal Cognition and Behavior: Executive Function: Inhibitory Control

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 242.21/DDD16

Topic: H.01. Animal Cognition and Behavior

Title: Genetic influences on distinct forms of impulsivity and cocaine sensitivity

Authors: *H. T. FRANKS[1], D. B. GABRIEL[2], A. VONGPHRACHANH[3], R. DEMATO[3], L. GRILL[3], B. LYONS[3], K. MCLARNON[3], T. WILLIAMS[3], H. CHEN[4], N. W. SIMON[2]
[1]Univ. of Memphis, Munford, TN; [2]Psychology, [3]Univ. of Memphis, Memphis, TN; [4]Dept Pharmacol, Univ. Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Selective differences in behavior can shape vulnerability to substance abuse disorder. Understanding the genetic basis of these traits may be effective for identifying and treating addiction prone individuals. One such behavioral pattern is **impulsivity**, defined broadly as deficits in self-regulation. Impulsivity is a multi-faceted construct, with two elements that are readily quantifiable in rodent models: impulsive action, the inability to withhold a prepotent response, and impulsive choice, a preference for immediate gratification over larger, delayed rewards. Here, we assessed genetic patterns underlying different forms of impulsivity, as well as cocaine locomotor sensitivity and reinforcement. This was accomplished using inbred male and female Fischer 344 and Lewis rats obtained from different vendors (Charles River and Envigo). This genetic similarity between the substrains from different vendors enhances the ability to identify unique candidate genes underlying any heritable or comorbid behaviors of interest. We observed heritable phenotypic differences specific to each strain: impulsive action (but not choice) was enhanced in Lewis rats from Envigo but not from Charles River, and enhanced cocaine-induced locomotion was evident in Fischer rats from Charles River but not from Envigo. No differences between groups were observed in cocaine CPP, an indirect measure of cocaine reinforcement. Critically, the observed phenotypic differences were not comorbid across any substrains, which suggests that cognitive (impulsive action) and pharmacological (cocaine sensitivity) factors related to substance abuse arise from unique genetic origins.

Disclosures: H.T. Franks: None. **D.B. Gabriel:** None. **A. Vongphrachanh:** None. **R. Demato:** None. **L. Grill:** None. **B. Lyons:** None. **K. Mclarnon:** None. **T. Williams:** None. **H. Chen:** None. **N.W. Simon:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.01/DDD17

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI JP18K07855

Title: Optogenetic induction of neural synchronization in the mouse medial prefrontal cortex

Authors: *D. HAZRA[1], S. YOSHINAGA[2], K. YOSHIDA[3], K. F. TANAKA[4], K. DEGUCHI[2], K.-I. KUBO[5], K. NAKAJIMA[6]
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Abstract: Neural synchronization has been suggested to play crucial roles in cognitive tasks. High frequency oscillations typically appear in association with cognitive processes and are thought to reflect temporal coordination of neuronal responses. However, recent research has indicated that low frequency oscillations are induced in the medial prefrontal cortex (mPFC) of the mice in coordination with cognitive processes. Also, previous studies in our laboratory have pointed out that the local field potential (LFP) powers in low frequency bands were reduced in the mPFC of the mice with impaired working memory. In this study, we examined whether stimulating the mPFC neurons with a low frequency oscillation in intact mice would improve spatial working memory. As recent study has shown that layer II/III neurons of prelimbic cortex, which is a part of medial prefrontal cortex, projects mainly to the nucleus accumbens or amygdala and is involved in the social spatial learning, a type of cognitive processes, we targeted layer II/III neurons specifically in this study. By using the *in utero* electroporation technique, we transfected Channelrhodopsin 2 (C128S mutant), which is very sensitive to the light stimulation, into the layer II/III neurons of the mPFC. The behavioral tests with or without the light stimulation were performed and the effect of the optogenetic stimulation was evaluated. We assessed working memory by the Y-maze test and motor activity and anxiety by the open field test. We also evaluated changes of LFPs and immunostained for c-Fos to see the excitation of neurons by optogenetic stimulation. Further electrophysiological analysis and immunostaining, use of other mutants of Channelrhodopsin 2 are in progress to investigate the effect of light stimulation onto the neural activities and working memory.

Disclosures: D. Hazra: None. **S. Yoshinaga:** None. **K. Yoshida:** None. **K.F. Tanaka:** None. **K. Deguchi:** None. **K. Kubo:** None. **K. Nakajima:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.02/DDD18

Topic: H.01. Animal Cognition and Behavior

Title: The effects of acute catecholamine precursor depletion on visual working memory and motivation

Authors: *M. KUSI[1], M. PARÉ[2], C. CRANDELL[2]
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Abstract: Catecholamines (CAT) are thought to influence cognition. We previously observed that boosting CAT transmission with reuptake inhibitors significantly enhanced motivation but only has marginal effects on working memory in rhesus monkeys (Oemisch et al. 2016; Thurston et al. 2015; Kusi et al. 2017). Here we tested whether systemically depleting CAT transmission impairs working memory and reduces motivation. We first determined that limiting the intake of the CAT precursors tyrosine and phenylalanine in two adult, female rhesus monkeys reliably reduces the plasma concentrations of these essential amino acids by >80% after 3-4 hours. We then assessed during that period the animals' working memory from their performance in a visual sequential comparison (VSC) task, which manipulates memory load. In addition, the animals' motivation was assessed using a fixation task with progressive ratio (PR) schedule of reinforcement. We also considered task engagement – the proportion of VSC trials that the animals aborted – as an alternative measure of motivation. For each animal, data from 5 CAT depletion sessions were compared to 5 vehicle controls as well as >60 regular sessions. In one animal, CAT depletion marginally impaired her working memory capacity, but significantly reduced her motivation (lower breaking point) and VSC task engagement (more aborted trials). In the other animal, CAT depletion impacted her performance neither in the VSC task nor in the PR task, but it significantly lowered her VSC task engagement. These observations are in line with our previous work on enhancing CAT transmission. Overall, our findings suggest that CAT play a central role in motivation and exert an indirectly influence on working memory task performance.

Disclosures: M. Kusi: None. **M. Paré:** None. **C. Crandell:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.03/DDD19

Topic: H.01. Animal Cognition and Behavior

Support: ONR MURI N00014-16-1-2832

Title: Compressed temporal representation during visual paired associate task in monkey prefrontal cortex and hippocampus

Authors: *N. A. CRUZADO[1], Z. TIGANJ[2], S. L. BRINCAT[3], E. K. MILLER[4], M. W. HOWARD[1]
[1]Dept. of Psychological and Brain Sci., [2]Ctr. for Memory and Brain, Dept. of Psychological and Brain Sci., Boston Univ., Boston, MA; [3]The Picower Inst. for Learning and Memory and Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [4]Picower Inst. Learning Memory, Massachusetts Inst. Technol., Cambridge, MA

Abstract: Recent models of memory depend on representations of a compressed temporal history of past events. Time cells, neurons that fire at particular times within a task, are one possible mechanism to support a representation of past time. Time cells have been observed extensively in mice and rats and they have also recently been discovered in primate lPFC. For models of memory to be able to account for tasks that require both item and temporal information, such as judgment of recency tasks, it is not sufficient that time cells fire during a circumscribed period of time, but that different stimuli initiate distinct sequences of time cells. These stimulus selective time cells would fire in response to particular stimuli at particular time delays. A recently published study reports stimulus specific time cells in macaque lPFC. We reanalyzed a dataset of neurons from macaque PFC and hippocampus using a maximum likelihood model to identify stimulus selective time cells during a paired associate learning task. We found robust stimulus selective time cells that tile the task duration in both hippocampus and PFC. Consistent with other reports, the temporal history was compressed, as shown by the spread in time fields and decreasing number density of time cells with the passage of time. Because of the way the task was organized, we were able to establish that the neurons in the hippocampus and PFC were representing a compressed temporal history of past events. We also used a linear classifier to determine how the cells encoded stimulus information. Cross-temporal classification in both PFC and hippocampus was consistent with stimulus specific time cells. These results are discussed in the context of other studies of time cell phenomena and mathematical models of memory representation.

Disclosures: Z. Tiganj: None. **S.L. Brincat:** None. **E.K. Miller:** None. **M.W. Howard:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.04/DDD20

Topic: H.01. Animal Cognition and Behavior

Support: NIDA DA039351

Title: Ensemble decoding of spatial and mnemonic information in lateral prefrontal cortex

Authors: *F.-K. CHIANG[1], J. D. WALLIS[2], E. L. RICH[1]
[1]Dept. of Neurosci. and The Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Dept. of Psychology and Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA

Abstract: The capacity of working memory (WM) is limited to approximately four items. However, we rarely notice this constraint because we are able to implement mnemonic strategies to overcome this limitation, such as grouping items together into “chunks”. In visuospatial WM tasks, neural activity in lateral prefrontal cortex (LPFC) encodes the spatial information required to perform the task. We have recently shown that this spatial tuning is modulated by mnemonic strategies, in this case stereotyped sequencing of spatial targets. However, it remains unclear how these neurons contribute to other mnemonic strategies such as chunking. To assess this, we re-analyzed data from two monkeys performing a spatial self-ordered search task with six identical visual targets. The subjects were required to saccade to each target, one at a time in any order, returning their eyes to the center after each target. Therefore, the subjects had to use WM to keep track of which targets had been visited and prepare for next target selection. To determine whether population activity represents multi-target spatial information in this task, first, we used linear discriminant analyses (LDAs) to categorically decode information about target locations or saccade orders from simultaneously recorded ensembles of LPFC neurons. Target locations were more accurately decoded than saccade orders, and the accuracy of the decoder to predict saccade orders increased when subjects performed more stereotyped selection. These results indicate that population activity in LPFC primarily represents multi-target spatial information. Next, we assessed how this relates to target chunking. We defined mnemonic chunking by groups of targets that were frequently recalled together and used graph theoretic approaches to quantify behavioral chunking in trial blocks. Preliminary data indicate that stronger chunking reduces error rates, consistent with the notion that chunking increases WM capacity. Using linear models, we can reconstruct two-dimensional spatial locations of targets held in WM from populations of LPFC neurons, and further analyses will combine these approaches to determine how chunking changes the spatial information represented by LPFC neurons. In addition, we will assess how these signals evolve within a trial, as the subjects update information held in WM.

Disclosures: F. Chiang: None. **J.D. Wallis:** None. **E.L. Rich:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.05/DDD21

Topic: H.01. Animal Cognition and Behavior

Support: Dow Scholars Program

Title: The effects of obesity on executive functions in both outbred and selectively bred obesity-prone and obesity-resistant Sprague Dawley rats

Authors: *C. MISKELLEY, P. VOLLBRECHT
Hope Col., Holland, MI

Abstract: Understanding the neurological effects of obesity is imperative to public health, particularly with global projections indicating that obesity rates will continue to rise. While many studies have examined the peripheral effects of obesity, far fewer studies have examined central effects beyond the hypothalamus. Obesity has been shown to have a negative effect on executive functions attributed to the prefrontal cortex, such as working memory, inhibitory control, and decision making. However, little is known of the mechanistic pathway linking obesity and cognitive deficits, nor is the relationship between cognitive deficits and obesity well understood. Here, we investigate whether cognitive deficits exist prior to obesity development, whether obesity development leads to cognitive deficits, or if diet independent of weight gain leads to cognitive deficits

In order to explore whether cognitive deficits exist prior to obesity, we utilized selectively bred obesity prone and obesity resistant rats. Obesity-prone and obesity-resistant rats tend to diverge in weight during early adulthood (roughly 70 days). Therefore, behavioral tasks which examine prefrontal cortex function were utilized prior to divergence in weight (~65 days). Tasks included Object in Place and Egocentric Morris Water Maze. Behavioral tests suggest no differences in cognitive function exist between strains prior to the onset of obesity.

We next examined the effects of diet and/or obesity on cognitive function in outbred male Sprague Dawley rats. Rats were fed either a standard rat chow diet, a “junk food” diet, consisting of a mixture of typical highly palatable foods such as potato chips and peanut butter, or a high fat diet (60% fat). Animals fed a junk food diet increased food intake briefly (3-4 days) but did not gain significantly more weight than chow fed animals over time. High fat-fed animals gained significant weight compared to both chow and junk food fed animals. Following diet manipulation, prefrontal cortex-mediated tasks including Object in Place, Egocentric Morris Water Maze, and Attentional Set Shift task were run for each group. Our data suggest that cognitive deficits are not present in an obesity-prone model prior to obesity development.

Furthermore, a highly palatable diet, independent of weight gain, did not lead to the development of cognitive deficits. Finally, outbred rats fed a high fat diet gained significantly more weight while displaying cognitive deficits in select behavioral tasks. Therefore, we propose that cognitive deficits are likely a result of obesity development and may be further exacerbated by genetic susceptibility.

Disclosures: C. Miskelley: None. **P. Vollbrecht:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.06/DDD22

Topic: H.01. Animal Cognition and Behavior

Support: Mitacs Elevate Fellowship to V.Zlatkina
NSERC CREATE scholarship to F. Ayad
NSERC RGPIN-2014-04729

Title: Marmoset SMART chair for automated in-cage training on cognitive tasks

Authors: *V. ZLATKINA[1,2], F. AYAD[1], M. PETRIDES[1], S. FREY[2]
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Abstract: Marmosets are a valuable translational research model that can be used to study cognitive functions in primates. For example, these small monkeys have typical primate granular prefrontal cortex and can be used to explore various cognitive control processes. However, unlike macaques, marmosets are very sensitive to changes in the surroundings and they can become overly anxious upon removal from the familiar environment. The aim of the present research has been to develop an advanced automated in-cage testing apparatus for marmosets, a smart chair, that will be used for behavioral training, first, and for electrophysiology recordings, subsequently. The marmoset smart chair incorporates radio-frequency identification (RFID), proximity sensors, weighing mechanism, touchscreen, and a reward delivery system in a compact debris-resistant transparent enclosure. The information acquired by the system is recorded and available to the investigators, as needed. Having the freedom to interact with the chair at will, and the capacity to observe each other, increases the marmoset learning curve significantly. A family of four marmosets learned their way through the chair, touching the screen, and receiving their reward in a matter of days. These animals are in the process of learning a set of cognitive tasks of increasing complexity, starting with the delayed non-match to sample task, to explore gradually the limits of their working memory capacity. Among the main advantages of using the smart chair for cognitive experiments is the ability to control the task and observe the ongoing performance remotely and allowing the animals to learn at their own pace in

a stress-free environment at the high level of their capacity. The smart chair tracks and records subject progress using the RFID tag to allow the monkeys to recommence their training from the last completed session. During a trial, the weight is measured regularly, allowing the detection of abrupt changes in weight during the day or between days, that can be alarming for this species. The proximity sensors provide feedback about the exact position of the animals inside the smart chair and can be coupled with the reward system to encourage the animals to excel at performing their task.

Disclosures: V. Zlatkina: A. Employment/Salary (full or part-time):; Rogue Research Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Rogue Research Inc. **F. Ayad:** None. **M. Petrides:** None. **S. Frey:** A. Employment/Salary (full or part-time):; Rogue Research Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Rogue Research Inc..

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.07/DDD23

Topic: H.01. Animal Cognition and Behavior

Title: Crows show attentional control over visual working memory

Authors: *E. FONGARO, J. ROSE
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Abstract: Working memory is the neural system for short-term maintenance and manipulation of information. One critical property of this system is its limited capacity that is often seen as a 'bottleneck of cognition'. We recently showed that this capacity of working memory is comparable between crows and primates.
It is well established that humans can maximize working memory capacity using attention, either prior to stimulus presentation (pre-cue), or even after stimuli have disappeared (post-cue). Here we explore this attentional control of working memory in crows. We trained two crows (Corvus corone) in touchscreen-equipped operant chambers on a change detection task. The animals were required to hold 2, 4 or 6 colors in working memory. On some trials, we used pre- or post-cues to direct the animals' attention to one spatial location. A head-tracking system controlled the gaze-direction of the animals during the task.
We found that the animals benefit from both pre- and retro-cues compared with un-cued trials. These results show that crows, like humans can utilize attentional cues (pre-cue) to efficiently select critical stimuli for working memory maintenance. Importantly, the animals can also utilize cues to improve working memory capacity even after the stimuli are already held in working memory and no longer present on screen. This strongly implies that crows can engage in a form

of executive control over information already held in working memory. In order to investigate the neuronal mechanisms of this attentional control over working memory, we now record local field potentials and single cell activity while the animals perform in this protocol.

Disclosures: E. Fongaro: None. **J. Rose:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.08/DP14/DDD24

Topic: H.01. Animal Cognition and Behavior

Title: Electrophysiological features that track working memory performance in macaque monkeys

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Abstract: Impaired working memory (WM) performance is a central deficit in Alzheimer's Disease (AD) and may provide biomarkers which inform early AD diagnosis. However, the electrophysiological mechanisms underpinning impaired WM performance are not understood. We conceived of these mechanisms as features which track WM performance. The goal for this exploratory research project was to identify the features that track WM performance. This work is a follow-up to the Salazar et al. 2012 study which found that visual objects are encoded in the fronto-parietal brain network during a delayed match-to-sample WM task performed by two female rhesus macaque monkeys. The dataset from that study was analyzed here to identify features which track WM performance in macaque monkeys using local field potential (LFP) brain activity during correct and incorrect trials of the WM task. Experiments were conducted to discover features in the time domain and the frequency domain that track WM performance. As part of those experiments, event-related potentials were constructed as voltage time series. A mutual information classifier was used to determine which time points during the task were most predictive of task performance. Artificial intelligence techniques including deep learning were used to discriminate between trial classes. Next, spectrograms were plotted using time-frequency LFP data. The multi-taper method was used for a time-frequency decomposition analysis of power and phase-based synchrony measures of coherence. Nonparametric permutation statistical tests were used to establish significant differences between trial classes. Time points in the late portion of the delay period of the task were found to discriminate between trial classes better than other time points. Late LFP voltages thus served as effective features in the time domain.

Measures of theta power and beta coherence were found to track WM performance, thereby serving as frequency-based features. Discovery of these features sets the stage for human experimentation that utilizes novel measurement and stimulation protocols for early diagnosis and possible treatment of AD.

Disclosures: B. Conklin: None. **N.M. Dotson:** None. **R.F. Salazar:** None. **C.M. Gray:** None. **S.L. Bressler:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.09/EEE1

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 EY018861
Howard Hughes Medical Institute

Title: Prefrontal-subthalamic nucleus projection modulates memory-guided behavior

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Abstract: The prefrontal cortex (PFC) plays a key role in the memory-guided behavior, but how memory-relevant information is encoded in different subpopulations of PFC neurons to guide behavior is unclear. Subthalamic nucleus (STN) is an important structure for motor control, and it is monosynaptically innervated by PFC layer 5 neurons, but whether or how STN-projecting PFC neurons contribute to memory-guided behavior is unclear. Here we use *in vivo* two-photon calcium imaging to monitor the activity of STN-projecting PFC neurons in mice during a delayed Go or No-Go auditory task. Compared to the No-Go trials, STN-projecting PFC neurons show rapidly reduced delay activity in Go trials. Such differential delay activities are not significant in V1-projecting PFC layer 5 neurons. Optogenetic manipulation reveals that activation of STN-projecting PFC neurons enhances the task performance by inhibiting inappropriate responses, while inhibition of STN-projecting PFC neurons impairs the performance. These data suggest that the projection from PFC to STN plays an important role in memory-guided behavior.

Disclosures: B. Li: None. **Y. Dan:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.10/EEE2

Topic: H.01. Animal Cognition and Behavior

Support: NINDS Grant NS059312
NIMH Grant MH081162
McKight Foundation Grant
NSF Grant EPSCoR RII Track-2

Title: Widespread spatio-temporal dynamics of LFP power during short-term visual memory in the macaque monkey

Authors: *S. J. HOFFMAN[1], N. M. DOTSON[1,2], C. M. GRAY[1]
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Abstract: Short-term memory enables information to be held, processed and utilized at a later time. This is a fundamental process for cognitive behaviors. In object based visual short-term memory a number of operations must unfold rapidly, likely involving disparate regions of the brain. Although this type of memory has been thoroughly investigated, little is known about the variations in local field potential (LFP) spectral power across the cortex as a whole during such cognitive tasks. In order to investigate this process we recorded broadband neural activity from a range of areas roughly spanning a cortical hemisphere in macaque monkeys trained to perform an object based delayed match-to-sample task (Dotson et al., 2017). When qualitatively comparing the median magnitude of spectral power during the task epochs (sample presentation period and delay periods) relative to the presample, fixation period, there are widespread and robust patterns of change. During stimulus presentation in the lower frequencies (delta-alpha) many prefrontal, and to a lessor degree parietal regions show an enhancement in power, with somatosensory and visual areas showing slight suppression. This low frequency enhancement in prefrontal regions increasingly falls off as the delay period progresses, and in some cases flips to a suppression in power relative to the presamable (fixation) period. At higher frequencies (beta-gamma) early visual areas with a more foveal retinotopic representation show a strong sample evoked enhancement in power. This stimulus evoked enhancement in high frequency power quickly falls off during the delay period of the task. In prefrontal, frontal, somatosensory and parietal areas during the sample period a slight suppression in power is observed. As the task progresses into the delay periods and towards the match-onset this suppression in high-frequency (beta-gamma) power becomes even greater, especially in frontal motor and somatosensory areas. Converse to the above changes, many regions, such as the non-foveal early visual areas show

only moderate changes in power, and overall show a balanced activity profile. In some cases, these changes might reflect processing and encoding of information in those areas (e.g. stimulus evoked enhancement in early visual areas), while in other cases these variations might reflect maintenance of information. These results demonstrate that there are widespread and robust changes in spectral power that occur in a task-dependent manner during visual short-term memory.

Disclosures: S.J. Hoffman: None. **N.M. Dotson:** None. **C.M. Gray:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.11/EEE3

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01EY026924
NSF BCS1439221
NIH EY014800

Title: The impact of prefrontal persistent activity on inferotemporal responses and object information maintenance

Authors: *E. REZAYAT[1], M.-R. A. DEHAQANI[2,1], K. L. CLARK[3], Z. BAHMANI[1], B. NOUDOOST[3]
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Abstract: Neurons in the Frontal Eye Field (FEF) part of the prefrontal cortex maintain an elevated, spatially-selective activity during the memory period of object working memory tasks (Clark et al. J Neurosci 2012). Whether and how this spatial signal in FEF contributes to the maintenance of object information in other brain areas remains unknown. To answer this question, we simultaneously recorded the neuronal activity in the inferotemporal cortex and the FEF of two monkeys performing an object working memory task (the delayed-match-to-sample task). In this task the animal had to remember a sample object throughout a delay period, and then choose the sample object when it was presented along with a distracter. In half of the trials the sample was presented at a location inside the FEF response field (RF), which also overlapped with the IT RF and in the other half the sample was presented 180 degrees opposite to that location. Target and distracter were always presented at two opposite locations, both 90 degrees

away from the sample location. Simultaneously recording spiking activity and local field potentials in the FEF and IT cortices enabled us to quantify the relationships between location and object information carried in these areas. We have found that the magnitude of location signal in the FEF is correlated with the power of LFPs in IT cortex. Spike-field coherence within and between areas also varies based on the location and object held in working memory. This study provides insight into the interactions between prefrontal and temporal cortices underlying the maintenance of object information.

Disclosures: E. Rezayat: None. **M.A. Dehaqani:** None. **K.L. Clark:** None. **Z. Bahmani:** None. **B. Noudoost:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.12/EEE4

Topic: H.01. Animal Cognition and Behavior

Support: NUS-NUHS Memory Networks Program
Ministry of Education Tier 2 Academic Research Fund

Title: Decoding in the presence of code morphing in the prefrontal cortex

Authors: *S.-C. YEN[1], A. PARTHASARATHY[2], R. HERIKSTAD[1], C. TANG[2], L. CHEONG[1], A. Y. Y. TAN[1], C. LIBEDINSKY[1,2]
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Abstract: The prefrontal cortex maintains working memory information in the presence of distracting stimuli. It has long been thought that sustained activity in individual neurons or groups of neurons was responsible for the maintenance of information in the form of a persistent, stable code. However, we have recently shown that information in the lateral-prefrontal cortex (LPFC) is reorganized or morphed after the presentation of a distractor into a different pattern of activity. This raises the question of how downstream neurons are able to decode the information before and after the distractor presentation in the presence of this code-morphing. One hypothesis is that there exists a subspace in which the pre-distractor (Delay 1) and post-distractor (Delay 2) responses overlap, thus allowing information to be easily decoded despite the code-morphing. We investigated this hypothesis by using optimization techniques to identify a subspace transformation that minimized the distance between the Delay 1 and Delay 2 responses in a population of mixed selective LPFC neurons (n = 61 single units). The performance of a decoder trained and tested using Delay 1 responses in the transformed space was 74.6 ± 5.26%, and 75.5 ± 3.09% for Delay 2 responses. These performance values were not significantly

different from those obtained using the original response space ($p > 0.05$ for both Delay 1 and Delay 2). Critically, in the transformed space, the decoders did not show any difference in performance when they were trained and tested in different delays ($p > 0.05$; performance when trained in Delay 1 and tested in Delay 2: 73.7 ± 3.02%; performance when trained in Delay 2 and tested in Delay 1: 73.4 ± 4.7%). This contrasts with performance values of 45.4 ± 3.94% and 54.3 ± 3.7%, respectively, in the original response space. In order to gain a better understanding of code-morphing, we constructed a simple recurrent network model of prefrontal neurons, and showed that neurons with recurrent connections exhibited non-linear mixed selectivity and code-morphing reminiscent of those observed in our data. We successfully trained a set of output neurons to decode information in a stable fashion in the presence of the code-morphing exhibited by the non-linear mixed selective neurons. We hypothesize that the connection weights between the recurrent neurons and the output neurons perform a subspace transformation similar to the transformation found above in our data. This suggests that mixed selectivity provides populations with the ability to represent information flexibly while preserving information in certain subspaces to facilitate readout by downstream neurons.

Disclosures: S. Yen: None. **A. Parthasarathy:** None. **R. Herikstad:** None. **C. Tang:** None. **L. Cheong:** None. **A.Y.Y. Tan:** None. **C. Libedinsky:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.13/EEE5

Topic: H.01. Animal Cognition and Behavior

Support: NIH T32-EB020087 (JZK)
NSF GRFP DGE-1321851 (JZK)
the Alfred P. Sloan Foundation (DSB)
e John D. and Catherine T. MacArthur Foundation (DSB)
the ISI Foundation (DSB)
the NIH R01 NS099348 (DSB)
NSF BCS-1441502 (DSB)

Title: The network topology of neural systems supporting avalanche dynamics predicts stimulus propagation and recovery

Authors: *H. JU[1], J. Z. KIM[2], D. S. BASSETT[3]
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Abstract: Neural systems display avalanche behavior characterized by uninterrupted sequences of neuronal firing. Previous empirical and computational work has demonstrated that the distribution of avalanche size and duration obeys a power law, which is a hallmark of critical systems. Theoretical models of such critical systems suggest that these dynamics support optimal information transmission and storage. However, the mechanism by which avalanches support these information capacities or other computations in neural systems remains unknown. Here, we study a generalized spiking model composed of neurons connected in a directed network that produces neuronal avalanches whose size and duration are well-fit by power laws observed in empirical data. By estimating the average behavior of this model, we demonstrate analytically and via simulations that the network topology can be designed to best propagate and recover desired patterns of stimulation, as measured by the Euclidean distance between network states and mutual information. With this relationship between network topology and optimally propagating stimuli, we identify characteristic topological features that contribute to lasting stimulus propagation using network connectivity derived from microelectrode array data from mouse somatosensory cortex slice cultures. Specifically, we find that these networks are organized into clusters that each propagate a specific pattern of stimulation. In addition, these clusters are often composed of strongly and bi-directionally connected neurons. Collectively, our results suggest that cortical networks with avalanching behavior more fundamentally support cluster-based, long-lasting propagation and recovery of a few crucial patterns of stimulation. Our results further imply that avalanching neural networks could contribute to cognitive faculties that require persistent activation of neuronal patterns, such as working memory or attention.

Disclosures: H. Ju: None. **J.Z. Kim:** None. **D.S. Bassett:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.14/EEE6

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01MH085666 to Wen-Jun Gao
Dean's Fellowship for Themed or Collaborative Research 2017 to Sarah Monaco

Title: Conditional GSK3β knockout in GABAergic parvalbumin interneurons affects behaviors and electrophysiological properties in adult and adolescent mice

Authors: *S. MONACO[1], A. J. MATAMOROS[3], G. HAN[3], E. BLACK[3], R. A. ESPAÑA[2], W.-J. GAO[4]
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Abstract: The ability to perceive, filter, prioritize, update and ultimately respond appropriately to incoming stimuli requires efficient prefrontal cortex (PFC)-dependent processing, with both N-methyl-D-aspartate receptors (NMDARs) and GABAergic interneurons playing a major role. However, what remains to be known is how NMDARs on GABAergic interneurons are regulated and how this affects cognitive function. We hypothesize that GSK3β is one common factor linking NMDARs, GABAergic signaling, and PFC-dependent cognition. Therefore disruption of this enzyme may serve as one underlying factor that successively leads to the downstream pathological phenotypes observed in schizophrenia. To elucidate the role GSK3β plays in GABAergic parvalbumin (PV) interneurons, we have developed a novel conditional mouse model in which GSK3β is genetically removed from PV-expressing neurons and labeled with a tdTomato reporter. PV-specific GSK3β KO mice require fewer days to learn a working memory task, but exhibit no differences on working memory at variable delays. PV-specific GSK3β KO mice demonstrate normal locomotion compared to control littermates. However, following amphetamine administration, male PV-GSK3β KO mice demonstrate a blunted response to amphetamine-induced locomotion. Correspondingly, male PV-GSK3β KO mice exhibited an increased acoustic startle response, demonstrating a dopaminergic dysregulation in males compared to females. Electrophysiologically, PV-GSK3β KO mice exhibit a lower action potential threshold as well as reduced sEPSC amplitude and frequency in pyramidal cells, which are the downstream targets of PV neurons. Gaining a better grasp on this signaling cascade will help provide an essential framework for understanding how GSK3β regulates NMDA receptors in the PFC, specifically within PV interneurons**.**

Disclosures: S. Monaco: None. **A.J. Matamoros:** None. **G. Han:** None. **E. Black:** None. **R.A. España:** None. **W. Gao:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.15/EEE7

Topic: H.01. Animal Cognition and Behavior

Support: NIMH093354

Title: Assessing the effects of muscarinic M1 receptor stimulation on dorsolateral prefrontal cortical neuronal firing on working memory related activity and behavioral performance in primates

Authors: *V. C. GALVIN[1], S.-T. YANG[1], A. S. LOWET[1], T. C. LIGHTBOURNE[2], A. F. ARNSTEN[1], M. WANG[1]
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Abstract: Acetylcholine nicotinic a7 receptors (nACha7R) have been investigated as a therapeutic target to treat working memory and other cognitive deficits in dorsolateral prefrontal cortex (dlPFC) in schizophrenia. Clinical trials have shown mixed results from these compounds. Previous data from our lab on the effects of iontophoretic application of nACha7R agonists on neuronal activity in dlPFC *in vivo* indicate an inverted-U based response, suggesting these mixed results may be due to a narrow window of optimal therapeutic dose range. Acetylcholine muscarinic M1 receptors (M1R) are also expressed in cortex and PFC, show reduced expression in PFC in a subset of schizophrenic patients, and have been a more recent focus for therapeutic target development to treat cognitive deficits. In this study we assessed the effects of direct manipulation of M1Rs on neuronal activity in dlPFC of primates performing a spatial working memory task. We tested the effects of both selective antagonists and agonists, as well as a novel M1R-selective positive allosteric modulator (PAM). In parallel to the single cell experiments, we also tested these compounds on animal behavior to assess therapeutic potential. We performed both intra-PFC infusions in a delayed alternation T-maze in rats, and systemic application in primates performing a working memory task. At the cellular level, we found activation of M1Rs significantly enhanced activity during the delay period, and blockade of M1Rs significantly reduced neuronal activity during the delay. At the behavioral level, we found intra-PFC infusion of the M1R PAM improved performance and prevented performance impairment from simultaneous NMDA receptor blockade. Additionally, we found systemic treatment with the M1R PAM improved working memory performance in primates. These data suggest selective M1R PAMs may provide promise as a novel treatment strategy for cognitive deficits from dlPFC dysfunction in schizophrenia.

Disclosures: V.C. Galvin: None. **S. Yang:** None. **A.S. Lowet:** None. **T.C. Lightbourne:** None. **A.F. Arnsten:** None. **M. Wang:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.16/EEE8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 2R15NS060117-02

Title: Role of IL-6 in obesity-induced cognitive deficit using the Morris water maze

Authors: *T. SIMON, V. PEÑA-GARCIA, B. TENG, L. BANNER, A. OYETUNDE
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Abstract: High fat diets (HFD) have been shown to cause consistent low grade inflammation in the brain leading to cognitive deficits. This neuoinflammatory response is composed of a vast

repertoire of immune signals and cellular components. A major contributor in this response is interleukin 6 (IL-6). IL-6 is a plurifunctioning cytokine denoting the fact that its function changes with concentration, cellular origin, and age of its host. In a physiological state, IL-6 is implicated in "filtering" unnecessary information during the consolidation stage of long term potentiation, however it can shift to an immune role in a pathological condition, such as neuroinflammation. Due to its notable part in inflammation, IL-6 is currently being considered as a potential therapeutic target, but the dynamic nature of IL-6 has made it difficult to study producing inconsistent results amongst researchers. To address the role of IL-6 in obesity-induced cognitive decline we have studied the behavioral changes in IL-6 KO vs wildtype (WT) mice following consumption of a HFD. The Morris Water Maze is a Hippocampal –dependent learning that assesses spatial memory performance in rodents. ImageJ and Animal Tracker software has enabled various parameters to be tested during the Morris Water Maze such as: time to platform, distance to platform, velocity, and immobility time. Comparisons between four groups, WT (C57BI6/J) on Lab Diet, WT on HFD (60%), IL-6 KO on a lab diet, and IL-6 KO on HFD (60%), has been evaluated. These results suggest that removal of IL-6 from C57BI6/J mice allows for continued memory acquisition, void of notable negative effects to their spatial memory.

Disclosures: T. Simon: None. **V. Peña-Garcia:** None. **B. Teng:** None. **L. Banner:** None. **A. Oyetunde:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.17/EEE9

Topic: H.01. Animal Cognition and Behavior

Support: R01EY026924
BCS1439221
EY014800

Title: A computational microcircuit model to account for nonlinear interactions of top down working memory signal with bottom up sensory input within area MT

Authors: *B. NOUDOOST[1], W. NESSE[2], Z. BAHMANI[3]
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Abstract: Recording in the middle temporal (MT) area, Bahmani et al. (Neuron 2018) have recently shown that during a spatial working memory (WM) task, the power of local field potential (LFP) oscillations in the alpha-beta band (8-25 Hz) increases and the timing of spikes

lock stronger to the phase of these oscillations. Whereas these oscillatory changes in the presence of a top-down WM signal do not result in an overall firing rate change, in the presence of a visual input these oscillations are associated with a greater gain of sensory signals. In order to account for these nonlinear interactions between top-down working memory and bottom-up sensory input, we developed a computational model based on local inhibitory circuits that exhibits LFP-like collective oscillations. The model provides predictions regarding how excitatory and inhibitory neurons should act differently in response to top-down and bottom-up inputs. We examined the validity of these predictions by re-analyzing the Bahmani et al. dataset. We segregated the broad spiking and narrow spiking neurons, as they are suggested to represent putative excitatory and inhibitory cells, respectively. We found that compared to inhibitory neurons, the timing of spikes in excitatory neurons exhibit a stronger locking to the LFP oscillation. The combination of neural results supported by the modeling findings provide valuable insight regarding the attentional modulation of sensory responses: top-down inputs, owing to distinct connectivity patterns, modulate bottom up linear response gain by activating the network in a nonlinear manner, producing emergent local rhythms and representational enhancement.

Disclosures: B. Noudoost: None. **W. Nesse:** None. **Z. Bahmani:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.18/EEE10

Topic: H.01. Animal Cognition and Behavior

Support: R01 EY-012135

Title: Sequential presentation of spatial target may bias multi-item memory toward independence

Authors: *C. D. HOLMES[1], L. H. SNYDER[2]
[1]Neurosci., Washington Univ. in St. Louis, Saint Louis, MO; [2]Dept of Neurosci., Washington Univ. Sch. Med., Saint Louis, MO

Abstract: Working memory, which encompasses the short-term storage of information, is critical for cognitive function. Working memory allows for multiple pieces of information to be stored at once. Yet, working memory has a finite capacity. An open question is how multiple memories are stored. At one extreme, multiple memoranda could be multiplexed together. For example, three points in space may be remembered as a (single) triangle. This is often referred to as “chunking”. At the other extreme, individual memorandum could be stored independently. If this were the case, we would expect individual pieces of information to interact little.

We trained animals to perform one- and two-item spatial working memory tasks. Animals were presented with one or two targets before a delay. After the delay, the same targets were presented along with an additional novel target. The animal's task was to make a saccade to the novel target. As expected, memory performance decreased when targets were closer together. However, performance was greater when targets were distributed between left and right visual hemifields, even when controlling for target distance. These data suggest that concurrent memory representations can interfere with one another, but also support a recent finding that each hemifield has its own memory store.
We used a mathematical model to estimate individual target memory rates from hit and error rates. Because we did not explicitly test for memory of both items on each 2-item trial, we could not obtain an exact solution. Instead we solved for a range of possible solutions and then considered the extreme cases. For items presented simultaneously, the range of possible solutions included both constructive (chunking) and destructive (competitive) interference between two memorized items. For items presented sequentially, there was almost no interaction, suggesting that memorized information was maintained independently.
Our findings suggest that multiple spatial memoranda may be stored competitively or be chunked together, but the effect size is small and approaches independence. We may be able to bias the extent to which representations are stored independently by separating memoranda in time.

Disclosures: C.D. Holmes: None. **L.H. Snyder:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.19/EEE11

Topic: H.01. Animal Cognition and Behavior

Support: Biotechnology & Biological Sciences Research Council (BB/M010732/1)
ONR (N00014-14-1-0681)
NIMH (R00MH092715)
NIMH (R37MH087027)
ONR MURI grant (N00014-16-1-2832)
Wellcome Trust (203139/Z/16/Z)
James S. McDonnell Foundation Scholar Award (220020405)

Title: Intrinsic neuronal dynamics predict distinct functional roles during working memory

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Abstract: Working memory (WM) is characterized by the ability to maintain stable representations over time; however, neural activity associated with WM maintenance can be highly dynamic. Here, we explored whether complex population coding dynamics during WM relate to the intrinsic temporal properties of single neurons. We analysed multi-electrode recordings from lateral prefrontal cortex (lPFC), the frontal eye fields (FEF) and lateral intraparietal cortex (LIP) of two monkeys (*Macaca mulatta*) preforming a complex change detection working memory task. For each neuron, we estimated the decay constant of baseline activity, also termed intrinsic timescale. We found that long timescale cells, played a greater role later during processing, dominating coding in the delay period. In contrast, cells with short timescales, carried memory information relatively early during memory encoding in lPFC and encoded mnemonic information with a higher temporal dimensionality. We also observed a link between functional connectivity at rest and intrinsic timescale in FEF and LIP. Our results indicate that individual differences in the temporal processing capacity estimated at rest predict complex neuronal dynamics during WM; ranging from rapid, dynamic encoding of stimuli to slower, but stable, maintenance of mnemonic information.

Disclosures: D.F. Wasmuht: None. **E. Spaak:** None. **T. Buschman:** None. **E.K. Miller:** None. **M.G. Stokes:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.20/EEE12

Topic: H.01. Animal Cognition and Behavior

Support: Canadian Institutes of Health Research
Alberta Innovates Health Solutions
Natural Sciences and Engineering Research Council

Title: Impaired cognitive function after perineuronal net degradation in the medial prefrontal cortex

Authors: *J. W. PAYLOR[1,2], E. WENDLANDT[2], Q. GREBA[3], J. G. HOWLAND[3], I. WINSHIP[1]
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Abstract: Perineuronal nets (PNNs) are highly organized components of the extracellular matrix that surround mature neurons in the central nervous system. These structures play a critical role in restricting neuronal plasticity, particularly as the brain matures. Consistent with this, their presence has been associated with functional and structural stability of the neurons they are associated with. Recently, numerous studies have identified deficits in PNNs in the post-mortem tissue of individuals who suffered from schizophrenia and it is thought that their absence may contribute to dysregulation of neural plasticity. Unfortunately, little is known about the direct consequences of perineuronal net loss. The current study sought to examine behavioural changes after targeted disruption of PNNs in the medial prefrontal cortex of adult rats. We injected the enzyme Chondroitinase ABC into the mPFC of Long-Evans rats at ~ postnatal day 65. Over the next two weeks, we administered a battery of cognitive tasks including set-shifting, prepulse inhibition, crossmodal object recognition, and an oddity task. Animals treated with chondroitinase had impaired performance on the oddity task, recognizing and maintaining the representation of unique objects in their environment. Chondroitinase-treated animals were also unable to perform better than chance in the crossmodal object recognition task. Interestingly, animals treated with chondroitinase did not perform differently that controls on prepulse inhibition or set-shifting, assessments of sensorimotor gating and cognitive flexibility, respectively. We also confirmed posthumously that chondroitinase treatment resulted in a loss of extracellular matrix staining and PNN density. There was no change in parvalbumin inhibitory interneuron density, but there was a significant increase in the number of parvalbumin interneurons that expressed c-Fos in the chondroitinase-treated rats. These findings suggest that PNN loss alone can impair cognitive function, particularly in behavioural assessments related to recognition memory. Given the impairment of recognition memory in schizophrenia, changes in PNNs should be given continued consideration as part of the core pathophysiology of schizophrenia and related disorders.

Disclosures: J.W. Paylor: None. **E. Wendlandt:** None. **Q. Greba:** None. **J.G. Howland:** None. **I. Winship:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.21/EEE13

Topic: H.01. Animal Cognition and Behavior

Support: CIHR 153111

Title: The effects of opening perineuronal nets in the medial prefrontal cortex with chondroitinase ABC on performance of the trial-unique, delayed nonmatching-to-location (TUNL) task in rats

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Abstract: Perineuronal nets (PNNs) are extracellular matrix structures that surround subsets of neurons in the brain and are involved in neurodevelopment and synaptic stabilization. They can be degraded with the enzyme chondroitinase ABC (ChABC), which digests the glycosaminoglycan chains of one of their major components, chondroitin sulfate proteoglycans (CSPGs). PNNs are critical for normal firing of PV-containing GABAergic interneurons in the prefrontal cortex, which play a role in working memory. The trial-unique, delayed nonmatching-to-location (TUNL) task is an automated touchscreen task that has been proposed to distinguish between processes involved in working memory and pattern separation, with the prefrontal cortex and hippocampus enabling working memory and pattern separation, respectively. In this experiment, the medial prefrontal cortex was targeted with ChABC to see how working memory would be affected following degradation of PNNs. Long Evans rats were habituated to the touchscreen chambers, shaped to nose-poke an illuminated stimulus to receive a food pellet reward, and then trained in the TUNL task. When a criterion of >70% accuracy on large separations was reached on 6s delay trials, surgery was performed with either infusions of penicillinase (PEN) as a control (n=12), or ChABC (n=12). Rats were then tested 5-8 days post-surgery in order to allow time for recovery and food restriction. Initially, over the first 3 days of testing, rats performed the standard 6s TUNL format that they were accustomed to. No significant within group or between group differences were found prior to or after surgery (PEN pre-surgery= 72.83% task accuracy, PEN post-surgery= 71.19%, ChABC pre-surgery= 72.75%, ChABC post-surgery= 66.97%). Rats were then tested for interference using a 2s delay with minimal inter-trial interval (ITI), and no significant differences were observed (ChABC = 74.95%, PEN = 75.96%). When presented with a novel 20s delay task to challenge working memory, the ChABC group did significantly better than the PEN group (ChABC = 58.04%, PEN = 52.47, p=0.027). There was no difference in selection trials between these groups. Overall, this suggests that breaking PNNs in the medial prefrontal cortex may affect the function of PV-containing GABAergic interneurons and lead to a period of increased synaptic plasticity, allowing novel tasks that tax working memory to be acquired at a faster rate.

Disclosures: M.D. Anderson: None. **Q. Greba:** None. **G.A. Scott:** None. **J.W. Paylor:** None. **I.R. Winship:** None. **J.G. Howland:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.22/EEE14

Topic: H.01. Animal Cognition and Behavior

Support: Seed grant money

Title: Altered developmental emergence of fear learning and memory in rats fed an obesogenic diet

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Abstract: Obesity alters cognitive and emotional processing. Paralleling clinical findings, we showed impaired extinction of learned fear and altered prefrontal-amygdala pathways in obese rats. Here, we investigated the novel idea that consumption of an obesogenic Western-like high-fat diet (WD) alters the developmental trajectories of cued fear learning and extinction responses across adolescence. Lewis rats (*postnatal day* 28) were fed for eight weeks with either the experimental WD diet (41 % kcal from fat), the match control low-fat diet (LFD; 13 % kcal from fat) or control chow diet (17 % kcal from fat). Acoustic startle reflex (ASR) and fear potentiated startle (FPS) responses were assessed longitudinally at weeks 1, 4, and 8 after commencing the diets to determine startle, cued fear, and attentional processing. We found that one-week exposure to the WD impaired fear extinction learning. In agreement with previous findings, rats fed a WD for 4 weeks exhibited reduced ASR responses. We found that rats fed a WD for 8 weeks exhibited impaired fear learning responses. Interestingly, the WD rats that underwent fear conditioning before the development of obesity exhibited normal fear responses at 8 weeks. We found reduced dopaminergic markers in the prefrontal cortex and amygdala in WD rats relative to LFD rats (WD vs. LFD: 38% reduction in dopamine receptor 1 and 53% reduction in tyrosine hydroxylase). Altogether, our findings demonstrate that consumption of an obesogenic diet during adolescence has a short- and long-term consequences in the developmental trajectories of conditioned fear responses. These results identify potential behavioral and molecular risk factors for psychopathology in the obese population.

Disclosures: J.D. Vega-Torres: None. **I. Alicea-Polanco:** None. **J.D. Figueroa:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.23/EEE15

Topic: H.01. Animal Cognition and Behavior

Support: NIH K01 MH106824
NARSAD

Nellie Ball

Title: Pharmacological manipulation of the rat cerebellar cortex at crus I disrupts performance in an interval timing task

Authors: *J. P. HESKJE[1,2], H. HALVERSON[2], A. JYOTIS[2], R. WILLIAMS[2], K. L. PARKER[2]
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Abstract: The cerebellum is a key cognitive region in the brain and recent work indicates that cerebellar stimulation may be therapeutic for cognitive dysfunction in disease. While effective, how cerebellar stimulation modifies cerebellar circuits to influence cognition remains unknown. Cognition can be investigated in rodents using timing tasks that require executive processes such as attention and planning. Our previous work indicates that inactivating the lateral cerebellar nuclei (LCN) with GABA agonist muscimol, impairs performance on an interval timing tasks where rodents make a motor indication to estimate the elapse of a temporal interval. To further probe the cerebellar role in this task and to understand how cerebellar transcranial magnetic stimulation which targets the cerebellar cortex and is unlikely to reach deeper structures like the nuclei, we infused a retrograde tracer into the LCN to identify regions of the cerebellar cortex that project there. In congruence with previous primate work, our results indicate that Crus I in the cerebellar cortex is densely connected to the LCN. To probe the role of Crus I in suprasecond time estimation, GABA agonist muscimol (0.5ul, 1 mg/ml) was infused into the right Crus I in 6 rats trained in the interval timing task. We report that time estimation was significantly disrupted indicating a role for Crus I in cognitive processes. GABA antagonist GABAzine, (0.5ul, 0.0002mg/ml) was also infused as an approach to stimulate Crus I and this manipulation did not have any effect on timing performance. Work is currently underway to pair these manipulations with Purkinje Cell recordings to further understand how cerebellar stimulation may influence cerebellar function and if stimulating Crus I may influence cognition in rodents that have frontal cortex dysfunction and timing impairments. This work supports a role for Crus I in the cerebellar cortex in cognitive function and may provide evidence for how cerebellar stimulation can improve cognition.

Disclosures: J.P. Heskje: None. **H. Halverson:** None. **A. Jyotis:** None. **R. Williams:** None. **K.L. Parker:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.24/EEE16

Topic: H.01. Animal Cognition and Behavior

Support: NIH K01 MH106824
NARSAD
Nellie Ball

Title: Cerebellar abnormalities in the prickle2 mouse model of autism-like behavior

Authors: *P. ABBOTT[1], J. P. HESKJE[5], M. BELOW[1], K. WALSH[1], A. J. NESSLER[2], Y. KIM[1], S. WU[1], L. P. SOWERS[1], J. HARDIE[1], J. D. AXELROD[6], A. LEE[3], A. G. BASSUK[1], K. L. PARKER[4]
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Abstract: Autism spectrum disorders involve abnormalities across brain systems, resulting in a constellation of symptoms including behavioral inflexibility, cognitive dysfunction, learning impairment, altered social interactions, and perceptive time difficulties. Recently, it was discovered that a common gene variant involved in non-canonical Wnt signaling, *prickle2,* was present in individuals with autism. Corroborated findings in *prickle2* knock-out and heterozygous mice suggest patterns of behavior similar to individuals with autism including altered social interaction on the three-chambered social task and behavioral inflexibility on the Barnes maze. Additionally, *prickle2* disruption results in hippocampal neuronal abnormalities including reduced dendritic branching, synapse number, and post-synaptic density size. Autism can also involve the cerebellum. As *prickle2* is strongly expressed in Purkinje cells, this animal model presents a unique opportunity to investigate cerebellar abnormalities associated with autism-like phenotypes. We studied *prickle2*-disrupted mice on several cerebellar-associated timing tasks, including interval timing and eyeblink conditioning. Preliminary data suggest that *prickle2*-disrupted mice have timing-associated deficits, and a battery of motor tasks suggests no significant impairments. Additionally, we explored structural and physiological abnormalities in animals with *prickle2* disruption using immunohistochemistry and whole-cell patch clamp recordings. These data suggest a role of the cerebellum in temporal processing and could inspire novel cerebellar-targeted treatments for cognitive impairments in autism spectrum disorders.

Disclosures: P. Abbott: None. **J.P. Heskje:** None. **M. BeLow:** None. **K. Walsh:** None. **A.J. Nessler:** None. **Y. Kim:** None. **S. Wu:** None. **L.P. Sowers:** None. **J. Hardie:** None. **J.D. Axelrod:** None. **A. Lee:** None. **A.G. Bassuk:** None. **K.L. Parker:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.25/EEE17

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant K01 MH106824
NARSAD
Nellie Ball
Pappajohn Biomedical Institute

Title: Contribution of the lateral cerebellar nucleus and medial frontal cortex to working memory and interval timing task performance in rats

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Abstract: The rat lateral cerebellar nucleus is homologous to the dentate nucleus of humans and non-human primates and appears to relay the majority of the cognitive output of the cerebellum to the cerebral cortex. The role of the cerebellum in cognitive processing is still unclear, but it is hypothesized that the cerebellum contributes through projections to association cortices like the prefrontal cortex, via thalamic relays. Consistent with this hypothesis, the cerebellum has been implicated in frontal cortex-dependent executive functions, and stimulation of the lateral cerebellar nucleus modulates single unit activity in the medial frontal cortex. The medial frontal cortex has been well established as necessary for spatial working memory and interval timing performance. Importantly, in instances of frontal cortex dysfunction (e.g., in neuropsychiatric disorders) cerebellar stimulation may help rescue performance in cognitive tasks. Here we investigated the individual contribution of the medial frontal cortex and lateral cerebellar nucleus to spatial working memory in the delayed alternation task, as well as supra-second interval timing in switch task and fixed interval procedures. We also tested whether pharmacological stimulation of the lateral cerebellar nucleus can rescue task performance during periods of pharmacological frontal disruption. We report that inactivation of the medial frontal cortex (e.g., via the GABA-agonist Muscimol) impairs performance in all of these tasks, while lateral cerebellar nucleus inactivation with Muscimol did not impair performance. Additionally, pharmacological stimulation of the lateral cerebellar nucleus using the GABA-antagonist GABAzine recovered performance in the fixed interval timing task when frontal D1-dopamine receptors were blocked pharmacologically.

Disclosures: K. Heslin: None. **K. Walsh:** None. **B.J. Decorte:** None. **K.L. Parker:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.26/EEE18

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant R01 EY016773

NIH grant R01 EY017077
Guy T. Carswell Scholarship

Title: Neuronal properties determining temporal dynamics of primate prefrontal activity in working memory

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Abstract: A debate exists on whether information is maintained in working memory based on a stationary or dynamic neural code. In order to examine how firing patterns of individual neurons determine population temporal dynamics, we analyzed data recorded from the dorsolateral prefrontal cortex of naïve monkeys and the same monkeys after training in a spatial working memory task. We examined the response patterns of 165 prefrontal neurons that responded selectively to the location of visual stimuli and maintained an elevated level of activity during the working memory period. Neurons active during the delay period of the working memory task could be divided into two main types. Neurons exhibiting a dynamic pattern of activity (characterized by ramping activity over the delay period - "anticipatory" neurons) become more numerous and less stationary in their spatial preference during the course of the delay period as a result of training. Neurons exhibiting a stationary pattern of activity (characterized by maintained firing in the delay period after a stimulus presentation - "sustained" neurons) were present both before and after training. Support vector classifiers were used to quantify the information content represented by the two types of neuron types. More information about the location of a visual cue could be decoded from the dynamic neurons in the last 500 ms of the delay period compared to the first 500 ms of the delay period, and this advantage was accentuated after training. In contrast, more information could be decoded from stationary neurons at the beginning of the delay period and information content decayed during the course of the trial. These results suggest that stationary and dynamic neurons play complementary roles in the representation of spatial information in working memory. Additionally, neurons with dynamic working memory coding are present in naïve subjects, but dynamic representation of information is further enhanced by training. Our findings explicate how the activity patterns of prefrontal neurons give rise to observed network dynamics.

Disclosures: T.R. Kellogg: None. **X. Qi:** None. **M. Riley:** None. **C. Constantinidis:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.27/EEE19

Topic: H.01. Animal Cognition and Behavior

Support: NEI RO1 EY11749
Grant P30 EY01319 to the Center for Visual Science

Title: Unilateral inactivation of lateral prefrontal cortex (LPFC) affects the retention of contralateral spatial and motion information during memory-guided comparisons

Authors: S. J. MURPHY[1], A. L. FOSTER[1], *T. PASTERNAK[2]
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Abstract: When observers compare stimulus features across time and space they retain information not only about these features but also about their location. We examined the contribution of the LPFC to this ubiquitous perceptual link between features and their locations as they are retained in visual working memory. We focused on the retention of visual motion and its location and used a behavioral paradigm that allowed direct comparison between the two types of working memory. In the *memory for direction task*, the monkeys compared two moving stimuli, S1 and S2 separated by a delay, and reported whether they moved in the same or in different directions. In the *memory for location task*, the two moving stimuli appeared at the same location or were spatially separated and the monkeys reported whether the locations of the two stimuli were the same or different. Neuronal recordings revealed striking parallels in the LPFC activity during these two tasks, with many neurons showing selectivity for the task relevant stimulus feature, followed by periods of selectivity during the delay in a pattern suggestive of a distributed network code (Wimmer et al, Ariadne 2016). This similarity in neuronal activity during memory-guided comparisons of directions and locations may be indicative of a common, or analogous neural substrate for representing sensory information during both working memory tasks. To assess the behavioral contribution of these neurons to memory-guided comparisons of direction and location, we made unilateral injections of muscimol (10µg/µl) into the LPFC (area 8Av). During each task, the precision with which the information about direction or location was retained, was measured by varying the difference between S1 and S2. The effect of inactivation on memory for direction was also assessed by measuring motion coherence thresholds. Thresholds were measured at short (0.25 and 0.5s) and long memory delays (1.5 and 2s) with 4-5^{o} patches of moving random dots presented in contralateral and ipsilateral hemifields. Inactivation resulted in impaired location and direction thresholds and these deficits were limited to the contralateral stimuli and long memory delays. The similarity of the deficits in memory for location and motion produced by the temporary inactivation of the LPFC provides direct demonstration of the key role this region plays in retaining both types of information. The contralesional nature of the deficits observed during both tasks highlights the importance of the interactions between the LPFC, which carries behaviorally relevant visual signals from across the visual field, and sensory neurons processing and representing contralateral stimuli.

Disclosures: S.J. Murphy: None. **A.L. Foster:** None. **T. Pasternak:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.28/EEE20

Topic: H.01. Animal Cognition and Behavior

Support: NIMH grant R01 MH097695

Title: Intermittent nucleus basalis stimulation enhances prefrontal activity

Authors: *X. QI[1], G. T. PATE[1], D. T. BLAKE[2], C. CONSTANTINIDIS[1]
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Abstract: The action of acetylcholine in the neocortex is critical for executive function. Cholinergic drugs can improve cognitive function in patient populations as well as normal adults. Recent studies in non-human primates have demonstrated behavioral improvement by bilateral intermittent electrical stimulation of the neocortical source of acetylcholine, the Nucleus Basalis (NB) of Meynert. Here we tested the effects of unilateral NB stimulation on prefrontal activity and behavior. Two adult male monkeys were implanted with electrodes targeting the Nucleus Basalis unilaterally; one subject in the left and one in the right hemisphere. Stimulation produced desynchronization of LFP power spectrum in the 5-15 Hz frequency range. The monkeys were trained to perform a spatial working memory task. They observed two stimuli presented in sequence with a delay period between them, and had to make a memory-guided eye movement toward the first stimulus if the fixation point was white, and the second stimulus if the point was blue. Intermittent stimulation, consisting of 60 pulses of stimulation delivered for 20 sec every minute, improved behavioral performance in the working memory task, particularly when the target stimulus appeared contralateral to the site of stimulation, and the distractor stimulus appeared ipsilateral. Neuronal activity was collected from 112 neurons in the dorsolateral prefrontal cortex of the two monkeys. NB stimulation increased neuronal activity, particularly during the delay period of the task, but did not affect phasic responses to visual stimuli in the receptive field, themselves. These results provide a neural mechanism behind the behavioral effects of cholinergic stimulation on cognitive function. Further, they demonstrate that unilateral stimulation is an effective means of improving cognitive performance.

Disclosures: X. Qi: None. **G.T. Pate:** None. **D.T. Blake:** None. **C. Constantinidis:** None.

Poster

243. Animal Cognition and Behavior: Working Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 243.29/EEE21

Topic: H.01. Animal Cognition and Behavior

Support: NIMH grant R01 EY017077
the Wake Forest Clinical and Translational Science Institute

Title: Prefrontal mechanisms of feature working memory

Authors: *H. TANG[1], A. B. PERSILY[1], M. C. ROBERTSON[1], G. T. PATE[1], X. QI[1], D. T. BLAKE[2], C. CONSTANTINIDIS[1]
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Abstract: The mechanisms of working memory and the role of the prefrontal cortex have been the matter of much recent debate. Selective, persistent activity in prefrontal neurons during working memory tasks has long been thought to be the neural basis of working memory. Recent models have instead suggested that rhythmic discharges or "silent" non-spiking mechanisms mediate working memory, and that prefrontal cortex may only play a role in the representation of the locations of remembered stimuli rather than the contents of working memory. To understand how features of remembered stimuli are represented in memory, we trained a monkey to observe a Gabor grating presented over the fovea, and after a delay period of 1.6 s, to report which of two stimuli was identical to this sample. Performance in this task was independent of stimulus location. It depended instead on the similarity between the sample and test stimuli, and the use of marginally discriminable stimuli in behavioral trials allowed error rates to become appreciable. As the monkey performed the task, we recorded Multi-Unit Activity (MUA) from the dorsolateral prefrontal cortex with an array of chronic electrodes. A total of 37 MUA records obtained over eight sessions displayed selectivity for the orientation of the grating during the stimulus presentation or the delay period. When a MUA's preferred stimulus was presented as a sample, error trials were characterized by lower activity during the delay period (paired t-test, $p=1.3 \times 10^{-7}$). In other words, when neurons generated less persistent activity following presentation of their preferred stimulus, the monkey recalled Gabor orientations that deviated from the actual stimulus. This was not the result of generalized, lower activation in error trials. When non-preferred orientations were presented, error trials were characterized by higher activity during the delay period (paired t-test, $p=0.02$). These results are consistent with a bump-attractor model, whose peak of activity represents object features held in memory and whose drift causes incorrect recalls of features, consistent with fluctuations in individual neuron firing rate. While these results do not rule out the potential for non-spiking mechanisms to play a role

in working memory, they do demonstrate a temporally causal relationship between prefrontal cortex delay period activity and behavioral choice.

Disclosures: H. Tang: None. **A.B. Persily:** None. **M.C. Robertson:** None. **G.T. Pate:** None. **X. Qi:** None. **D.T. Blake:** None. **C. Constantinidis:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.01/EEE22

Topic: H.01. Animal Cognition and Behavior

Support: NIH 2R01080007
WaNPRC Base Grant P51 OD010425
University of Washington Institute for Neuroengineering (UWIN)
NIH5T90DA032436
Simons Foundation 325467, 368149
Washington Research Foundation (WRF)
McKnight Endowment Fund for Neuroscience
Neuroscience Training Grant 5T32NS099578-02

Title: Using virtual reality to identify hipoocampal activity related to features of experience in monkeys

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Abstract: Hippocampal neurons show predictable, transient responses correlated with an animal's experience. Extensive research in rodents has characterized this activity in terms of the responses to the animals' spatial location, while research in primates has identified cells that respond based on where an animal is looking. It remains unclear whether the activity of neurons in the hippocampus are best described as having spatial responses or if this activity more accurately reflects reliable experiences, such as those structured by a task. Here, we investigated the activity of single neurons in the hippocampus as monkeys performed a spatial memory task in virtual reality. Monkeys were trained on a delayed-spatial-alternation task in a visually rich virtual Y-maze. Hippocampal neurons were simultaneously recorded from >60 channels using a chronically implanted hyperdrive with independently movable electrodes targeting the full anterior-posterior and medial-lateral extent of the hippocampus. Task-related variables were recorded, including the monkey's avatar position and the monkey's gaze relative both to the screen and in the virtual world.

Although gaze in the virtual world was highly correlated with avatar location, we compared the predictive power of these features using inhomogeneous Poisson generalized linear models. Models showed significant fit to location (117/271 cells tested) and virtual gaze (58/271). Cells with significant virtual gaze responses tended to have significant responses to the avatar's location (47/58), likely reflecting the correlated nature of these behavioral features. A large portion (70/117) of cells with responses to location did not show responses to virtual gaze, suggesting that the avatar position can be independently tracked by the hippocampus. Gaze on the screen rarely returned significant model fits (6/271), perhaps reflecting the immersive nature of the VR environment.
Our results indicate that single units show stable, reliable responses to distinct features of the task. These representations include place cells with consistent responses to the monkey's position in virtual space, as well as cells that respond to virtual gaze location. In addition, we also identified neurons that respond to reward locations and during the delay period. These results suggest that hippocampal activity reflects the progress of the monkey through the task, exhibiting reliable responses to both spatial and non-spatial task features that span the entirety of each trial.

Disclosures: Y. Browning: None. **J.W. Rueckemann:** None. **A.L. Fairhall:** None. **E.A. Buffalo:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.02/EEE23

Topic: H.01. Animal Cognition and Behavior

Support: NIH 2R01080007
WaNPRC Base Grant P51 OD010425
Pfizer, Inc. Neuroscience Research Unit

Title: Impaired cognitive flexibility in aged rhesus monkeys

Authors: *A. DEDE[1], S. A. SCHLEUFER[2], C. I. O'LEARY[1], E. A. BUFFALO[1]
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Abstract: Rules allow for abstract mapping between stimuli and responses. As environmental demands change, animals update rules and alter behavior. This can be challenging when rules need to be updated despite identical perceptual conditions. For example, when going to work, one may scan vehicles on the road for a yellow vehicle, a small pink mustache on a dashboard, or a large, boxy vehicle. Whether one is searching for a taxi, an app-enabled ride share, or a bus will determine attentional allocation. Studies have shown that updating attentional set is impaired

in aging, but the mechanisms of this decline are unclear. The Wisconsin Card Sorting Task (WCST) is a classic test of the ability to shift attentional set. We adapted the WCST for use in monkeys. On each trial, monkeys fixated a central cross and then were presented with four stimuli on a computer screen. Each stimulus was comprised of color, shape, and texture (*i.e.*, a blue striped star), and was chosen from a pool of 64 unique stimuli. Within a block of trials, one color, texture, or shape was the target, resulting in 12 possible rules. Responses were made with eye movements, and an 800ms fixation on one of the four stimuli in a display was taken as the monkey's choice. The monkey recieved food reward for selecting the stimulus that contained the target feature. When the monkey made 8 consecutive correct responses or 16 out of the previous 20 responses, the target feature was changed without any cue. This paradigm is similar in complexity to the human WCST, can be trained relatively quickly, and allows for the observation of between 10 and 40 learning events per experimental session. We compared the performance of 2 aged monkeys to 2 young monkeys, and we found that aged monkeys showed less flexibility than young monkeys. On average, old monkeys required 55.7 trials to learn each target to criterion, while young monkeys required only 42.0 trials ($p<.001$). In addition, learning in the old monkeys reflected a slow accumulation of ability, while learning in the young monkeys was more often characterized by a step-function, suggesting sudden insight. These data suggest that this task could be used to characterize the neurophysiological mechanisms of age-related decline in cognitive flexibility in a monkey model.

Disclosures: A. Dede: None. **S.A. Schleufer:** None. **C.I. O'Leary:** None. **E.A. Buffalo:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.03/EEE24

Topic: H.01. Animal Cognition and Behavior

Support: NIH 2R01080007
WaNPRC Base Grant P51 OD010425
University of Washington Institute for Neuroengineering (UWIN)
NIH5T90DA032436
Simons Foundation 325467, 368149
Washington Research Foundation (WRF)
McKnight Endowment Fund for Neuroscience
Neuroscience Training Grant 5T32NS099578-02

Title: Oscillatory activity in the monkey hippocampus during attentive processing

Authors: *J. W. RUECKEMANN, A. D. GARCIA, A. E. NG, E. A. BUFFALO
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Abstract: Theta-frequency activity in the hippocampal local field potential is an important hallmark of attentive processing in rodents, reflecting coordinated activation and synchronous transmembrane currents across large populations of hippocampal neurons. However, theta-band activity has been difficult to study in the monkey, likely due to the irregularity of hippocampal oscillations in primates and signal contaminants, like volume-conducted artifact. Here, in order to isolate signal sources that are specific to the hippocampal laminae, we made MRI-guided acute recordings of the monkey (rhesus macaque) hippocampus using multisite linear probes. During recordings, the monkey actively watched movies of birds feeding, and attentive engagement was confirmed through analysis of eye movements. ICA-based deconvolution techniques were utilized to characterize the spatial topography of signals contributing to the local field potentials, allowing for localization of current sources and rejection of components that were common across all channels. Using this approach, we found that the local circuitry of the monkey hippocampus exhibits a narrow theta-band oscillation (~10Hz peak frequency) that occurs in intermittent bouts. Importantly, this oscillation gates intrinsic activity within the hippocampus, as demonstrated by robust phase-amplitude coupling of gamma-band activity in the local field potential and phase-locking of hippocampal neuron spiking. The transient nature of hippocampal theta in the monkey during attentive processing is notably different from the rodent, which exhibits virtually constant theta band activity during exploratory behaviors. These data suggest that the taxonomy of oscillatory processing states may be more diverse during awake behaviors in the primate hippocampus than the rodent, calling for a potential revision of the canonical binary division between attentive and quiescent states.

Disclosures: J.W. Rueckemann: None. **A.D. Garcia:** None. **A.E. Ng:** None. **E.A. Buffalo:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.04/EEE25

Topic: H.01. Animal Cognition and Behavior

Support: NIH 2R01080007
WaNPRC Base Grant P51 OD010425

Title: Entorhinal activity indexes mnemonic pupillary responses in monkeys

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Abstract: It is unclear how the moment-to-moment activity of neurons in the hippocampal formation influences behavioral responses. In both monkeys and humans, pupillary responses

have been shown to reflect general image novelty and recognition memory. Here we investigated the relationship between pupillary responses and single-unit activity in monkey entorhinal cortex (EC).
Pupil size, gaze position and the spiking activity of individual EC neurons were recorded in two rhesus macaques freely viewing large, complex images for up to five seconds. Between image presentations, monkeys were rewarded for performing a directed saccade task, thus allowing eye calibration throughout the experiment. In each recording session, monkeys viewed 90-120 novel images that were each presented twice.
The percent change in pupil size was computed across the two presentations of an image starting 500 ms after image onset until the monkey looked away from the image or the trial ended (mnemonic pupillary response). This allowed pupil size to be compared for identical stimuli and after the typical pupil constriction at image onset. The difference in cell spike count was computed across the two presentations of an image in the time window 20-500 ms after image onset image (neuronal memory response). This allowed us to target early neural responses which potentially drive the mnemonic pupillary response.
We found that in both monkeys, the size of the neuronal memory response was correlated with the size of the mnemonic pupillary response, on an image-by-image basis. Additional analyses showed that both of these responses also correlated with other changes in viewing behavior that reflect recognition memory for the images.
Taken together, these findings identify a neural correlate for mnemonic pupillary responses in the EC, theoretically reflecting memory strength for unique images. Because the EC projects directly to brain areas implicated in motor control of the pupil (e.g., anterior cingulate cortex (Joshi et al., 2016, Munoz & Insausti, 2005)), it is possible that this EC activity drives mnemonic pupillary responses. Future research to determine how the output of the hippocampal formation impinges on motor structures in real time will provide a fundamental advance in our understanding of how memory influences behavior.

Disclosures: M.L. Meister: None. **E.A. Buffalo:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.05/EEE26

Topic: H.01. Animal Cognition and Behavior

Support: Labex Memolife
Fondation Bettencourt Schueller

Title: Novel behavioral correlates of optogenetically identified noradrenergic neurons of Locus Coeruleus

Authors: S. WIENER[1], L. XIANG[1], A. HAREL[1], H. GAO[1], A. E. PICKERING[3], *S. J. SARA[2,4]
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Abstract: The brainstem nucleus locus coeruleus (LC) is the major source of forebrain norepinephrine (NE). The NE system has been implicated in cognitive functions, including decision-making and behavioral flexibility. One hypothesis is that LC activation promotes rapid shifts in cortical attentional networks following changes in environmental contingencies. Recent work also supports the noradrenergic system as critical for mobilizing resources and preparing appropriate responses to deal with challenging situations. We recorded LC unit activity in rats performing in a self-paced automated T-maze where the rat initiated the trials. The maze size and layout allowed for a wide range of movement and rapid changes in response reward contingencies. A photodetector on the maze stem 20 cm from the start box triggered visual cue onset, while return arm photodetectors triggered the cue off. Rats were first trained to perform visual discrimination and then reward contingencies were changed to a left or right turn, still in the presence of the now irrelevant visual cue. In one rat, previously injected with a viral vector specifically targeting noradrenergic neurons, the noradrenergic identity of responsive units was confirmed optogenetically. LC unit firing rate increased just *prior* to light-triggering photodetector crossings. This increase was positively correlated with acceleration; moreover, LC activity onset preceded acceleration onset by about 35 ms. This is consistent with the LC-NE system being involved in mobilizing effort when the rat initiates a trial. Finally, in all three sessions where the animal shifted between task contingencies for the first time, the LC firing rate *after* VC onset increased significantly after the rule shift, before the animal adapted its behavior to the new contingency, supporting a role for LC in reorienting attention as environmental contingencies change

Disclosures: S. Wiener: None. **L. Xiang:** None. **A. Harel:** None. **H. Gao:** None. **A.E. Pickering:** None. **S.J. Sara:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.06/FFF1

Topic: H.01. Animal Cognition and Behavior

Support: Alzhiemers Association

Title: Setting the thermostat for cerulean fire in Ts65Dn mice

Authors: *E. D. HAMLETT[1], S. L. CARROLL[2], A.-C. GRANHOLM[3]
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Abstract: Background: The locus coeruleus (LC) regulates arousal and has a significant effect on sensory processing and memory performance. During the preclinical Alzheimer's disease (AD) phase, LC degeneration has a significant impact on executive function, working memory, and attention. For individuals with Down syndrome (DS) related AD, 60% or greater loss of LC-NE neurons with a severe amyloid plaque and Tau neurofibrillary tangle. Based on this knowledge, we hypothesize that noradrenergic activity affects the progression of DS-AD. In the Ts65Dn mouse model of DS, LC degeneration occurs early and provides opportunities to study LC contributions to memory performance, adrenoreceptor (AR) signaling and neuroinflammation.
Objective: To better isolate LC contributions to memory, we administered hM4 *inhibitory* or hM3 *stimulatory* designer receptors exclusively activated by designer drugs (DREADDs) via an adeno-associated virus into the LC under control of a synthetic PRSx8 promoter, to selectively control LC neuron activity by exogenous administration of the inert ligand, clozapine-*N*-oxide (CNO).
Methods: Thirty minutes after CNO administration, we employed a series of behavioral tasks including open field locomotion, novel object recognition, and water radial arm-maze. Adrenoreceptor and inflammatory markers were quantified in the brain by immunofluorescence imaging.
Results: hM3 stimulation of the LC enhanced performance in novel object recognition and water radial arm maze task while reducing hyperactivity in Ts65Dn mice. hM4 inhibition of the LC decreased performance in novel object recognition and water radial arm maze task with no effect on locomotion or hyperactivity in Ts65Dn mice. Notable proteomic responses occurred in adrenoreceptor levels and inflammatory markers after 10 days of LC inhibition.
Conclusions: DREADDs enabled discreet control of LC activity in a neurodegenerative paradigm and allowed novel investigations of specific LC-specific contributions to memory performance, adrenoreceptor dynamics, and neuroinflammation. Adrenoreceptors seem to follow different compensatory response patterns to LC activity manipulation.

Disclosures: E.D. Hamlett: None. **S.L. Carroll:** None. **A. Granholm:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.07/FFF2

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIMH Grant 1R01MH102394 – 01A1

Title: Prelimbic cortex integrates behavioral context with task-coding during spatial working memory maintenance

Authors: *J. J. STOUT, JR, A. C. GARCIA, A. L. GRIFFIN
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Abstract: Spatial working memory (SWM) is the ability to encode, maintain, and retrieve spatially-relevant information to guide a decision. Numerous studies have investigated the prefrontal mechanisms that support SWM processes, but it is not fully understood what spatial representations are supported by the medial prefrontal cortex (mPFC) during memory maintenance. Using *in vivo* electrophysiological recordings from rodent prelimbic (PL) and anterior cingulate (ACC) cortices (two sub-regions of the mPFC that have dissociable functional roles in behavior), we examined neuronal and population activity patterns during the delayed non-match to position (DNMP) task. The DNMP task provides a means to investigate neuronal activity during the encoding (sample) phase, maintenance (delay period) phase, retrieval (choice) phase, and inter-trial interval. We report that PL cortex population activity discriminates between the early and late portions of the delay, and the early and late portions of the ITI, possibly reflecting task-related preparatory processes. Interestingly, and in line with previous work examining mPFC activity, we demonstrate that PL cortex population activity discriminates between the end of the delay and inter-trial interval, suggesting that PL plays a role in task-coding (discriminatory differences in neuronal activity that is dependent on a phase of the task). Finally, we are the first to our knowledge to report that PL cortex population activity distinguishes between trial-types (sample L-choice R vs sample R-choice L) on the DNMP task during early, but not late memory maintenance. Trial-type coding could reflect a recent or future experience, task-coding, or distinct trial-type experiences, which we collectively refer to as behavioral context. Thus, these findings suggest that representations in PL cortex monitor behavioral context and task-phase during SWM maintenance

Disclosures: J.J. Stout: None. **A.C. Garcia:** None. **A.L. Griffin:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.08/FFF3

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIMH Grant R01MH102394 – 01A1

Title: Medial septal inactivation disrupts the maintenance of information over a temporal delay

Authors: *M. DONAHUE, Z. M. GEMZIK, A. L. GRIFFIN
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Abstract: Spatial working memory (SWM) is defined as the ability to process and maintain spatially-relevant, goal-directed information over a temporal gap. An intact hippocampus (HPC) is known to be essential for SWM task performance. However, it is not known if HPC contributes to the encoding, maintenance, or retrieval of spatial information. One way to disrupt activity in the HPC is by suppressing activity in the medial septum (MS), one of the septal nuclei that projects to all cell fields of the HPC and provides the rhythmic drive for HPC theta oscillations. HPC theta is one of the most prominent oscillations in the HPC and is hypothesized to contribute to SWM. Therefore, we compared the effects of optogenetic suppression of MS activity that was delivered selectively during the encoding, maintenance and retrieval phases of two different HPC-dependent SWM tasks: a delayed non-match to position (DNMP) task and a visual-tactile conditional discrimination working memory (CDWM) task. During the DNMP task, suppression of the MS specifically during the maintenance phase impaired choice accuracy. During the CDWM task, suppression of the MS during the entire trial reduced choice accuracy, with further manipulations showing that this deficit is due to MS inactivation during the retrieval phase of the task. Together, these results suggest that the MS supports the maintenance of goal-relevant information over a temporal delay during SWM tasks. This deficit may be due to an interruption of the ability to both maintain information over a temporal gap and plan a future decision using previously encoded information.

Disclosures: M. Donahue: None. **Z.M. Gemzik:** None. **A.L. Griffin:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.09/FFF4

Topic: H.01. Animal Cognition and Behavior

Support: JST PRESTO JPMJPR1684
JSPS KAKENHI 16H04653
Takeda Science Foundation
Naito Foundation
Lotte Research Promotion Grant
JST CREST JPMJCR13W1
JSPS KAKENHI 23220009

Title: Orchestrated ensembles activity constitute hippocampal memory engram

Authors: *K. GHANDOUR[1], N. OHKAWA[1], C. A. FUNG[2], H. ASAI[1], Y. SAITOH[1], T. TAKEKAWA[3], R. OKUBO-SUZUKI[1], S. SOYA[4], H. NISHIZONO[1], M. MATSUO[1], M. OSANAI[5], M. SATO[6], M. OHKURA[7], J. NAKAI[7], Y. HAYASHI[8], T. SAKURAI[4], T. KITAMURA[9], T. FUKAI[2], K. INOKUCHI[1]
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Abstract: It is hypothesized that a memory is encoded in a subset of neurons, which is activated by physiological input derived from a corresponding event, called engram. The c-fos-TetTag system has proven the engram theory, by manipulation of, activity-dependent, gene expression cells driven by learning. However, the physical and basic activities that occur during learning and post learning in that group of cells, is still poorly understood. Here we show that engram cells exhibit a remarkable synchronous activity representing the contextual memory in the form of several ensembles in engram cells. These ensembles carry on their activity not only during learning but also during post-learning sleep and retrieval sessions, in contrast to non-engram cells. A compatible imaging system was established to observe the neuronal activity of ∼1000 CA1 neurons and the labeled engram cells; through a photoconvertible fluorescent protein Kikume Green Red (KikGR). The neuronal activity of hippocampal CA1 neurons was observed, through Ca^{2+} influx with GCaMP7 in freely-moving animals by miniature head-mount fluorescent microscopy. Our advanced imaging system of engram cells and non-engram cells provides deeper insights into the dynamics of the neural activity during contextual memory processing. Engram cells exhibit highly repetitive activity corresponding to remarkable synchrony during novel context exposure. Population vector distance (PVD) analysis indicates that total activity patterns of engram cells are stable and consistent across other sessions; sleep (NREM and REM) and retrieval, not only during learning. Furthermore, Non-negative Matrix Factorization (NMF) analysis extracted characteristic ensembles activity that were constructed by a subgroup of engram cells, representing the persistent synchronous activity even during post-learning sleep (NREM and REM) sessions and retrieval session, but not in a distinct context. In contrast, these features were not seen in non-engram cells. These results suggest that there are several fundamental characteristics of the engram cells that give them superiority in encoding the ongoing event and consolidating the past ones.

Disclosures: K. Ghandour: None. **N. Ohkawa:** None. **C.A. Fung:** None. **H. Asai:** None. **Y. Saitoh:** None. **T. Takekawa:** None. **R. Okubo-Suzuki:** None. **S. Soya:** None. **H. Nishizono:** None. **M. Matsuo:** None. **M. Osanai:** None. **M. Sato:** None. **M. Ohkura:** None. **J. Nakai:** None. **Y. Hayashi:** None. **T. Sakurai:** None. **T. Kitamura:** None. **T. Fukai:** None. **K. Inokuchi:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.10/FFF5

Topic: H.01. Animal Cognition and Behavior

Support: MEXT KAKENHI JP 25115002
JSPS KAKENHI JP 23220009
CREST, JST
JSPS KAKENHI JP 24680034
Hokuriku Bank Grant for Young Scientists
The Uehara Memorial Foundation
The Takeda Science Foundation

Title: Manipulation of fear memory association by posterior parietal cortex

Authors: *A. SUZUKI[1,2], S. KOSUGI[1,2], E. MURAYAMA[1,2], N. OHKAWA[1,2,3], M. MATSUO[4], H. NISHIZONO[2,4], K. INOKUCHI[1,2]
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Abstract: The association of fear memory occurs when a conditioned stimulus (CS) is paired with an unconditioned stimulus (US). Although previous studies suggested that some of brain regions responded to CS and US signals, it is still unclear how the association regulates. Here we show that the cellular ensemble in Posterior Parietal Cortex (PPC) specifically modulates CS-US association without the processing of CS and US information. In the modified context-pre-exposure facilitation effect (CPFE) paradigm, optical silencing of PPC neurons which responded to context exposure (CS), when mice received footshock (US) in the same context, failed to associate the context (CS) and the shock (US). On the other hand, optical activation of PPC neurons which responded to context exposure, when mice received footshock in a different context, generated an artificial CS-US associative memory, in which mice showed a freezing response in the initial context where mice did not received footshock, but not in the neutral context. Furthermore, 15 min optically silencing of PPC neurons that responded during reactivation of CS-US associate memory that has been once formed immediately after CS exposure 1 day after reactivation suppressed fear memory when mice were tested 1 day later without optical silencing. Thus, manipulating the PPC activity diassociate CS-US associative memory. Our finding suggests that PPC contributes to stimulus integration and association of fear memory. Furthermore, our finding suggests that fear memory association are regulated by

manipulating the activity of PPC. This indicates that PPC is a novel therapeutic target in particular for the treatment of psychiatric disorders such as posttraumatic stress disorder (PTSD).

Disclosures: A. Suzuki: None. **S. Kosugi:** None. **E. Murayama:** None. **N. Ohkawa:** None. **M. Matsuo:** None. **H. Nishizono:** None. **K. Inokuchi:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.11/FFF6

Topic: H.01. Animal Cognition and Behavior

Support: MĚXȚ ĶÅĶĚŇĦİ JP 25115002
JȘPȘ ĶÅĶĚŇĦİ JP 23220009
ČŘĚȘȚ JPMJČŘ13Ẅ1

Title: Synapse-specific plasticity governs the identity of overlapping memory engrams

Authors: *K. M. ABDOU[1], M. H. SHEHATA[3], K. CHOKO[1], H. NISHIZONO[2], M. MATSUO[2], S. MURAMATSU[4], K. INOKUCHI[1]
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Abstract: Memories are formed through long-term changes in synaptic efficacy, a process known as synaptic plasticity, and are stored in the brain in specific neuronal ensembles called engram cells, which are activated during corresponding events. When two memories are associated, cell ensembles corresponding to each memory overlap and are responsible for the association. However, each memory has its own identity. How the brain stores and defines a specific memory identity out of intermingled memories stored in a shared cell ensemble remains elusive. Here, we show that synapse-specific plasticity represents specific memory entities, and that synaptic plasticity between specific engram assemblies is both sufficient and crucial for information storage. In auditory fear conditioning (AFC) in mice, after complete retrograde amnesia, optogenetic stimulation of the activated ensemble terminals of auditory cortex (AC) and the medial geniculate nucleus (MGm) in the lateral amygdala (LA) failed to induce fear memory recall, indicating that the memory engram no longer existed in that circuit. Complete retrograde amnesia of a given fear memory did not affect the linked fear memory encoded in the shared ensemble. Furthermore, potentiation or depotentiation of the plasticity at synapses specific to one memory affected the recall of that memory without influencing the linked memory. Thus, sharing of engram cells underlies the linkage between memories, while synapse-specific plasticity guarantees the identity and storage of individual memories.

Disclosures: K.M. Abdou: None. **M.H. Shehata:** None. **K. Choko:** None. **H. Nishizono:** None. **M. Matsuo:** None. **S. Muramatsu:** None. **K. Inokuchi:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.12/FFF7

Topic: H.01. Animal Cognition and Behavior

Title: The role of cholinergic and GABAergic basal forebrain neurons in coding outcome expectation during pavlovian conditioning

Authors: *P. HEGEDÜS[1], B. HANGYA[2]
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Abstract: The basal forebrain (BF) has widespread cholinergic, GABAergic and glutamatergic projections which are thought to mediate multiple cognitive functions including learning and attention. We recently demonstrated that BF cholinergic neurons respond to reward and punishment and this response is scaled by the unexpectedness of the reinforcer (Hangya et al, 2015). Additionally, putative GABAergic neurons of the BF also display activation proportional to behavioral salience (Lin et al., 2008). These studies raise the possibility that the BF may be involved in broadcasting signals related to outcome expectations. To directly test this hypothesis, we trained mice on an auditory pavlovian cued outcome task, in which two pure tones of different pitch predicted likely reward (water) and unlikely punishment (air puff) or vice versa. Next, we recorded and optogenetically identified single neurons from the frontally projecting portion of the BF (horizontal limb of the diagonal band of Broca, HDB) while mice were performing the task. Both reward and reward predicting cues activated a subset of BF neurons, consistent with possible reward prediction error coding in the BF. Interestingly, we found that identified parvalbumin (PV) positive neurons were responding differentially to reinforcement valence by phasic activation to punishment but not to reward. On the other hand, cholinergic neurons were responding rapidly to both reward predicing cues and reinforcement and this response was scaled by the reward probability, partially consistent with a reward prediction-error coding behavior. We have also found a strong correlation of cholinergic activation with shorter reaction times during the task, therefore a stronger phasic answer of the colinergic neurons predicted a faster behavioral response. Understanding the circuitry of outcome expectancy during reinforcement learning may clarify how the BF participates in associative learning and facilitate translational research aiming at revealing the roles the BF plays in cognitive decline.

Disclosures: P. Hegedüs: None. **B. Hangya:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.13/FFF8

Topic: H.01. Animal Cognition and Behavior

Support: Department of Biotechnology, Govt. of India
The Tata Institute of Fundamental Research, Department of Atomic Energy, Govt. of India

Title: A multilevel analysis of deficient fear learning in a novel model of FXS

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Abstract: Fragile X syndrome (FXS) is the most common inherited cause of mental impairment and the most common known monogenetic cause of autism. Classical symptoms include pronounced gaze aversion, excessive shyness, and acute anxiety. The emotional deficits observed in humans with FXS suggest dysfunction of the amygdala. Rodent models of FXS show impaired long-term potentiation (LTP) of the principal neurons in the basolateral amygdala. LTP like process in the amygdala is known to underlie the formation and recall of associative auditory fear memories. Moreover, auditory processing is known to be impaired in *Fmr1* KO mice. Taken together this predicts that associative fear memory could be impaired in the FXS. Hence, in the present study, we examined the ability of a novel rat model of FXS to form and recall amygdala-dependent auditory fear memories. In addition, we also explored the molecular and physiological correlates of fear memories. We used 2 months old rats from *Fmr*$^{1-/y}$ Sprague Dawley colony and exposed to fear conditioning in which conditioned stimulus (CS), elicits fear responses after being associatively paired with an aversive unconditional stimulus (US). Simultaneously, with fear behavior, auditory evoked potentials from the lateral nucleus of the amygdala were also recorded before and after fear conditioning. In addition, biotinylation with estimation of surface proteins and activation of mGluR5 in the amygdala was also performed. As a result, *Fmr1* KO rats showed an impairment in the recall of auditory fear memory. Consistent with this, the slope and amplitude of auditory evoked potentials (AEPs) in response to the tone, is also lower in these rats. Moreover, *Fmr1* KO rats also do not show a conditioning induced potentiation of AEP slope and amplitude in the amygdala. The lower expression of GluR1 and NR1 in the amygdala of KO rats at basal levels as well as after the recall of fear memory correlates with the reduction in AEP amplitude. Furthermore, the frequency of mEPSCs is also lower in the amygdala neurons of *Fmr1* KO rats compared to WT neurons. A 10 min bath application of the mGluR5 agonist,

DHPG increases the frequency of mEPSCs in the amygdala neurons of both WT and KO rats. This implies that an acute treatment with a mGluR5 agonist is sufficient to rescue the impaired frequency of excitatory currents in the amygdala of *Fmr1* KO rats. This raises the possibility that an acute treatment with DHPG may also rescue the impaired amygdala LTP and impaired fear memory seen in *Fmr1* KO rats.

Disclosures: P.K. Mishra: A. Employment/Salary (full or part-time):; INSTEM. **G. Fernandes:** None. **S. Chattarji:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.14/FFF9

Topic: H.01. Animal Cognition and Behavior

Title: Long-term potentiation in the amygdala of the tambaleante tbl/tbl mouse

Authors: *J. N. DIAZ[1], E. JUÁREZ-CORTES[2], J. ARMENGOL[3], A. RODRÍGUEZ-MORENO[3]
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Abstract: Long-term potentiation (LTP), expressed as an increase in synaptic strength, is considered an excellent approach to explain the cellular and molecular bases of learning and memory. *Tambaleante* mouse (*tbl*/*tbl)* presents a spontaneous mutation in the E3 ubiquitin ligase protein (HERC1), present a loss of Purkinje cells and suffers an ataxic syndrome. Given that the presence of a mutation in HERC1 in humans correlates with cognitive deficits, we investigated here whether *tbl*/*tbl* mice show alterations in short-term synaptic plasticity (STP) and long-term potentiation (LTP). Field excitatory postsynaptic potentials (fEPSP) were obtained from slices from control and *tambaleante* mice containing the amygdala, stimulating the cortical afferents (external capsule) or the thalamic afferents (internal capsule) and recording from the lateral or basolateral amygdala, respectively. After 10 minutes of basal stimulation at 0.2 Hz, a theta burst stimulation protocol was applied to induce LTP consisting in: 10 trains of 4 stimuli of 100 microseconds duration, at 100 Hz, with an interval inter stimulus of 10 ms and with 200 ms between trains; this protocol was repeated 5 times every 5 seconds, to return immediately to the basal stimulation for 1 hour. We analyzed the slope and amplitude of the maximum peak of the fEPSP, and the magnitude of LTP after 1 hour of recording post protocol stimulation. In mutants, we observed a decrease in STP. LTP could not be detected in these mutant mice. These results suggest that the cognitive deterioration presented by individuals carrying a mutation in HERC1

might be due in part to a decrease in synaptic strength and it could involve an alteration to the ubiquitin-proteasome pathway.

Disclosures: J.N. Diaz: None. **E. Juárez-cortes:** None. **J. Armengol:** None. **A. Rodríguez-Moreno:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.15/FFF10

Topic: H.01. Animal Cognition and Behavior

Support: HHMI

Title: Neural ensemble dynamics in the medial prefrontal cortex underlying shifts in cognitive strategy

Authors: *F. L. WANG[1,2], T. H. KIM[1,3], O. HAZON[1,4], M. J. SCHNITZER[1,4,5]
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Abstract: Substantial evidence indicates that the medial prefrontal cortex (mPFC) plays a crucial role during shifts in cognitive strategy. For instance, inactivation of mPFC impairs the ability to shift between different cognitive strategies[1-2], and electrophysiological recordings in behaving rodents have revealed mPFC neural activity that is temporally linked to strategy shifts[3-4]. However, it remains unclear how mPFC neural ensemble dynamics might underlie the brain's representation of, and shifts between, different cognitive strategies. Here we used a miniature, head-mounted fluorescence microscope to image the calcium dynamics of hundreds of individual mPFC neurons in the prelimbic cortex (PrL) of mice performing a strategy-switching navigation task. In this task, mice switched between a hippocampus-dependent, allocentric (spatial) navigation strategy and a striatum-dependent, egocentric strategy (or *vice versa*) to earn a water reward. Bilateral inactivation of mPFC impeded the animals' capacities to switch between these two strategies, but not their abilities to perform the task well when applying a fixed strategy. Analysis of the neural calcium imaging datasets revealed distinct subsets of PrL neurons with contemporaneous and anticipatory coding for multiple different task parameters, including the mouse's spatial location and its receipt of reward. Notably, the dynamics of these neural populations were preferentially modulated during strategy switching trials, as compared to other trials with similar sensory stimuli and motor responses. We are presently studying how the ensemble level dynamics of these cell populations might reflect and underlie the representations of and shifts between different strategies. Overall, our work reveals the large-scale neural population activity of frontal cortical neurons in mice performing a task requiring cognitive flexibility and paves the way to future studies of the neural ensemble codes underlying other

modes of cognitive control. References: 1. Birrell & Brown (2000) Medial Frontal Cortex Mediates Perceptual Attentional Set Shifting in the Rat. *J Neurosci*. 20(11):4320-4324; 2. Floresco et al. (2008) Inactivation of the medial prefrontal cortex of the rat impairs strategy. *Behavioural Brain Research*. 190:85-96; 3. Rich & Shapiro (2009) Rat prefrontal cortical neurons selectively code strategy switches. *J Neurosci*. 29(22):7208-7219.2; 4. Durstewitz et al. (2010) Abrupt Transitions between Prefrontal Neural Ensemble States Accompany Behavioral Transitions during Rule Learning. *Neuron*. 66, 438-448.

Disclosures: F.L. Wang: None. **T.H. Kim:** None. **O. Hazon:** None. **M.J. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix Inc.. F. Consulting Fees (e.g., advisory boards); Inscopix Inc..

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.16/FFF11

Topic: H.01. Animal Cognition and Behavior

Title: A domestic pig model for large-scale electrophysiological recordings during conditional associative memory tasks

Authors: *A. DRAPER, H. V. VINEREAN, A. T. MATTFELD, T. A. ALLEN
Florida Intl. Univ., Miami, FL

Abstract: To understand complex cognition neurophysiological studies of large-scale networks of neurons are necessary. While human studies using BOLD fMRI have shown evidence for task-related networks across the brain these studies lack the ability to evaluate mechanisms at the cellular level. Similar brain networks are assumed to support cognition across mammals (Lu et al., 2012), but the most common rodent and primate models present challenges in achieving high-volume multisite single-unit recordings in behaving animals. Rats are too small for large scale multisite recordings and primate research involves many practical and ethical issues. Here we present the domestic pig as a solution to some of these issues. Pigs have large brains and thick skulls allowing for large implants targeting multiple brain regions. We first trained pigs (*Sus scrofa domesticus*) to perform a conditional associative learning paradigm identical to a task used in humans. For the pig, the task was adapted to use a touchscreen interface. During the task, pigs learn to associate three arbitrary images with arbitrary responses. That is, one image is associated with a left snout touch, while another image is associated with a right snout touch. These two images comprise our fixed associations. The third image is associated with both a left and a right snout touch depending on the identity of the previous trial's image. This is referred to as the conditional association. Correct responses elicited a tone coupled with the delivery of a

food pellet. Incorrect responses triggered a buzzer and no food reward. Pigs were shaped on the rules of the task in less than 3 weeks. Pigs performed 600 trials a day with daily unique stimulus sets. On fixed associations performance reached ~95% accuracy after 25-30 trials. On conditional associations performance reached ~90% accuracy after 90-100 trials. Behavioral performance mirrored that observed in humans using the same task. Next, we developed a method for untethered chronic large-scale electrophysiological recordings in pigs. A 3D printable protective enclosure was designed to support eight separate chronic electrode probe assemblies each implanted in a different brain region. This approach proved stable enough to withstand the shock of collisions due to head hits and flopping over during sleep.

Disclosures: A. Draper: None. **H.V. Vinerean:** None. **A.T. Mattfeld:** None. **T.A. Allen:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.17/FFF12

Topic: H.01. Animal Cognition and Behavior

Support: DFG CRC 1280 Extinction Learning
DFG RTG 2185/1 Situated Cognition
RUB Research School

Title: The neuronal mechanism of extinction learning and the renewal effect

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Abstract: Extinction learning is a fundamental process for animals to adapt to the ever-changing environment. During extinction, organisms learn to disconnect associations between certain events that have been previously learned. This process enables animals to re-learn about specific events which might have altered their contingencies over time. However, the originally learned memory trace is not erased during the process of extinction. Rather than simply forgetting the old memory, extinction learning establishes an inhibitory connection to prevent this memory from being retrieved. There is a large body of evidence supporting the hypothesis that the original memory trace persists, for example the renewal effect. It refers to the resurgence of the initially learned behavior once an organism is tested in a different context compared to the context in which it extinguished the association. Although the effects of renewal have been tested in a variety of experiments, electrophysiological data demonstrating how this type of learning is processed within the brain on a single neuron level is sparse. We conceived an experimental design in which animals go through all three stages of the renewal process (acquisition, extinction, renewal) during each experimental session. This setup enabled us to record steadily

during the renewal phase within one animal over several months. We used pigeons (*Columba livia*) as experimental subjects and implanted them with electrodes to record from a higher cognitive structure within the bird brain, the nidopallium caudolaterale (NCL). Our recordings demonstrate that the NCL as an associative forebrain region encodes learning processes reflecting all learning stages of the experiment. Furthermore, the recorded neural signals are associated with contextual and relative reward processing. These preliminary results suggest that higher associative structures such as the NCL are strongly involved in learning and re-learning.

Disclosures: J. Packheiser: None. **R. Pusch:** None. **O. Gunturkun:** None. **J. Donoso:** None. **S. Cheng:** None.

Poster

244. Animal Cognition and Behavior: Learning and Memory: Physiology

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 244.18/FFF13

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R01MH083686
Simons Foundation 10009887
HHMI international student research fellowship

Title: Neural circuit dynamics underlying cognitive states in the mouse cortex during a virtual navigation task

Authors: *Y. LU[1], D. W. TANK[1,2,3]
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Abstract: Cognitive maps are thought to be important components of the neural systems guiding future actions in complex environments, but their neural implementation remains poorly understood. Here we studied cortical population dynamics in mice during a virtual-navigation-based delayed match-to-sample task where the final choice of left or right turn relies on correct transitions and maintenance of cognitive states based on a learned internal model, possibly corresponding to states in a cognitive map. In this task mice navigated down a virtual Y maze to obtain a reward. In the initial segment of the maze (sample period), mice were presented with a visual cue (wall pattern). In the second segment of the maze (delay period) the sample wall pattern was removed. Upon arrival at the Y-junction (test period), the animal was presented with two choice arms: one arm had the same wall pattern as the sample period (match) and the other arm had a different pattern (non-match). Mice were rewarded for entering the arm with the wall pattern that matched the pattern during the sample period. Thy1-GCaMP6f mice learned to perform this task at >85% accuracy. Following training, we performed systematic mapping of

cortical activity using large-scale cellular resolution two-photon calcium imaging across different cortical areas. A large (8mm x 6mm) cranial window provided chronic, bilateral optical access to the entire posterior dorsal surface of the cortex, including V1, most of extrastriate cortices, and higher-order association areas. We identified several cortical areas, including retrosplenial cortex (RSC), with neural activity that could be interpreted as a cognitive map of task relevant variables. Specifically, we observed the neurons in RSC fired at specific locations along the maze forming sequences of activity that spanned the entire trial. Individual cells may have distinct firing patterns corresponding to different task states, indicating global remapping due to neural network state change. Using deep learning techniques on time series from hundreds of simultaneously recorded cells, we were able to decode task-relevant information related to the animal's current position in the virtual environment, its upcoming choice, and the identity of the sensory cues held in short-term memory. Using a non-linear dimensionality reduction technique (seq2seq variational autoencoder), we found that the progression of population dynamics through different cognitive states can be explained by a low-dimensional manifold in the neural activity state space, which is strongly correlated with the animal's behavior in single trials.

Disclosures: Y. Lu: None. **D.W. Tank:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.01/FFF15

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG003376
P51 RR000169

Title: Convolutional neural networks for fast and accurate 3D reconstruction of histological sections

Authors: *C. KYLE[1,2], J. STOKES[4], J. MELTZER[1,2], M. R. PERMENTER[5], J. A. VOGT[5], A. D. EKSTROM[4,6], C. A. BARNES[1,2,3]
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Abstract: While *in vivo* imaging offers an excellent view of the brain's "macro" structure, it lacks the resolution and intensity markers required to identify details of interest to many neuroscientists. Histological sectioning offers the ability to identify chemical and cytoarchitectural markers, but does not maintain the structure of the intact brain. This

necessitates methods of 3D histological reconstruction. A significant remaining challenge of this field is to balance the computation time with the accuracy of a reconstruction scheme. Previous work on histological reconstruction has used either intensity-based warping techniques, which are slow due to iterative image-wide multiplication, or landmark or feature-based registration which reduces computational complexity at the expense of accuracy (Pichat et al., 2018, *Medical Image Analysis*). We propose a new automated approach for histological leveraging recent advancements in machine learning to perform image registration using convolutional "spatial transformer networks", which accurately perform non-rigid registration without iteration. Our method involves a global search strategy. First the MRI is resampled for a given θ-yaw, θ-pitch, z-position, xy-plane resolution, and z-plane resolution. These terms account for position and for shrinkage or expansion that occurs during sectioning. Next, histological sections are registered to the MRI, estimating x-position, y-position, θ-roll, and non-rigid terms for each section. These terms account for deformations that occur during the tissue mounting process. Next, a cost function is computed that considers: 1) The intensity-based similarity between the histology and MRI, 2) regularization terms that quantify the deformation energy of the registration, and 3) an estimate of the probability of reconstruction derived from pre-computed intensity-based similarity distributions S(dx,dy,dθ) between neighboring histological sections. This process is used to search θ-yaw, θ-pitch, z-position, xy-plane resolution, and z-plane resolution for the optimal solution. With these parameters selected, we overtrain the spatial transformer networks to find the best x, y, θ-roll, and non-rigid terms for each section. We find this approach is extremely accurate and drastically reduces execution time allowing researchers to integrate histological data into 3D structural MRI images quickly, accurately, and automatically. Applications include quick integration of new histological data into existing brain atlases, creation of *de novo* brain atlases, and construction of MRI-based probabilistic atlases that provide information on histological markers.

Disclosures: C. Kyle: None. **J. Stokes:** None. **J. Meltzer:** None. **M.R. Permenter:** None. **J.A. Vogt:** None. **A.D. Ekstrom:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.02/FFF16

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG050548
F31 AG055263

Title: Tract-specific white matter correlates of age-related reward devaluation deficits in macaque monkeys

Authors: *N. M. DE LA PENA[1,2,3], D. T. GRAY[2,3], L. UMAPATHY[4], S. N. BURKE[7], T. P. TROUARD[2,5], C. A. BARNES[2,3,6]
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Abstract: The ability to revalue reinforced stimuli according to changing biological or psychological needs is critical for adaptive, reward-driven behaviors. Alteration in this cognitive function is known to occur during cognitive aging in both humans and macaque monkeys. Lesion and functional imaging studies suggest that interactions between the orbitofrontal cortex (OFC) and amygdala are critical for proper revaluation performance. Tracer-based anatomical studies in nonhuman primates suggest that the OFC and amygdala are monosynaptically connected via at least two separate white-matter tracts (e.g., Lehman et al., 2011): the uncinate fasciculus and the amygdalofugal pathway through the anterior segment of the internal capsule. Diffusion tensor imaging (DTI) approaches allow for quantitative estimates of white-matter integrity, and in humans these estimates have been shown to decrease across the lifespan in the uncinate fasciculus (Hasan et al., 2009), although no studies have examined the significance of this with respect to cognition. Our group has previously shown that, in macaques, the volume of the OFC is reduced with age, and that these alterations significantly correlate with reward devaluation performance (Burke et al., 2014). Given the data showing that OFC-amygdala disconnection lesions impact revaluation performance (Izquierdo and Murray, 2004), we hypothesize that communication between the OFC and amygdala should show age-related changes that relate to worsened revaluation performance. Here we apply DTI and probabilistic tractography to assess the uncinate fasciculus and amygdalofugal tracts. The data indicate a selective relationship between the integrity (fractional anisotropy: FA) of the UF of old animals and revaluation behavior. The amygdalofugal pathway did not show this relationship. These results suggest that, in nonhuman primates, age-related declines on revaluation abilities are not due to a general degradation of connectivity between the amygdala and OFC, but rather to changes specific to the fibers contained within the uncinate fasciculus pathway.

Disclosures: N.M. De La Pena: None. **D.T. Gray:** None. **L. Umapathy:** None. **S.N. Burke:** None. **T.P. Trouard:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.03/FFF17

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG050548
F31 AG055263

Title: Thalamocortical white-matter integrity and the relationship between auditory function and cognitive decline in aged macaque monkeys

Authors: *D. T. GRAY[1,2], S. N. BURKE[6], J. R. ENGLE[1,7], L. UMAPATHY[3], T. P. TROUARD[1,4], C. A. BARNES[1,2,5]
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Abstract: Hearing loss, or presbycusis, is a hallmark of normative brain aging, with an estimated eighty percent of individuals over age 50 experiencing reduced hearing capacity to some degree. It has been known for some time that auditory processing abilities correlate with cognitive function, even when cognition is assessed using non-auditory tasks (e.g., Humes et al., 2013). Despite these relationships, no direct brain measurements have been made in an attempt to link age-related cognitive decline with presbycusis. To this end, we assessed a colony of adult and aged macaque monkeys 1) on a battery of behavioral tasks meant to probe multiple cognitive functions, 2) with temporally precise physiological estimates of auditory function (auditory brainstem and mid latency responses), and 3) with structural and diffusion-weighted magnetic resonance images to extract quantitative estimates of volume and connectivity between distinct auditory and cognitive brain regions using probabilistic tractography. Our results suggest that aged macaques are impaired on several tasks thought to require both frontal and medial temporal lobe function, as well as show a reduction in temporal processing of auditory information, both findings that have been reported previously (e.g., Hara et al., 2012; Ng et al., 2015). Only performance from specific tasks significantly correlated with estimates of temporal auditory processing, whereas other tasks did not relate to these same measures. Estimates of the white-matter integrity along the thalamic auditory radiations correlated both with estimates of temporal auditory processing and with reversal learning memory, but not any other cognitive domain tested here. These correlations preliminarily suggest that the white-matter integrity of thalamocortical fibers may contribute to the observed relationships between specific aspects of cognitive decline and presbycusis. To expand upon this concept, these correlations will be presented alongside similar analyses using estimates from the thalamic radiations connecting anterior and midline thalamic nuclei with the prefrontal cortices and medial temporal lobes.

Disclosures: D.T. Gray: None. **S.N. Burke:** None. **J.R. Engle:** None. **L. Umapathy:** None. **T.P. Trouard:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.04/FFF18

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG003376
P51 RR000169
F31 AG055263

Title: A direct comparison of dye- and imaging-based removal of lipofuscin-induced autofluorescence from primate brain tissue

Authors: *W. PYON[1,2], D. T. GRAY[1,2], S. ASHFORD[1,2], C. A. BARNES[1,2,3]
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Abstract: Brain tissue contains autofluorescing elements that are potentially detrimental to accurate identification of neurons in brain tissue. In fluorescence imaging studies this autofluorescence can be visually indistinguishable from immunolabeled cells and can significantly impact the ability to detect the desired signal from noise. Because some autofluorescent bodies such as lipofuscin tend to accumulate with age, this can create a serious problem for studies examining multiple age groups. Lipofuscin is an intracellular collection of various lipids and trace metals within lysosomes that evades degradation and can amass to surround the entirety of a neuron's cell body (Brizzee et al., 1974). This particular autofluor has been shown to possess a spectral profile which spans the emission ranges of commonly used fluorophores utilized in fluorescent microscopy (Edwin and Jackman, 1981; Feldman et al., 2015). The most widely used method to combat this autofluorescence involves sequestering the fluorescent emission with lipophilic dyes such as Sudan Black B (Romijn et al, 1999). While effective, this treatment seems to come at the cost of potentially reducing and sometimes completely obscuring the emission of fluorescent probes used in immunohistochemical experiments (Schnell et al., 1999). Fortunately, with the advent of more sophisticated fluorescence detection systems, it is possible to record spectral data on a pixel-by-pixel basis. These methods can be used for a non-chemical, imaging-based approach for autofluorescence removal. The present study compares the spectral imaging and linear unmixing technique with the Sudan Black B (SBB) treatment method. Images of tyrosine hydroxylase- (TH) and calbindin-immunolabeled (Cb) cells from the midbrains of aged rhesus macaques are acquired on a Zeiss LSM880 inverted confocal microscope, and then undergo image segmentation analysis and cell counting. Results suggest improved preservation of fluorescence signal in Cb-Unmixed

over Cb-SBB treated images based on an automated thresholding algorithm (on average 52 ± 3% fewer signal pixels after SBB-treatment). Furthermore, on average, more cells were counted in Unmixed images compared to SBB images (TH: 9.83 ± 2.48% and Cb: 33.56 ± 5.49%). Together these data suggest that the spectral imaging and unmixing method improves the visibility of individual immunolabeled cells for analysis and that this method is a viable alternative to Sudan Black B-treatment.

Disclosures: W. Pyon: None. **D.T. Gray:** None. **S. Ashford:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.05/FFF19

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG049465

Title: Age-dependent correlation between spatial and working memory does not extend to object recognition

Authors: *N. J. CAREY[1,2], M. A. ZEMPARE[1,2], C. J. NGUYEN[1,2], K. M. BOHNE[1,2], M. K. CHAWLA[1,2], S. SINARI[3], M. J. HUENTELMAN[5,1], D. BILLHEIMER[3], C. A. BARNES[1,2,4]
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Abstract: As average life expectancies continue to increase around the world, it is critical to understand the normative characteristics of brain and cognition during aging. While it is well-documented that certain changes in learning and memory are to be expected as we age, it is also well-appreciated that there is significant variability in the extent to which different domains of cognition are impacted in any given individual. To better understand the complexity of individual differences in cognition during aging across the lifespan, we designed a battery of behavioral tests that assess the functional integrity of distinct brain regions. This battery consists of the spatial and cued versions of the Morris watermaze, spontaneous object recognition (SOR), and a delayed matching-to-place working memory task. Male Fisher 344 rats were examined at three ages: young adult (6mo), middle-aged (15mo), and aged (23mo) at the beginning of testing. The first step in our analysis process is to assign cognitive category levels on the basis of performance on the hippocampus-dependent spatial version of the Morris watermaze: low, average, or high within a given age group. These spatial cognition categories were then compared to working memory performance within young animals: the high-performing animals

on the spatial task were also high performing on the prefrontal cortex-dependent working memory task. The opposite was true for the aged group of rats, however, as the old animals that performed poorly on the spatial version of the water maze, performed well for their age group on the working memory version of the task. The middle-aged rats showed relationships between spatial and working memory that were intermediate between the young and aged groups. With respect to the perirhinal cortex-dependent object recognition memory task, there were significant differences across age, consistent with previous observations in aged rats, monkeys (Burke et al., 2012), and humans (Ryan et al., 2012). These changes in recognition memory were not related to the spatial cognitive category for any age group, even though both the perirhinal cortex and hippocampus are required for adequately using cue recognition for processing spatial input (Burke et al., 2018 in press). Additionally, there was no correlation between SOR performance and working memory performance across age, where comparable delays were used in both tasks. Taken together, these data emphasize the importance of understanding the relationship between the function of these brain regions across age, as it may provide insight into how these processes can be optimized for the highest quality of life as human life expectancy continues to rise.

Disclosures: N.J. Carey: None. **M.A. Zempare:** None. **C.J. Nguyen:** None. **K.M. Bohne:** None. **M.K. Chawla:** None. **S. Sinari:** None. **M.J. Huentelman:** None. **D. Billheimer:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.06/FFF20

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG003376

Title: Aged-related impairments in spatial reference frame updating

Authors: *A. W. LESTER[1,2], C. J. BLUM[1,2], A. J. KAPELLUSCH[1,2], C. A. BARNES[1,2,3]
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Abstract: Both the hippocampus and the medial portion of the entorhinal cortex (MEC) contain functionally distinct sub-networks of spatially modulated neurons which are believed to work cooperatively to support spatial navigation. The two broad categories of spatial feedback utilized to anchor and update the spatial firing of these cells are allocentric (i.e., external) and egocentric (i.e., self-motion). As with older adults, aged rats show robust impairments on a number of different spatial navigation tasks (Lester et al., 2017). There is some evidence that these

navigation impairments are accompanied by a bias away from using an allocentric navigation strategy towards relying on an egocentric strategy. To test the degree and timing with which aged animals utilize these two forms of spatial information, a novel behavioral arena was developed in which rats are trained to traverse a circular track and to stop at a learned goal location that is fixed with respect to a panorama of visual cues projected onto the surrounding walls. By instantaneously rotating the cues we are able to put allocentric and egocentric reference frames in direct and immediate conflict and characterize how quickly and accurately aged animals utilize allocentric feedback to navigate to a new rotated goal location. Behavioral data collected from five young (9 - 15 mo) and four aged (23 - 30 mo) animals reveal that both age groups are able to update their behavior following cue rotation, although aged rats tend to perseverate to the original goal location more often. Young rats, by comparison, were more likely to stop at some intermediate location between the original and rotated goal location. These findings suggest that when spatial reference frames are put in conflict, young rats settle on a strategy that combines both sources of spatial information, while aged animals adhere more rigidly to only one spatial reference frame. We are currently collecting electrophysiology from both CA1 and MEC while animals perform the task. Based on our behavioral findings, we predict that when spatial reference frames are put into conflict, the CA1 place cells in young animals will show variability in terms of which reference frame they anchor to (as in Lee et. Al., 2004). We predict that aged CA1 place cells, by comparison, will have a greater tendency to remain anchored to the already established reference frame. If the age-related behavioral changes we observe are due to intrahippocampal network impairments, spatially-modulated cells of upstream MEC should show comparable realignment in both age groups.

Disclosures: A.W. Lester: None. **C.J. Blum:** None. **A.J. Kapellusch:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.07/FFF21

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
R01 NS091299
P30 AG019610

Title: Dynamic expression of RNA stress granule componentsin behaviorally characterized young, middle aged and old rats

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Abstract: RNA Stress Granules (SGs) are dynamic cytoplasmic structures that assemble in response to various cellular insults. During this process, these non-membrane bound organelles sequester specific mRNAs causing inhibition of translation initiation, resulting in cell protection during times of stress. Upon stress removal, RNA SGs disassemble and translation is reinitiated. These changes in RNA SGs have been linked mechanistically to age-related neurodegenerative disease suggesting that they may play a key role in the aging process. In order to examine how SGs may be influenced by the aging process, we investigated the expression of RNA SG-associated proteins including PABP, FMRP, TIAR and EIF2alpha and found that there is a region-specific distribution across rat brains, and that there are dynamic changes in the transcript levels of SG components in both flies and rats. Similar dynamic changes in rat brains were found for translation initiation factors EIF4G2, EIF4E-BP, EIF4A1 and EIF4E during aging. These molecular analyses were performed on brain regions isolated from young adults (6-8 mo, middle-aged (15-17 mo) and old (23-25 mo) rats that were previously assessed for their spatial and working memory using the Morris watermaze. Reverse transcription (RT) qPCR analyses of rat cerebellum and hippocampus brain regions revealed that the PABPC1, EIF2alpha, EIF4G2, EIF4E-BP, EIF4A1 and EIF4E transcripts show no significant differences in young or old rats in the hippocampus, however middle aged rats show a significant increase in EIF4E transcript only. In the cerebellum, all tested transcripts show robust changes during aging and interestingly, EIF4E-BP transcript is significantly reduced in aged animals only. The Morris watermaze task revealed that aged rats were memory impaired compared to both middle aged and young animals, and middle aged rats were also memory impaired compared to young rats. A linear regression analysis between RT qPCR for each of the tested transcripts and spatial memory in the hippocampus revealed no significant correlation. The relatively small changes in transcript levels in the hippocampus may reflect a lack of involvement of RNA SGs in hippocampus-dependent learning under normal conditions in aging. Because the changes in SG-associated transcripts were larger in the cerebellum, we are currently investigating an association of RNA SGs in that structure with motor system assays. In addition, we are investigating RNA SG component expression in the prefrontal cortex in relation to the working memory behaviors we have obtained from these animals.

Disclosures: R.J. Eck: None. **M.K. Chawla:** None. **B. Siddegowda:** None. **N.J. Carey:** None. **M.A. Zempare:** None. **C.J. Nguyen:** None. **C.A. Barnes:** None. **D.C. Zarnescu:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.08/FFF22

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
R01 AG003376
F32 AG033460
HHMI 5200006942

Title: Lateral but not medial entorhinal cortex population representations become more sparse with age

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Abstract: The hippocampus undergoes biological changes with age that are associated with changes in memory function. Subregions of the hippocampus receive major inputs from and send back projections to superficial and deep layers of Entorhinal Cortex (EC), respectively. Yet, how behaviorally-relevant neural activity in EC may change with age remains poorly understood. In contrast to the well-studied Medial Entorhinal Cortex (MEC), Lateral Entorhinal Cortex (LEC) neurons do not show substantial spatial selectivity in their firing patterns. Rather, LEC is thought to be involved in representing non-spatial features of experiences, including odors. In this study, we examined whether LEC and MEC neuron populations are selectively activated in response to distinct odors during track running, and hypothesize that aging may alter EC activity patterns that contribute to memory dysfunction. To test this, adult and aged rats were trained to run on a track in a constant environment. After training, one behavioral group (AA) experienced the same set of 6 odors around the track during two run sessions separated by 20 mins. A second group (AB) also ran two sessions, but the odor stimuli were distinct between the epochs. We used cellular compartment analysis of temporal activity by fluorescence *in situ* hybridization (catFISH) to visualize the time-dependent subcellular distribution of *Arc* mRNA in EC principal cells. We identified neurons activated during the first, second, or both sessions in superficial and deep layers of EC. We found that AA and AB behaviors elevated LEC and MEC activity compared to a control condition. Population activity, however, failed to distinguish the distinct A and B odor experiences. This suggests that EC neural population activity stably represents higher order features of the behavioral experience regardless of altered odor input. Surprisingly, more cells reached *Arc* activation thresholds during the second epoch than the first in LEC, but not in MEC. This may indicate that LEC circuits are sensitive to priming by similar past experience. Furthermore, a lower proportion of LEC neurons participated during the behavior in aged rats than in adult rats, while activation in MEC was preserved in aged animals. This result is in line with data from humans that show that anterolateral, but not dorsomedial, EC becomes hypoactive with age and that this reduction is related to cognitive deficits (Reagh et al., 2018). Exactly how the sparser network representations in aged rat LEC contribute to altered behavioral function across the lifespan awaits further investigation.

Disclosures: A. Comrie: None. **J.P. Lister:** None. **M.K. Chawla:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.09/FFF23

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation

Title: Specificity of activity-regulated transcript localization in somatic and dendritic neuronal compartments

Authors: C. BLEUL[1], M. K. CHAWLA[2,3], M. D. DE BOTH[1], *C. A. BARNES[2,3,4], M. J. HUENTELMAN[1]
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Abstract: Next generation RNA sequencing (RNA-Seq) provides the ability to construct an unbiased whole transcriptome map, digitally quantify transcript levels, and can interrogate splice form abundance. Specific RNA species are known to be expressed and can redistribute within hours or less to the dendrites where local translation can occur. Much is left to be discovered about the function of these dendritic mRNAs, however, evidence suggests that they play a key role in synaptic plasticity and transmission. We propose that the creation of a complete catalog of activity-regulated transcripts will enable a hypothesis-driven investigation of neurological disease with a focus entirely on verified activity regulated genes. In this study, we utilized RNA-Seq to identify transcripts from total RNA obtained from laser-capture microdissected (LCM) sub-fields of the hippocampal formation (dentate gyrus [DG], CA1, and CA3) of 9 month old Fisher344 rats. Three adjacent 15 um thick cryostat sections were rapidly stained with fluorescent Nissl green, the cell soma and corresponding neuropil regions (10 different regions in total) were laser captured and the RNA isolated and prepared for sequencing using the SMARTer Stranded Total RNA-Seq Pico Input Mammalian Library Prep Kit (Clontech-Takara). Results from caged control (CC) animals and electroconvulsive shock (ECS) treated animals sacrificed at 10 minutes, 30 minutes, 1 hour, 2 hours, 4 hours and 24 hours post exposure were analyzed and compared. Following ECS treatment, we found that known immediate early genes like Arc, Homer1, Egr1 and Fos were significantly differentially expressed in the different hippocampal regions. Of note however, specific patterns of activation were demonstrated. For example, Homer 1 only demonstrates activity regulation in the DG soma compartment. Arc, on the other hand, demonstrates activity regulation across the hippocampus and in both dendritic and soma compartments. We also explored the relationship between the neurotrophins and their receptors following ECS. Ngf is activity regulated in the DG soma, however the primary receptor for Ngf,

Ntrk1, exhibits no activity regulation. Bdnf, on the other hand, is activity-regulated in the soma compartments across all three hippocampal sub-fields however its receptor, Ntrk2, is only activity-regulated in the DG soma. These initial findings demonstrate the utility of our experimental approach to confirm known and identify novel discoveries related to activity-regulated transcription, potentially leading to a deeper understanding of the molecular mechanisms associated with cognition and possible treatments for neurological disease.

Disclosures: C. Bleul: None. **M.K. Chawla:** None. **M.D. De Both:** None. **C.A. Barnes:** None. **M.J. Huentelman:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.10/FFF24

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
state of Arizona and DHS

Title: NPTX2 knockout rats: A novel model for protection of synaptic function in aging and disease

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[1]Evelyn F. McKnight Brain Inst., [2]Div. of Neural Systems, Memory and Aging, [3]Dept. of Biomed. Engin., [4]Departments of Psychology, Neurol. and Neurosci., Univ. of Arizona, Tucson, AZ; [5]Departments of Neurosci. and Neurol, Johns Hopkins Sch. Med., Baltimore, MD

Abstract: Neuronal Pentraxin 2 (NPTX2) is an immediate early gene involved in binding and clustering of AMPA receptors at synapses and mediates homeostatic scaling of circuits. In the hippocampus, this involves the synapses of excitatory pyramidal cells onto inhibitory parvalbumin-containing basket cells. Thus, low NPTX2 levels may tilt the excitatory-inhibitory balance of hippocampal circuits toward excitation. NPTX2 has been proposed to play a role in protection of synaptic function in aging and the progression of Alzheimer's disease (AD; Xiao et al., 2017), and levels of NPTX2 in brain are predictive of whether individuals with pathologically defined brain levels of amyloid plaques and tangles are cognitively symptomatic (demented) or asymptomatic (cognitively normal). That is, if levels of NPTX2 are high in brain, as in the case of normal controls and asymptomatic AD, then cognition is intact - if NPTX2 is low in brain, as in symptomatic AD, the individuals are demented. In fact, NPTX2 levels in CSF are a more sensitive predictor of cognitive status than are markers for amyloid or tau (Xiao et al., 2017). To investigate this role of NPTX2, we have begun to examine behavior, brain structural

integrity by high resolution MRI, and function with single unit and EEG recordings from area CA1 of the hippocampus in NPTX2 knockout (NPTX2 KO) rats compared to wild-type (WT) controls. The larger study will examine these variables across the lifespan at 6, 12, 18 and 24mo. We report here preliminary data from the young group. So far, we do not detect overall performance differences between the young NPTX2 KO rats in spatial or working memory versions of the Morris watermaze, in motor behavior on a rotarod, or in anxiety tests using the elevated zero maze. Interestingly, the NPTX2 KO rats exhibited twice as many interruptions of on-going behavior during the spatial and working memory tasks. In the spontaneous object recognition task, the WT animals spent more time than did NPTX2 KO animals with the novel object (mean ratio novel/familiar, KO= 1.26 +/- 0.11, WT = 2.10 +/- 0.05), suggesting poorer overall recognition memory. Additionally, the NPTX2 KO rats explored the objects considerably less than did WT rats (mean number object alternations, KO = 4.1 +/ -3.3; WT = 10.0 +/- 3.0). Hippocampal volume in this young age group of NPTX2 KO rats was not different compared to WT controls (mean normalized hippocampal volume KO = 0.041 +/- 0.0, WT = 0.040 +/- 0.0). Electrophysiological studies are on-going. The results of these experiments should lead to a better understanding of NPTX2's potential role in the protection of synaptic function during aging and in neurodegenerative disease.

Disclosures: M. Zempare: None. **N.J. Carey:** None. **K.M. Bohne:** None. **L. Do:** None. **T.P. Trouard:** None. **P.F. Worley:** None. **C.A. Barnes:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.11/GGG1

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R37AG036800
NIH Grant R01AG052258
NIH Grant R01AG049711
Evelyn F. McKnight Brain Research Foundation

Title: Frontal upregulation of serine racemase alters cognitive flexibility in middle age rats

Authors: *B. YEGLA, T. FOSTER, A. KUMAR
Evelyn F. and William L. McKnight Brain Inst., Gainesville, FL

Abstract: Aging is characterized by hippocampal- and prefrontal-mediated cognitive deficits. A decrease in N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic function contributes to impaired synaptic plasticity and is associated with cognitive impairments. Given NMDAR hypofunction in aging, D-serine, a NMDAR co-agonist, is a promising target for maintaining

cognitive function in aging. Levels of serine racemase (SR), which synthesizes D-serine, decline with age. Thus, enhancing NMDAR function via increased SR expression in middle age, when subtle declines in cognition emerge, was predicted to enhance performance on a prefrontal-mediated task sensitive to aging. Male Fischer-344 rats (12 mo; N=7) were injected bilaterally in the medial prefrontal cortex with 2µL of lentivirus (LV) for SR upregulation (LV-SR) or control virus (LV-GFP). Rats were 85% food restricted and trained on the operant attentional set-shift task to examine cognitive flexibility. This task includes visual discrimination (VD), where rats select one of two levers based on the location of a light cue. Correct responses resulted in food rewards. Rats then made an extradimensional shift to an egocentric response strategy, selecting a lever based on its location (right or left) irrespective of the light. An intradimensional shift required selection of the opposite lever from the previous trial type (from right to left). Rats had to reach criterion (8 consecutive correct responses) before advancing through each phase. Trials to criterion, errors, omissions, and percent correct responses were collected and analyzed. Following completion, rats were perfused to evaluate the location of viral infection. All rats required more trials to criterion for VD than the extra- or intra-dimensional shift ($F_{1,5}$=12.68, p=0.02). Based on the reduced omission rate (t_5=14.13, p=0.01) and trials to criterion (t_5=2.23, p=0.07) during VD, LV-SR rats exhibited a faster learning rate compared to controls. Their capacity for the extradimensional shift was not impacted, though performance on the intradimensional shift was impeded in LV-SR rats, whereby correct performance was lower (t_5=4.70, p=0.04) due to greater errors (t_5=3.39, p=0.06) compared to controls. Immunohistochemical analyses displayed expression of LV-SR in the cortex and white matter. LV-SR significantly increased SR expression (t_5=2.53, p=0.05), with an approximate 26% upregulation in the prefrontal cortex. Thus, prefrontal SR upregulation in middle age rats improved attentional selection during VD but impaired flexibility, suggesting NMDAR activity acts as a gate or switch between maintaining and shifting attention.

Disclosures: B. Yegla: None. **T. Foster:** None. **A. Kumar:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.12/GGG2

Topic: H.01. Animal Cognition and Behavior

Support: R37AG036800
RO1AG052258
RO1AG049711
Evelyn F. McKnight Brain Research Foundation

Title: Both GluN2A and GluN2B contribute to the induction of the redox-mediated potentiation of NMDA receptor synaptic function at CA3-CA1 hippocampal synapses of aged animals

Authors: *A. KUMAR[1], T. C. FOSTER[2]
[1]Dept Neuroscience, McKnight Brain Inst., Univ. of Florida, Gainesville, FL; [2]Dept Neurosci., Evelyn F. and William L. McKnight Brain Inst. Univ. Florida, Gainesville, FL

Abstract: A decrease in N-methyl-D-aspartate (NMDA) receptor synaptic responses during aging contributes to impaired synaptic plasticity and is associated with impaired cognition. Electrophysiological studies have described NMDA receptor hypofunction during aging, due to an oxidized redox state of neurons. The current studies employed extracellular field potential recordings to investigate contribution of GluN2A and GluN2B subunits in the induction of redox-mediated potentiation of NMDA receptor synaptic responses at CA3-CA1 hippocampal synapses in aged animals. Acute hippocampal slices were prepared from aged (~25 mo) male F344 rats. NMDA-mediated synaptic field potentials were isolated by addition of picrotoxin (20 μM) and DNQX (30 μM). In most cases, a control slice was recorded in a separate chamber (n = 19 slices). To determine if NMDA receptor activity was required for reducing agent, dithiothreitol (DTT)-induced potentiation of the NMDA receptor response, baseline field potentials were recorded followed by bath application of various antagonists (NVP-AAM077, 0.4 μM, n = 5; ifenprodil, 5 μM n = 8; RO-6981, 4 μM, n = 5, or zinc, 1 μM, n = 3). An ANOVA indicated a treatment effect [$F(4,36) = 3.87$, $p < 0.05$]. Post hoc tests indicated that GluN2A receptor antagonist, NVP decreased the synaptic response (85 ± 8 mean percent decrease ± SEM) relative to vehicle, ifenprodil, or zinc. A new baseline was recorded, DTT (0.5 mM) was bath applied, and the DTT-mediated potentiation of the NMDA response was examined. A treatment effect was observed for the DTT-mediated growth of the NMDA receptor synaptic response ($p < 0.001$). DTT increased the synaptic response 63 ± 9% for control slices. The magnitude of DTT-mediated increase in the NMDA receptor response was reduced by NVP (8 ± 7%), and by GluN2B receptor antagonist, ifenprodil (20 ± 3%) or RO-6981 (21 ± 10%). The responses under antagonist conditions were not different from each other and were significantly ($p < 0.001$) decreased relative to vehicle. Zinc had no effect on the ability of DTT to increase the response (61 ± 9%). The results suggest that GluN2A and GluN2B are involved in the induction of DTT-mediated growth of the NMDA receptor mediated synaptic response.

Disclosures: A. Kumar: None. **T.C. Foster:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.13/GGG3

Topic: H.01. Animal Cognition and Behavior

Support: R37AG036800
RO1AG052258
RO1AG049711
Evelyn F. McKnight Brain Research Foundation

Title: Adulthood infections alters synaptic gene transcription and contributes to age-related memory loss

Authors: *J. D. BARTER[1], A. RANI[3], A. KUMAR[2], T. C. FOSTER[4]
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Abstract: Early-life events (inflammation, stress) can act through epigenetic mechanisms to promote the emergence of pathological phenotypes, later in life. As such, early-life events may contribute to individual variability in age-related cognitive decline. This study was designed to determine if infections during adulthood confers cognitive vulnerability with advancing age. For this study, male 6 month old Fischer 344 X Brown Norway hybrid rats were injected once a week for 7 weeks with lipopolysaccharide (LPS; 1 mg/kg) or control (n=8 per group). At 12 months of age, animals were tested on an episodic version of the spatial water maze task. At this time point (i.e. 6 months post-treatment), no effect of treatment was observed for on cognitive performance. In contrast, a tendency (p=0.061) for a treatment effect was observed for episodic spatial memory, when animals were tested at 18 months of age (i.e. 12 months post-treatment). A trend (p=0.06) for an LPS mediated impairment was also observed for another hippocampal-dependent task, inhibitory avoidance. Following behavioral characterization at 18 months of age, we performed next-generation sequencing on the CA1 region of the hippocampus to understand the mechanisms behind these behavioral differences. Transcriptional analysis revealed 202 genes that were upregulated with prior LPS treatment. Gene cluster analysis indicated upregulation of genes for biosynthetic process (1.2E-2). There were 372 genes that were downregulated due to prior LPS treatment. Specific genes that were downregulated with treatment included *Camk2b*, *mTOR*, and *Nsmf*, which are known to mediate neuronal plasticity. Further, enrichment analysis for downregulated genes indicated decreased expression of genes linked to the glioma KEGG pathway (4E-02), the dendrite (29 genes; 5.9E-3), postsynaptic density (16 genes; 2.1E-3), and histone modification (21 genes; 2.8E-2). This data suggests that infections during adulthood can interact with aging leading to long-term negative effects on transcription and/or cognitive performance. Due to the long-term nature of the effects, as well as altered gene expression linked to histone modification, we speculate that the differential expression of mRNA may occur through an epigenetic mechanism. Current studies are increasing the number of animals in the study and
testing the idea that the interaction of age and inflammation on gene expression involves epigenetic mechanisms.

Disclosures: J.D. Barter: None. **A. Rani:** None. **A. Kumar:** None. **T.C. Foster:** None.

Poster

245. Aging: Anatomical, Physiological, and Cognitive Alterations

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 245.14/GGG4

Topic: H.01. Animal Cognition and Behavior

Support: Intramural Research Program of the NIA, grant AG10606

Title: GABAergic interneuron activation is increased in the hippocampus of aged rats with memory impairment

Authors: *C. BANUELOS[1], C. MYRUM[1], J. KITTLESON[1], K. WEISS[1], P. R. RAPP[2]
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Abstract: Accumulating evidence indicates that hippocampal hyperactivity contributes to age-related memory impairment in a circuit-specific manner. GABAergic interneurons within the hippocampus play a crucial role in maintaining network homeostasis by providing strong inhibitory control over principal cell firing. Disruptions in interneuron activation could greatly impact hippocampal networks and may underlie age-related decline in cognitive function mediated by the hippocampus. In this study, we used a subconvulsive dose (25 mg/kg, i.p.) of the muscarinic receptor agonist, pilocarpine, to induce neuronal activity in young (6 months) and aged (24 months) Long Evans rats that were behaviorally characterized in a hippocampus-dependent water maze task. Performance reliably reveals substantial individual variability in aged rats such that approximately half perform on par with young (aged unimpaired), while the remainder display deficits indicative of hippocampal dysfunction (aged impaired). Histological sections through the dorsoventral extent of the hippocampus were processed for double immunofluorescence labelling of activated (c-Fos+) GABAergic interneurons (GAD67+) in young and aged rats that received either saline (young n = 5, aged n = 10) or pilocarpine (young n = 5, aged n = 10). The percentage of GABAergic interneurons double-labeled for c-Fos was subsequently quantified by exhaustively counting immunopositve cells at high magnification. Significantly more interneurons were activated in the hippocampus of rats that received pilocarpine than saline, confirming that the pilocarpine dose used was sufficient to induce neuronal activity ($p < .001$). Pilocarpine-induced inhibitory interneuron activation was significantly elevated in the hippocampus of aged rats compared to young ($p = 0.046$). The age-related increase in activation was restricted to interneurons in the dorsal ($p = 0.027$) hippocampus (ventral hippocampus, $p = 0.307$), and was driven largely by aged impaired rats that, as a group, displayed significantly more activated interneurons than young ($p = 0.017$). Whether this effect is coupled with the CA3 hyperactivity previously reported in the aged impaired hippocampus remains to be determined. Overall, the data support the emerging theme

that disrupted excitatory/inhibitory balance in the hippocampus is a significant driver of cognitive aging.

Disclosures: C. Banuelos: None. **C. Myrum:** None. **J. Kittleson:** None. **K. Weiss:** None. **P.R. Rapp:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.01/GGG5

Topic: H.02. Human Cognition and Behavior

Support: : NJ Governor's Council for the Research and Treatments of Autism
The Nancy Lurie Marks Family Foundation

Title: Real time streaming and closed loop co-adaptive interface to steer multi-layered nervous systems performance

Authors: *V. KALAMPRATSIDOU[1], S. KEMPER[2], E. B. TORRES[3]
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Abstract: Most research involving bodily motions occurs in open loop mode, whereby we collect data and examine it a posteriori to derive digital biomarkers of behavior from biophysical signals. This approach is informative of correlational states between the body and environmental sensory cues and/or context. However, we could also examine causal relations whereby the output signals from the nervous systems can be streamed in tandem and selectively re-parameterized to give feedback to the person and monitor real time continuous changes. In such closed-loop scenarios, we have a better opportunity to systematically steer the person's systems and learn about adaptive capacity. In this work, we designed a closed loop interface between a dyad of salsa dancers and a computer-music system, to selectively manipulate different levels of functionality in their nervous systems. We harnessed in tandem electroencephalography EEG (Neuroelectrics-Enobio 32 channels 500Hz) from the central nervous systems CNS; heart activity from the autonomic nervous system ANS (using one of the EEG leads) and peripheral PNS, kinematics using a grid of 10 sensors across the body (APDM 128Hz). We first transformed the biophysical time series signals from all sensors to micro-movement spikes, to standardize it and place it on similar number of frames. Then, we converted the spikes to sound and selectively played music back to the dancers using each of the channels and adapting the biorhythms in real time. For example, harnessing the female heart signals, streaming the sonified heart micro-movement spikes in real time and interfacing it with Max7 to play music back using the sound-features of the heart. This changed the heart stochastic signatures in the female. The

change manifested differently when the choreography was well-rehearsed and staged *vs.* when it was spontaneously improvised. For staged pieces, the heart stochastic signatures initially shifted with the heart-enhanced music, but remained steady afterwards. The kinematics signals across the body were not affected for the female, but the male's performance (who leads in the salsa dance) resulted in shifts of his legs signatures that mapped exactly to the female's heart shifts. On the other hand, for the spontaneous improvisation, the heart variability continued to drift and resulted in the shifts of the legs stochastic signatures for both dancers. In the next steps, we will selectively repeat these closed loop sonifications with the EEG and the kinematics signals to compare staged *vs.* improvised regimes and learn about causal influences and adaptiveness levels across the CNS, PNS and ANS.

Disclosures: V. Kalampratsidou: None. **S. Kemper:** None. **E.B. Torres:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.02/GGG6

Topic: H.02. Human Cognition and Behavior

Title: Digital biomarkers of brain-body coupled dynamics

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Abstract: Previous work has established two fundamentally different classes of complex movements (Torres 2011). The first being a *goal-directed movement,* which is a movement that has a specific end goal to accomplish under instruction. This is the movement an individual consciously intends to perform. The second movement class involves a consequential motion of the goal-directed movement, defined as the *supplemental movement*. The supplemental movement is not generally seen as the necessary movement in order to complete the goal of the intended movement. However, it has been found that the variability inherently present in these movements is highly informative of mental states, task context and the systems' adaptive capacity. We assessed the interplay between the intended goal-directed and the consequential supplemental movements in the context of martial arts with an eye for kinematics invariance to changes in movement dynamics (Torres 2002). Kinematic analyses from these complex boxing routines revealed that when the movement is intended to a goal, its variability remains far more robust to changes in dynamics (e.g. speed and loads) than when the movement is consequential. Indeed, while the motion trajectories of the end effectors remain invariant to speed or loads during complex motions that pursue a goal, supplemental segments do change the trajectories with speed or loads. We here report that this feature remains as well in the configuration space of

joint angles. Further, using different MOCAP systems (Polhemus Liberty 240Hz *vs.* Phase Space 480Hz), we confirm that the motor variability of the supplemental motions can blindly inform the context of the task and the degree of learning and adaptation the system undergoes. Indeed, the stochastic signatures of these classes of motions can blindly separate intended from supplemental motions, and reveal the context of the task. We further explore the differences in variability of the ebb and flow of goal-directed and their consequential supplemental movements in the context of the tennis serve and during boxing routines collected in tandem with brain neural activity using electroencephalography (EEG). We compare the activities of the brain-body networks during actual performance and during motor imagery. We report on hypothesized differences between the fundamentally different mental states of deliberate goal-directed *vs.* spontaneous consequential control. Torres, E. B. (2011). Two classes of movements in motor control. *Experimental brain research*, *215*(3-4), 269-283 Torres, E. B., & Zipser, D. (2002). Reaching to grasp with a multi-jointed arm. I. Computational model. *Journal of neurophysiology*, *88*(5), 2355-2367

Disclosures: R. Rai: None. **E.B. Torres:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.03/GGG7

Topic: H.02. Human Cognition and Behavior

Support: NJ Governor's Council for the Research and Treatments of Autism
The Nancy Lurie Marks Family Foundation

Title: Rethinking the study of social behaviors: Non-obvious digital biomarkers of social dynamics

Authors: *E. B. TORRES
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Abstract: Social interactions are ubiquitous in our daily existence, yet we are only aware of some visible aspects of these interactions. Those noticeable aspects include well-coordinated synergies within the body of each agent (intra-body) and synergies across the two bodies in motion (inter-body). Such couplings often gesture intended agreement (or disagreement) in conversation, prompting the agents to a next point along the cognizant continuum of their interaction dynamics. The latter tend to comply with some aim consciously set to steer the social exchange in a certain way. Because such activities are somewhat obvious and detectable by the naked eye, they have a higher probability of e.g. entering into the hand-coding of videos documenting the exchange, or being part of the description of behaviors that researchers carry on

during subjective behavioral analyses (e.g. using scoring clinical inventories). Indeed, these descriptive observational techniques dominate much of the clinical and research areas of the medical field and are invariably carried on in a one-sided fashion, i.e. only one person of the dyadic exchange that takes place at a clinic (e.g. to diagnose the patient, or to track the progress of a medical condition) gets to evaluate the other individual. As such, there are many *non-obvious* portions of the social dyadic interaction that are left out of the current behavioral analyses. These tend to spontaneously occur largely beneath awareness of the interlocutors and as such, they have escaped science and medicine. This work introduces new methods to assess dyads in a wholesome social context that objectively quantifies each participating individual in a personalized manner (coined here obvious digital biomarkers); but also includes self-emergent coupled dynamics (coined here non-obvious digital biomarkers) from the wholesome cohesiveness of the dyadic exchange. First, I introduce new data types to offer different parameterizations of motor signals from a plethora of wearable biosensors that capture a variety of motion outputs from multiple layers of the nervous systems. Then, I describe several analytical pipelines amenable to build biometrics to capture the continuous unfolding of self-emergent coupled dynamics from the social exchange. The methods are proposed as a new generation of non-obvious digital biomarkers of social interactions offered to study physiological underpinnings of social behavior in general.

Disclosures:

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.04/GGG8

Topic: H.02. Human Cognition and Behavior

Support: NJ Governor's Council for the Research and Treatments of Autism
The Nancy Lurie Marks Family Foundation

Title: Building objective cognitive scales with digital biomarkers

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Abstract: The fields of cognitive science and neuromotor control have evolved in separate silos, producing a gap between the sciences of cognition and motor behavior. Embodied cognition has made an attempt to bridge this disconnect, yet it has not delivered proper quantitative tools to that end. While translating our basic science in embodied cognition to the medical space, we developed new experimental designs and biometrics to deploy a new way to study cognitive

issues beyond mental theories and motor issues beyond biomechanics. Indeed, we offer a new suite of digital biomarkers with the potential to produce objective cognitive scales (Ryu and Torres, 2018) amenable to address neurodevelopmental and neurodegenerative disorders that affect both cognition and motion. A simple biomechanical pointing task was adapted to include decision making under varying degrees of cognitive loads (CL) and measure the integration of cognitive and motor performance. We here examine full upper body activity and introduce new parameterizations of the grid of 10 sensors we used to that end. Specifically, micro-movement spikes (Torres, 2013) capturing the moment-by-moment fluctuations in the peak amplitude and timings of the biophysical data are combined with weighted directed connected graphs to use Shannon information theory, network connectivity and stochastic analyses with an eye for self-emerging patterns in the frequency and temporal domains. We consistently found that mutual information formed stronger connectivity patterns on the side of the dominant hand during the cognitive decision making, with supporting activity gradually emerging in the nodes of the non-dominant side, as quantified by the signal to noise ratio. A stronger synergistic connectivity pattern on the dominant side of the limbs led as well to the gradual recruitment of the non-dominant side as CL systematically increased. Further, the goal-directed segment intended to the target was separable from the spontaneous retractions, whereby the clustering coefficient within the network connectivity consistently distinguished increasing levels of CL. Unexpectedly, the unintended segments better predicted the level of CL, further underscoring the relevance of such spontaneous movements as consequential to intended motions and critical to guide adaptive learning. We position the work to empirically inform optimality models of intelligent movement generation and offer new digital biomarkers that serve as a proxy of objective scales of (embodied) cognitive performance.

Disclosures: **J. Ryu:** Other; NJ Governor's Council for the Research and Treatments of Autism, The Nancy Lurie Marks Family Foundation. **E.B. Torres:** Other; The Nancy Lurie Marks Family Foundation, NJ Governor's Council for the Research and Treatments of Autism.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.05/GGG9

Topic: H.02. Human Cognition and Behavior

Support: Postdoctoral fellowship provided by FRSQ

Title: Global suppression of the motor network precedes internally-generated action errors

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[3]Montreal Neurolog. Inst., Montreal, QC, Canada; [4]Dept. of Movement Sci., KU Leuven, Leuven, Belgium; [5]CRIUGM - Univ. of Montreal, Montreal, QC, Canada

Abstract: A plethora of studies using a variety of neuroimaging techniques have allowed us to identify the neural substrates and plasticity mediating the acquisition of novel sequences of motor actions. Yet, such knowledge is based solely upon the individual's correct performance, as errors produced during practice are most of the time eliminated from the analysis. Consequently, there is little available information with regards to the neuronal circuitry engaged when errors are produced during practice. To fill this knowledge gap, we determined the behavioral and neural correlates of action errors during continuous stimulus-free execution of a motor task among 49 young adults. Participants underwent fMRI scanning while repeatedly tapping an explicitly known 5-element sequence on a keypad using their non-dominant hand. All incorrect keys preceded and followed by correctly performed and completed sequences were considered as an error. Results showed that tapping speed during errors was significantly slower compared to correctly-performed sequences. Trial-by-trial analysis revealed that the drop in performance speed was associated with strong bilateral decreases in neural activity within the motor cortico-striatal and associative fronto-parietal networks. Although no slowing in performance was observed immediately before or immediately after the errors, the observed global suppression of executive and associative motor regions preceded error onset. Such suppression was also paralleled by the rapid recruitment of an error-detection network, as reflected by a significant increase in neural activity within the pre-supplementary motor area, anterior cingulate cortex and anterior insula, bilaterally. However, during the post-error reinstatement of correct performance the error-detection network was rapidly disengaged. The motor system was simultaneously released from inhibition so that activity levels within motor cortical and subcortical areas did not differ from those measured during errorless performance periods. The observed error-specific changes in activity patterns were not associated with individual error-related changes in performance speed or error durations. Our results thus suggest that action errors are associated with global short-lived inhibition of the motor system, in line with the unified theory of unexpected events. Moreover, the present findings suggest that early onset of error-specific changes in activity patterns may constitute a neural mechanism that mediates the generation of errors and may serve as error predictors.

Disclosures: E. Gabitov: None. **O. Lungu:** None. **G. Albouy:** None. **J. Doyon:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.06/GGG10

Topic: H.02. Human Cognition and Behavior

Support: ARC DP160102871

Title: Involuntary conditioned motor preparation in primary motor cortex

Authors: *D. TRAN, I. HARRIS, J. HARRIS, E. LIVESEY
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Abstract: The existence of multiple (e.g. conscious and non-conscious) learning systems is highly contentious. The *Perruchet effect* is considered by many to be the best available evidence for independent processes in human conditioning. It refers to a dissociation between conscious expectancy of an outcome and the strength of conditioned priming in anticipation of the outcome, when measured as a function of recent conditioning history. However, in the standard Perruchet effect design, conditioning history is perfectly confounded with response history, meaning that the dissociation may not be based on conditioning at all, but rather simple recency-based priming. Here, we provide a novel solution to this methodological problem using transcranial magnetic stimulation (TMS) to probe motor preparation in the primary motor cortex—using motor-evoked potentials (MEPs) as an index of conditioned responding. Participants performed a go/no-go task in which they responded as quickly as possible to a "GO" cue and withheld responses to a "STOP" cue. The onset of each go/no-go cue was signalled by a fixation cross, which served as a preparatory stimulus and potential source of conditioned priming. In the intertrial interval, participants also rated their expectancy that the next trial would be “GO” vs. “STOP”. Critically, participants received single-pulse TMS on every trial, either during the fixation cross (cued-TMS) or the intertrial interval (before the fixation cross; uncued-TMS). We replicated the Perruchet effect in the behavioural data: Participants were faster to respond to a go cue after longer runs of preceding go trials, indicating stronger response preparation (and slower to respond after longer runs of preceding no-go trials, indicating weaker response preparation) despite explicit ratings indicating that expectancy for the go cue followed the *opposite* trend. MEPs revealed a similar pattern of increasing motor excitability after successive go trials but, critically, only on cued-TMS trials. Despite carefully matching response recency relative to the cued-TMS trials, uncued-TMS trials did not show this trend, suggesting that the pattern of response preparation was strongly dependent on the presence of the preparatory stimulus. These results clearly demonstrate Perruchet's dissociation at the neural level and provide strong evidence that the observed trends in reaction times are the result of associative priming based on learning a cue-outcome association. Taken together, our findings support the notion that conditioned responding and motor preparation in primary motor cortex can operate independently of conscious expectancy.

Disclosures: D. Tran: None. **I. Harris:** None. **J. Harris:** None. **E. Livesey:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.07/GGG11

Topic: H.02. Human Cognition and Behavior

Support: The University of Oklahoma, Office of the Vice President for Research

Title: Iron deficiency and reductions in brain energy expenditure during procedural learning: Effects on instantaneous and cumulative global field power

Authors: *M. J. WENGER[1,2], L. A. DE STEFANO[2], S. E. RHOTEN[2], T. P. WORTH[2]
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Abstract: Iron deficiency (ID) and iron deficiency anemia (IDA) are among the most prevalent nutritional deficiencies in the world. The effects of ID include declines in physical performance, productivity, and deficits in perceptual and cognitive performance. However, there are two difficulties in this literature: (a) in the majority of studies, the memory tasks selected are rarely chosen on the basis of the brain regions that are affected by variations in iron; and (b) the designs of the studies are rarely if ever informed by behavioral and neurobiological theories of memory. The present study is motivated by the differential distribution of and reliance on iron across brain regions, with a particular concern for the neural systems that support procedural vs. declarative memory. Two groups of women, one ID and not anemic (IDNA), and a matched group of iron sufficient (IS) participants learned two categorization tasks. The first was a rule-based task, which differentially relies on the medial-temporal/frontal circuits that support declarative memory. The second was an information integration task, which differentially relies on the corticobasoganglial circuits that support procedural memory. Participants performed both tasks while concurrent electroencephalographic (EEG) data was collected. Stimuli were gabor patches that could vary on spatial frequency, orientation, and amplitude. We focus here on the data from the information integration task, and on instantaneous and cumulative global field power (GFP) of the EEG, which we have previously shown to be correlated with energy expenditure. Our results show that those in the IDNA group reliably differed from those in the IS group on measures of serum ferritin (sFt), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC), with there being no differences on measures of hemoglobin (Hb) or inflammation. Critically, in the period 400-600 ms after stimulus onset, both instantaneous and cumulative GFP were reliably lower for IDNA vs. IS participants, and both instantaneous and cumulative GFP in this period were positively correlated with sFt. We interpret these findings with respect to the effects of ID on monoamine signalling and energetic efficiency.

Disclosures: M.J. Wenger: None. **L.A. De Stefano:** None. **S.E. Rhoten:** None. **T.P. Worth:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.08/GGG12

Topic: H.02. Human Cognition and Behavior

Support: This research was supported by the Intramural Research Program of the NIH, NINDS. SJH is supported by the NINDS Intramural Competitive Fellowship Program.

Title: Sensorimotor oscillatory phase-power interactions determine human corticospinal excitability

Authors: *S. J. HUSSAIN[1], L. CLAUDINO[2], M. BÖNSTRUP[3], G. NORATO[4], C. ZRENNER[5], U. ZIEMANN[6], E. R. BUCH[7], L. G. COHEN[8]
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Abstract: Neuronal networks exhibit oscillatory activity that coordinates local processing and interregional neural communication through alternating windows of excitation and inhibition. In sensorimotor networks, this oscillatory activity occurs within mu (8-12 Hz) and beta (13-30 Hz) bands, and exhibits time-varying changes in phase and power. Invasive recordings demonstrate that sensorimotor oscillatory phase and power reflect variations in sensorimotor cortical function. However, the impact of oscillatory phase-power interactions on corticospinal excitability, an established marker of human motor function, is not known. We addressed this gap in knowledge by evaluating phase-dependency of corticospinal excitability across a continuous range of sensorimotor oscillatory power levels in 20 healthy adults.
Single-pulse TMS was delivered to the scalp hotspot for the right first dorsal interosseous muscle at 120% of resting motor threshold during concurrent EEG. To isolate sensorimotor rhythms, data recorded from the C4 sensor (approximately overlying the stimulated motor cortex) were Hjorth-transformed (central: C4, surround: FC2, CP2, FC6, CP6). The instantaneous oscillatory phase in the mu and beta bands was estimated at the time of TMS, and pre-stimulus power in each band within 150 ms preceding TMS was determined. Phase-dependency of corticospinal excitability was evaluated across a continuous range of power levels using separate trial-by-trial linear mixed-effects models for each frequency band.

For mu oscillations, there was no effect of PHASE or POWER ($p>0.37$), but a significant PHASE x POWER interaction ($p=0.001$), evident as a more positive relationship between mu power and corticospinal excitability at troughs relative to peaks. The direction of mu phase-dependency was reversed with changing mu power levels, such that corticospinal excitability was higher during mu troughs compared to peaks when mu power was high, while the opposite was true when mu power was low. This interactive effect was frequency-specific, since no PHASE x POWER interaction was present for beta oscillations ($p>0.10$), although beta power was positively related to corticospinal excitability independent of beta phase (effect of POWER, $p=0.007$).
These results demonstrate that frequency-dependent interactions between sensorimotor oscillatory phase and power influence human corticospinal excitability, reconciling previous inconsistent results obtained across heterogenous power levels. We conclude that oscillatory phase-power interactions determine human corticospinal excitability to an extent not accounted for by oscillatory phase or power alone.

Disclosures: S.J. Hussain: None. **L. Claudino:** None. **M. Bönstrup:** None. **G. Norato:** None. **C. Zrenner:** None. **U. Ziemann:** None. **E.R. Buch:** None. **L.G. Cohen:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.09/GGG13

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant K01AG047926
Graduate and Professional Student Association JumpStart Grant

Title: Using diffusion tensor imaging to identify structural neural correlates of motor learning and visuospatial processes in cognitively-intact older adults

Authors: *J. LINGO VANGILDER[1], M. C. FITZHUGH[2], C. ROGALSKY[2], S. Y. SCHAEFER[3]
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Abstract: We have recently shown that by testing older adults' visuospatial function, we can predict their motor learning capacity. In fact, our studies show that older adults with above-normal visuospatial scores retained up to four times as much skill as those with below-normal visuospatial scores, regardless of baseline upper extremity motor function, age, and other impairments in language, attention, or delayed memory. We hypothesize that visuospatial tests have predictive value because they probe the health of critical neural structures for motor skill

learning. Classic neuropsychological studies have long supported the role of parietal cortex in visuospatial function and more recent neuroimaging studies have shown that the structural integrity of white matter tracts between parietal and frontal cortices is related to motor skill learning. More specifically, our preliminary data suggest that the right superior longitudinal fasciculus (SLF), a frontoparietal white matter tract, may be a candidate neural pathway for explaining our previous behavioral findings and for predicting motor skill learning in older adults. Although the parietal cortex has long been linked to visuospatial function, there are conflicting reports on the relationship between the structural integrity of neural pathways emerging from the parietal cortex (i.e., the right SLF) and different visuospatial abilities. Thus, the purpose of this ongoing study is to address the gap in knowledge of the relationship between right SLF structure and visuospatial function. Cognitively-intact older adults (n=5, age>65) completed the Rey Complex Figure Test and Recognition Trial (RCFT), an age-adjusted visuospatial exam that assesses visual construction and memory. Participants also underwent diffusion tensor magnetic resonance imaging to quantify right SLF fractional anisotropy (FA), a measure of white matter structural integrity. Results indicate that right SLF FA positively correlated with RCFCT overall score (R^2=0.269), where higher right SLF FA values predict better RCFCT scores. These preliminary data serve as proof-of-concept and support our hypothesis that visuospatial processes may be integrated in the right SLF such that clinical visuospatial testing may predict right SLF structural integrity. The results of this study may indicate that paper-and-pencil visuospatial tests currently used in clinical settings could be used as a cost-effective proxy for neuroimaging, particularly in cases of contraindication or lack of imaging resources.

Disclosures: J. Lingo Vangilder: None. **M.C. Fitzhugh:** None. **C. Rogalsky:** None. **S.Y. Schaefer:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.10/GGG14

Topic: H.02. Human Cognition and Behavior

Support: NSERC Canada (RGPIN-2014-04361)

Title: Increasing motor variability does not impair visuomotor adaptation and leads to better generalization across walking tasks

Authors: *A. BAKKUM, J. M. DONELAN, D. S. MARIGOLD
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Abstract: Some degree of variability in movement is common in all motor tasks. This motor variability has long been considered an undesirable consequence of a dynamic environment paired with an imperfect nervous system. Motor variability is often exacerbated in individuals with sensorimotor impairment, contributing to decreased balance and mobility, and suggesting that it is a negative outcome of nervous system damage. Sensorimotor impairments can also alter the normal relationship (or mapping) between sensory input and motor output, leading to decreased movement accuracy. These individuals must adapt to this altered mapping despite greater variability. Recently, though, studies argue that variability is purposeful movement exploration, which contributes to how the sensorimotor system functions and may facilitate motor learning. Here, we determined how increased motor variability when walking affects visuomotor adaptation and generalization. Two groups of participants adapted to a new visuomotor mapping induced by prims lenses while performing a precision walking task that required them to step on the center of a target. In the balance-unchallenged group, participants (N=4) performed the task without any additional walking manipulation. In the balance-challenged group, participants (N=6) performed the task with inflatable rubber hemispheres (radii: 8.5cm) attached to the soles of their shoes to reduce the control afforded by shifting the center of pressure under the base of support. This manipulation increased muscle activity ($p=0.049$) and motor variability (reflected by greater foot-placement error variability, $p=0.005$). Both groups adapted to the new visuomotor mapping, with the balance-challenged group showing a trend towards slower adaptation (first time constant of a double exponential fit, $p=0.068$). After the adaptation phase, participants then performed a single trial of the other group's task (i.e., the non-adapted task) with non-prism lenses to assess generalization of the learned mapping. Both groups also generalized to the non-adapted walking task. However, the balance-challenged group showed greater generalization (transfer index, $p=0.031$). We argue that disrupting balance exposes the sensorimotor system to increased motor variability and allows for greater trial-to-trial exploration while moving. We propose that this leads to the construction of a more robust internal model and may explain the enhanced generalization.

Disclosures: A. Bakkum: None. **J.M. Donelan:** None. **D.S. Marigold:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.11/GGG15

Topic: H.02. Human Cognition and Behavior

Support: CIHR
NSERC

Title: Whole-brain modular structure of spontaneous neural activity at rest predicts future sensorimotor learning and relearning

Authors: *D. STANDAGE, J. P. NASHED, C. N. ARESHENKOFF, J. R. FLANAGAN, J. P. GALLIVAN
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Abstract: Modularity is a fundamental principle of whole-brain organization, supporting functional specialization and robustness to change. These two properties are widely believed to be fundamental to learning, which is supported by multiple memory systems and implies functional and structural changes. In recent years, the use of graph theory to construct and analyze formal networks from functional magnetic resonance imaging (fMRI) data has proven to be a productive methodology for investigating modular structure during learning, where modules are detected with time-resolved clustering methods applied to multi-slice networks (Bassett et al, PNAS, 2011; Bassett et al, Nat Neurosci, 2015). Here, we used these methods to investigate modular structure before, during and after performance of a sensorimotor adaptation task. On each of two MRI sessions, separated by 24 hours, 34 participants moved a virtual cursor (via the hand) to one of eight possible visual targets. After 120 baseline trials, an instantaneous 45 degree rotation of the cursor was introduced and participants performed another 320 trials under this new sensorimotor mapping. In such visuomotor rotation tasks, participants' early task errors are thought to reveal the relative contributions of explicit and implicit learning processes. Based on these early task errors, we identified three highly distinguishable groups of participants. This group membership was not only predicted by the flexibility of modular structure during the task, but was also predicted by flexibility at rest, before even commencing the task on the first day. Group membership was also predicted by the propensity of brain regions to change modules independently of one another before the task, where this measure showed a negative correlation with early task error on the first day of testing, and a positive correlation on the second day. This finding suggests that learning on the first day changed the nature of the relationship between pre-task modular structure and relearning on the second day. The number and (inversely) size of modules during rest (before learning) also showed this effect. No such measures were correlated with learning during resting-state scans after task performance on either day. These findings demonstrate that rates of learning can be predicted by spontaneous whole-brain modular structure prior to task performance, and suggest that learning modifies this structure prior to relearning.

Disclosures: D. Standage: None. **J.P. Nashed:** None. **C.N. Areshenkoff:** None. **J.R. Flanagan:** None. **J.P. Gallivan:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.12/GGG16

Topic: H.02. Human Cognition and Behavior

Support: The Leverhulme Trust

Title: Cardiac modulation of saccades and fixations

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Abstract: Perception and reasoning fluctuate with oscillatory bodily states. For instance, time-locking visual events to distinct phases of the cardiac cycle alters the processing of this information. However, it remains unclear whether or not humans' overt behaviour is continuously produced in synchrony with such inner bodily signal. In the current study we recorded the oculomotor behaviour and electrocardiogram (ECG) of 32 human participants during a visual search comparable to 'the spot the difference' task. Specifically, we recorded saccades and fixations while participants compared differences in coloration between two bilateral arrays. This paradigm allowed us to trace an average of 3600 saccades and 1150 heartbeats per participant in ~16min of recording. We then computed histograms by calculating the number of saccades in consecutive bins from -200ms to 750ms after the R-wave, which signals the phasic change from diastole to systole in the ECG trace (from filling to ejecting the blood). We also calculated the total number of saccades and the length of the fixations in two time-windows of similar duration. The first window was bounded to the systolic phase at ~200ms after the R-wave, which has been reported as the period of maximal effect of the baroreceptors upon cognition. The second was bounded to the diastole phase at ~500ms after the R-wave, which has been reported as the quiescent period of the baroreceptors. In the analyses of the histograms, our results show a main effect of time bin, suggesting that the number of saccades generated along the cardiac cycle varies in a consistent manner. Post-hoc analyses revealed that indeed more saccades were generated during the early phase of the cardiac cycle compared to the later diastole phase. Furthermore, the number of saccades produced in this latter phase were significantly smaller than those expected in a uniform distribution. In the analyses of the bounded time windows, the results show that a greater number of saccades were generated in the systole phase compared to the diastole. Moreover, the subsequent analysis of participants' fixations supported this finding; longer fixations were found during diastole. In conclusion, by coregistration of eye movements and heartbeats signals, we found statistical evidence for a significant coupling of saccades and subsequent fixations with the heartbeat. Our results suggest

that the different phases of the cardiac cycle and potentially the cardioballistic fluctuations of the ejected blood around the body, modulate overt behaviour. We believe that these results provide original evidence for a mechanism in which humans sample the world according to oscillatory bodily states.

Disclosures: A. Galvez-Pol: None. **R. McConnell:** None. **J. Kilner:** None.

Poster

246. Human Cognition and Behavior: Sensorimotor Processing

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 246.13/GGG17

Topic: H.02. Human Cognition and Behavior

Support: 5T32HD055180-08

Title: Successful transfer of recently acquired motor skills may be dependent on enhanced visuomotor error monitoring during initial learning: An individualized movement-locked ERP analysis

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Abstract: A critical component of motor skill acquisition is the ability to transfer motor learning from one context to a novel, or more complex scenario. In rehabilitative settings, some patients seem to easily transfer such newly learned skills during the same training session, while other patients demonstrate interference effects when introduced to novel tasks during the same session. Such ability to generalize, or transfer skills, has been shown to be affected by the way in which the initial motor skill is encoded, with differential mechanisms being utilized for implicit and explicit learning. Multiple studies have demonstrated that the development of explicit awareness during motor learning interferes with transfer to a novel task during a within training session. However, such studies have utilized an intentional paradigm with which to induce explicit awareness. Much less is known about the effects of incidentally developed explicit awareness, or discovery learning, on generalization. Utilizing a previously identified indicator of incidental explicit awareness, the current study explored the neurobehavioral correlates associated with successful transfer to a novel, more complex motor task. Behavioral results revealed that development of explicit awareness alone, was not predictive of success or failure to transfer motor learning. Subsequent movement-locked ERP EEG analysis provides data suggesting that successful transfer may depend on enhanced neural resources for error monitoring and error processing of both the stimulus and movement execution during the initial learning of the motor task. Subjects showing enhanced stimulus-locked P2 activity along with enhanced movement-

locked N2/Pe activity over mesial premotor regions during initial learning demonstrated successful transfer to the novel motor task. Subjects not demonstrating the enhanced movement-locked N2/Pe activity failed to successfully transfer regardless of performance during the initial learning. As this movement-locked ERP activity is noted to appear early within the initial motor learning, the presented results may provide a tool with which to quickly identify the likelihood of successful generalization within a single training session.

Disclosures: L.A. Wheaton: None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.01/GGG18

Topic: H.02. Human Cognition and Behavior

Title: Evidence of shared action plan representations between free-choice and forced choice tasks

Authors: *B. P. RICHARDSON, L. R. FOURNIER
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Abstract: There is a debate in the literature as to whether free-choice (intention-based) and forced-choice (stimulus-based) action plans share similar or rely on different cognitive representational domains. If the feature codes representing the free- and forced-choice action plans are similar, they should interact when their feature codes represent the same action (e.g., right-hand response) vs. when their feature codes do not represent the same action (e.g., one represents a right-hand and the other a left-hand response). Past research shows that executing an action to an event can be delayed while retaining an action plan to another event if the two action plans partly overlap (e.g., require the same response hand but different keystrokes) vs. do not overlap (e.g., require different response hands and keystrokes). This partial repetition cost (PRC) occurs for forced-choice responses. We examined whether PRCs would occur when executing a free-choice response while retaining an action plan to a forced-choice response. If so, this would indicate that the representational domains for free-choice and forced-choice action plans are similar. Participants planned and retained an action to the first stimulus (A) in a sequence while executing an immediate response to a second stimulus (B), and then executed the retained action. We manipulated the feature overlap between actions A and B (partial or no overlap) and whether action B required forced- or free-choice responses. Results showed that PRCs occurred to a similar degree when action B required a forced- or free-choice response. Additionally, free choice responses for most participants showed either a hand bias or a bias to avoid partial feature overlap. This suggests that free-choice responses were selected to minimize response time and cognitive load. Moreover, the PRCs obtained for free-choice and forced-choice responses were

similar for participants who showed little to no bias and for those who showed an extreme bias in their free-choice responses. This suggests that action plans for forced- and free-choice responses share the same representational domain and compete for selection within the same action control system.

Disclosures: B.P. Richardson: None. **L.R. Fournier:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.02/GGG19

Topic: H.02. Human Cognition and Behavior

Title: The impact of monetary incentives on multi-voxel decoding of motor skill representations

Authors: T. J. ADKINS, *T. G. LEE
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Abstract: Although prior work has shown that increased motivation due to monetary incentives can lead to improved behavioral performance for a variety of learned motor skills, the neural mechanism by which this occurs remains unclear. Several studies have shown that skill-specific motor representations can be identified in cortical motor areas using multi-voxel pattern analysis (MVPA) on fMRI data. Here, examined both how the decoding of these representations change as a function of reward and whether specific changes in tuning in specific executive, motor, and reward-related brain regions can be related to changes in behavioral performance.
In an initial fMRI session, we trained 30 human participants to perform two separate sequences in a discrete sequence production (DSP) task. In a subsequent fMRI session, participants performed these learned sequences with opportunities to earn $5, $10, or $30 for fast and accurate performance. Increasing incentive values coincided with enhancements in skilled performance. We trained a linear support vector classifier to distinguish between patterns of BOLD activity for the two trained sequences. Preliminary results suggest that sequence identity can be identified from several regions including premotor/motor areas, lateral frontal cortex, posterior parietal cortex, caudate, and the cerebellum. Furthermore, sequence decoding is more accurate and widespread at the highest levels of incentive. This suggests the tuning of skill representations may mediate the influence of monetary incentives on skilled performance.

Disclosures: T.J. Adkins: None. **T.G. Lee:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.03/GGG20

Topic: H.02. Human Cognition and Behavior

Support: Leopoldina Postdoctoral Fellowship Nr. 57243032

Title: A rapid form of offline consolidation in skill learning

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Abstract: Introduction
Consolidation of motor skill is defined as greater resistance to interference caused by another task (stability) and/or as performance improvements after a rest period (offline gains). Offline gains are typically reported to occur after 24 hours. An emerging view is that the brain opportunistically consolidates previously encoded memories whenever it is not otherwise occupied by encoding new memories (Mednick et al. 2011). In typical motor skill learning tasks, short periods of active practice alternate with short periods of rest. We here explored whether offline performance improvements are evidenced between short rest periods during the training session itself and studied candidate neural correlates.
Methods
Subjects (n=27) naïve to the task practiced typing a 5-item numeric sequence repetitively as fast and accurately as possible with the left non-dominant hand. Training consisted of 36 alternating practice and rest periods (10 seconds each) for 12 minutes. We measured the finger tapping speed of correct sequences (keypresses per second; kp/s) and tapping accuracy. To dissect learning into improvements occurring within practice or rest periods, we quantified the difference in tapping speed at the beginning of each practice period compared to the end, and at the end of each practice period compared to the beginning of the next. Simultaneous magnetoencephalography (MEG) recordings were obtained to identify spatiotemporal brain activity related to motor learning.
Results
Consistent with previous work using this task, 95% of maximum performance was reached at an early stage at trial 10.7 (3.6 min of training). Over these first trials, total learning was 2.37±1.26 kp/s (non-parametric permutation test, $p<0.001$), within-practice learning was virtually nihil (-0.32±4.0 kp/s, n.s.) while within-rest learning was 2.69±3.3 kp/s ($p=0.003$). Accuracy was stable

along the entire training. Thus, total learning was completely accounted for by the rapid offline performance gains. Desynchronization of brain activity at beta (but not theta, alpha or gamma) rhythm during the rest periods in predominantly contralateral parietofrontal areas predicted the magnitude of trial-by-trial rapid offline learning.
Conclusions
Our results reveal a rapid form of offline consolidation during early motor learning, challenging classic measurements of online learning that mix within-session performance gains during periods of rest and practice. Beta desynchronization during rest periods could support strengthening of circuit connections required for rapid offline consolidation.

Disclosures: M. Bönstrup: None. **I. Iturrate:** None. **R. Thompson:** None. **G. Cruciani:** None. **N. Censor:** None. **L.G. Cohen:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.04/GGG21

Topic: H.02. Human Cognition and Behavior

Support: NIH grant R01 MH069456

Title: Memory recall and statistical learning during movement preparation

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Abstract: To investigate the influence of cognitive processes on motor control, previous studies have examined movement preparation and its basis in the cortex. At the same time, mnemonic functions that could aid in movement preparation by drawing upon past experience, such as memory recall and statistical learning, have instead been examined primarily in the hippocampus and surrounding medial temporal lobe (MTL). How does memory recall and statistical learning facilitate movement preparation, and how do brain systems thought to be necessary for each interact? Using a timed-response variation of the visuomotor association task, we controlled the amount of time available to human participants to prepare a reaching movement to one of several possible targets. We measured the minimum Preparation Time (PT) necessary to reach towards the correct target under various conditions. When no prior target-information is available, the minimum PT should be longer than when the location of the target is indicated prior to movement onset, either by showing the target directly or by displaying a symbol that is associated with a target. In one experiment, participants memorized the associations between symbols and target locations in advance. In a second experiment, participants had to learn these associations in a cross-situational learning task; thus, the minimum PT for symbol-cued trials

should initially match the trials with no cues but should converge to target-cued trials as learning occurs. Across 20 participants in each experiment, the mean minimum PT necessary to reach towards the correct target was approximately 270 ms when no cue was presented. When the upcoming target location was cued in advance, either directly or using a memorized symbol, the PT was essentially 0 ms. However, when the associations between symbols and targets had to be learned, the ability to use the symbols for movement preparation emerged gradually with experience in about 1 hour. When more symbols and targets were included, learning was slower, and when fewer symbols and targets were included, learning was faster. We will also investigate what information is encoded by motor cortical areas and the MTL during movement preparation in this task by repeating a version of this study during fMRI. We hypothesize that the hippocampus is important for learning the relationship between arbitrary symbols and target locations, and that once learned, it will retrieve and represent movement goals when cued with predictive symbols, to guide efficient motor behavior.

Disclosures: D.M. Huberdeau: None. **N.B. Turk-Browne:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.05/GGG22

Topic: H.02. Human Cognition and Behavior

Support: ANR-15-IDEX-0003

Title: Use-dependent learning is subject to corticospinal excitability: Data from motor imagery and motor preparation

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Abstract: Use-dependent learning relates to neuronal or behavioral modifications induced by the repetition of movements without systematic errors (Diedrichsen et al., 2010). In the current study, we used transcranial magnetic stimulation (TMS) to probe the neural plasticity induced by motor imagery and motor preparation. While excitability is facilitated during motor imagery, it is decreased (inhibition) during motor preparation. Here we ask whether a high level of corticospinal excitability is a prerequisite to use-dependent plasticity. During a pre-training session, we measured the direction of right thumb movements induced by TMS over left M1 when at rest. In a first experiment, we asked participants to imagine moving their thumb (training session) at 110°, 60° or 0° of the pre-training direction. During the post-training session, we observed that TMS-induced movements were deviated proportionally and transiently, i.e. it returned to baseline 30 minutes after training. In a second experiment, we asked participants to

prepare thumb movements in a direction perpendicular (90°) to the pre-training direction. Interestingly, the TMS-induced movements were not deviated during the post-training session. While motor imagery and motor preparation are two cognitive processes known to activate the motor system, only motor imagery, during which corticospinal excitability is facilitated, induces use-dependent learning.

Disclosures: C. Ruffino: None. **J. Gaveau:** None. **C. Papaxanthis:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.06/GGG23

Topic: H.02. Human Cognition and Behavior

Title: A hierarchical model for sequence processing predicts effects of context on neural response within cortical hierarchy

Authors: *H.-Y. CHIEN, J. CHEN, C. J. HONEY
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Abstract: *Background:* In real life, prior information continuously influences the perception and processing of the information in the present. For example, a word is understood differently within sentences. This temporal integration, which occurs over multiple timescales, is processed within a hierarchical architecture in the human brain: higher order regions integrate information over longer timescales compared to lower order sensory regions (Hasson et al., 2015). We previously proposed a hierarchical computational model – HTRACX – that can account for the multi-scale properties of human sequence processing. We now set out to test a novel prediction: that individual brain regions maintain a local information context, and that low-level regions establish a new context rapidly, while higher order regions establish new context representations more gradually.
Model Design: Our hierarchical model, HTRACX, is built by cascading a series of temporal auto-encoders, modified from a sequence learning model (French et al. 2011). Each level of the model learns the associations between sequences of elements and chunks in the input. Specifically, higher levels of the HTRACX model employ longer time constants, enabling them to preserve context over longer periods.
Testing Hierarchical Context Construction: We hypothesized that lower levels of the model should establish context more rapidly compared to higher levels. To test this, we measured the time taken for context variables in the model to become synchronized, when the current input sequence is shared, but the input history is different. We found that higher levels of HTRACX took longer to synchronize their responses when the same input sequences were presented in different prior contexts.

Context effect on brain response: To test this prediction in the brain, we performed a similar analysis in fMRI data. One group of 22 subjects listened to a 9 minutes auditory story in the fMRI scanner, and another group listened to a version of the story scrambled by sentences (mean duration 21.85s). We computed inter-subject pattern correlation across groups to measure the neural response within each sentence preceded by an intact or scrambled context. We found that the neural response gradually aligned, thus achieving a higher correlation in the later part of the sentence. As predicted by HTRACX, higher order regions reach such alignment slower than lower order regions.
Conclusion: Our model, HTRACX, for simulating sequence processing in the cortical hierarchy, predicts that context is constructed on different timescales in different brain regions, a phenomenon that we confirmed in fMRI data within a naturalistic language paradigm.

Disclosures: H. Chien: None. **J. Chen:** None. **C.J. Honey:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.07/GGG24

Topic: H.02. Human Cognition and Behavior

Support: NRF-2017R1A2B2006420

Title: Role of the executive functions in statistical learning

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Abstract: Statistical learning (SL) is a fundamental neurocognitive mechanism that enables us to extract complex probabilistic regularities embedded in the environment. However, individual differences in SL have not been comprehensively characterized yet. We hypothesized that SL would be influenced differently by individuals' executive function (EF) and working memory (WM) capacity. The study included two sessions on two separate days. In Session 1, participants performed various neuropsychological tests known to be involved in EF and WM. In Session 2, participants performed the Alternating Serial Reaction Time (ASRT) task that has previously shown to capture statistical learning of probabilistic associations. Participants were asked to press one out of the four buttons which corresponded to the target presented on the screen. The ASRT task had three different trial types: pattern trials with high probability condition, random trials with high probability condition (random-high), and random trials with low probability condition (random-low). The difference between random-high and random-low trials was

defined as ‘SL score.’ As random-high and random-low trials were separated solely by probability, we could examine pure SL effects. The learning task was divided into three periods to investigate the dynamic changes associated with learning. Also, we defined a ratio of bias as the number of incorrect responses when participants pressed the buttons of high-probability target instead of low-probability target. By calculating the bias, we could find whether participants achieved SL or not following the assumption that participants would expect an occurrence of a high-probability target more than a low-probability target over the course of SL. According to our results, participants showed significant SL both in terms of reaction times and accuracy. Regarding the bias, it increased significantly in the second period against the first period, suggesting increased expectation of high-probability targets as learning progressed. Similarly to previous studies, higher SL score seemed to be associated with weaker performance on some WM and EF measures, although these correlations did not reach significance. Interestingly, however, we found that higher SL score was significantly related to better performance (smaller conflict scores) on Stroop task [$r = -0.403$, $p < 0.05$], suggesting that inhibitory control may have a different role in SL compared to other aspects of WM and EF. Our findings can contribute to a better understanding of the neurocognitive underpinnings of SL.

Disclosures: J. Park: None. **K. Janacsek:** None. **D. Nemeth:** None. **H. Jeon:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.08/GGG25

Topic: H.02. Human Cognition and Behavior

Support: This work was supported by GIST Research Institute (GRI) grant funded by the Gwangju Institute of Science and Technology (GIST) in 2017.
This work was supported by the National Research Foundation of Korea (NRF-2016R1A2B4010897).

Title: Pink noise stimulation following sleep spindle activity may enhance the procedural memory consolidation during a nap

Authors: *J. CHOI, K. WON, S. HAN, E. KIM, Y. KIM, S. C. JUN
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Abstract: Researchers suggested that electrical and acoustic stimulation during sleep can have a positive effect on memory consolidation. They explained that entrainment of slow oscillation (SO) and sleep spindle through the stimulation during sleep can derive the improved memory consolidation. Over the years, related studies have reported that temporal relationship between SO and sleep spindle is also an important factor for the memory consolidation. In this study, we

attempted to evoke SO activity by delivering pink noise after sleep spindle detection so that SO and sleep spindle can have temporal relation.
Seven right-handed male participants (mean ± SD age: 27.5 ± 1.2 years) were recruited for this study. All the participants visited the laboratory three times for a nap on different days. The first nap was adaptation nap for measuring the sleep EEG data (32 channels including Cz for spindle detection) which were used to calculate a spindle power threshold of the sleep spindle detector. The second and third nap were stimulation or sham nap in pseudo-random order and they were spaced at least two weeks apart. During the stimulation nap, pink noise acoustic stimuli (62dB SPL, 50 ms) were delivered after the detection of the sleep spindle. Before and after the experiment, subjects conducted finger tapping task (tapping a five-digit sequence, e.g., 4-1-2-3-1) for the motor learning.
We found K-complex (KC) component from a trial-averaged waveform during the stimulation nap. KC is SO activity evoked by acoustic stimulation during the nap. Furthermore, an analysis for phase-locking component revealed that evoked KC was phase-locked with the stimulation onset. There is no other phase-locked component. After 15 minutes of stimulus began, a stronger delta band (1-4 Hz) activity was observed during the stimulation nap compared to the same time period of sham nap ($p < 0.05$). In the behavioral analysis, subjects showed a greater increment of finger tapping speed after the stimulation nap ($p = 0.0194$).
In this experiment, we evoked SO after the spindle activity by delivering pink noise stimulation during the nap. We found the clear auditory evoked potential (KC) by the stimulation, and it derived higher delta activity during the stimulation nap compared to sham nap. Furthermore, we observed stronger memory consolidation effect after the stimulation nap. These results may imply that SO following sleep spindle activity may stabilize the slow wave sleep (SWS) for ongoing sleep and enhance the procedural memory consolidation.

Disclosures: J. Choi: None. **K. Won:** None. **S. Han:** None. **E. Kim:** None. **Y. Kim:** None. **S.C. Jun:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.09/GGG26

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust Senior Fellowship Grant 106149

Title: Off-line reinforcement learning using forward models

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Abstract: Anecdotally we know that a difficult problem can often be solved by ‘sleeping on it’. Sleep has been shown to benefit insight, gist-extraction and some motor tasks, but the computational mechanisms by which performance can improve without an external teacher remain unclear. We hypothesized that off-line learning could be driven by simulated experience generated by a previously-acquired forward model. Put simply, during the day we learn ‘if I do *x*, then *y* happens’ (*forward* prediction) and during the night we invert this to learn ‘if I want *y* to happen, then I should do *x*’ (*inverse* control). This scheme has multiple advantages: model-free reinforcement learning of inverse controllers is time-consuming and requires a lot of training data, while forward models are well-defined and can be learned efficiently through supervised methods. We developed a novel abstract sequence task which allowed separate probing of forward prediction and inverse control to test three predictions arising from our hypothesis: (1) there should be no off-line gains in forward prediction, (2) there should be off-line gain in inverse control, and (3) off-line inverse gains should depend on the accuracy of forward prediction. Our inverse control task required subjects to acquire targets by pressing left/right keys that moved a cursor through sequences of seven locations. Accuracy was determined from subjects’ ability to acquire targets with the minimum number of key presses. In separate tests of forward prediction accuracy, subjects were asked to predict with a mouse click where the cursor would end up after a given sequence of key presses. Between two consecutive days of task performance, we observed robust off-line gains in inverse control but not forward prediction. Moreover, off-line gains were greatest for those subjects who performed forward prediction well at the end of day 1. Since inverse and forward learning rates on day 1 were correlated, we used multiple regression to disentangle their combined influence on off-line inverse gains revealing a significant positive influence of only forward prediction accuracy. In a second experiment with three learning sessions each separated by 12 hours, we found that this relationship held only for overnight periods including sleep and not for day-time waking periods. Neural network simulations confirmed that off-line reinforcement learning using forward models is an efficient strategy to learn such inverse tasks. We suggest that this powerful and biologically plausible architecture provides a computational framework within which to interpret neural activity during sleep and the behavioural consequences thereof.

Disclosures: A. Jackson: None. **A. Clarke:** None. **T. Stock:** None. **O. Jackson:** None. **W. Xu:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.10/GGG27

Topic: H.02. Human Cognition and Behavior

Title: The effect of visual input on the neural signatures of novel music sequence learning

Authors: *I. ZIOGA[1], P. M. C. HARRISON[2], M. T. PEARCE[2], J. BHATTACHARYA[3], C. D. LUFT[1]
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Abstract: In education, an important goal is to find the most effective way of presenting information to beginners. Several studies in the literature suggest multimodality is beneficial for music learning. However, these studies have used passive exposure (e.g. Loui et al., 2010) and neglected explicit instruction, which also plays an important role for the acquisition of musical knowledge. Here, we investigated the neural signatures of novel music sequence learning through active reproduction with auditory vs. audio-visual input, by studying the neural responses to high- vs. low-probability notes before and after learning. We expected that the event-related component N100 would be smaller in response to high- compared to low-probability notes, as it has been found to be sensitive to statistical probabilities of melodic sequences (Carrus et al., 2013)
In the training phase, participants (non-musicians) learned melodic sequences generated by an artificial musical grammar (Rohrmeier et al., 2011), which consisted of 18 different diatonic melodies, 8-22 notes long. For the testing phase, we presented melodies terminating with high- or low-probability notes with respect to the musical grammar, as calculated using the melodic expectancy model of Pearce (2005). The experiment took place on 4 consecutive days. On day 1-3, participants were trained on the melodies through active reproduction on a keyboard: they listened to the first 2 notes of a melody, and only after they reproduced them correctly, the next segment was increased by one note and so on. The audio-visual group (N=20) had each note colour-coded on screen, whereas the auditory group (N=20) had no colour indication and needed to rely only on the acoustic information to reproduce the sequences. Participants' learning of the melodic sequences was tested before and after training (days 1 and 4): they were presented with melodies and asked to judge if the final note was correct or incorrect, while EEG was recorded. At the behavioural level, we observed that participants successfully learned the melodies generated by the artificial grammar, but there was no significant difference between groups. At the neural level, we found an interaction between group and expectancy for the mid-frontal N100 amplitude after learning. Particularly, the auditory group elicited a smaller negativity in response to expected than unexpected notes. This difference was not present in the audio-visual group, suggesting that they might have not been able to perform this early discrimination. Our findings support that multisensory presentation in fact impairs the learning of an artificial musical style, as indexed by the early brain responses.

Disclosures: I. Zioga: None. **P.M.C. Harrison:** None. **M.T. Pearce:** None. **J. Bhattacharya:** None. **C.D. Luft:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.11/HHH1

Topic: H.02. Human Cognition and Behavior

Support: NSERC CGS-M

Title: HIIT the road Jack: The effects of exercise on piano learning

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Abstract: Rationale: Exercising after practice improves retention of motor skills (Roig et al., 2012). Specifically, high-intensity interval training (HIIT) *after* practice of a motor skill leads to better task performance one day and one week later compared to low-intensity interval training (LIIT) or no exercise (Thomas et al., 2016). Neurochemicals released during HIIT are presumed to enhance neuroplastic mechanisms related to learning during early consolidation (Skriver et al., 2014). The facilitating effects of HIIT have been demonstrated for the learning of implicit motor sequence tasks. However, little is known about the impact of HIIT on the consolidation of *explicit* motor skills in the context of real-world learning. Piano playing is a real-world task that involves explicit learning of motor sequences. In this exploratory study, we hypothesized that adults who perform HIIT after piano-sequence learning would exhibit better retention of the learned sequence than those who perform LIIT.
Methods: We recruited healthy volunteers between the ages of 18 and 35 who were non-musicians. Participants underwent a graded maximal exercise test (GXT) to determine their cardiorespiratory fitness ($VO2_{peak}$) and their maximum power output (W_{max}). At least one day later, participants practiced a piano sequence before completing an interval exercise protocol (IEP). The IEP consists of 3 repetitions of alternating intervals of 2-min low-intensity and 3-min high-intensity cycling (HIIT group: 60% & 90% W_{max}; LIIT group: 8% & 12% W_{max}). Participants were tested on the piano sequence one hour, one day, and one week after initial practice.
Statistical Analysis: Performance was quantified by pitch and rhythm accuracy, which are defined as the proportion of correct key presses and correct timing of presses, respectively.
Preliminary Results: We analysed data from 16 participants (n=7 HIIT, n=9 LIIT) using a two-way mixed ANOVA with between-subjects factor of intensity (HIIT, LIIT), and within-subjects factor of retention interval (1 hr, 1 day, 7 days), and gender, fitness, and baseline performance during acquisition as covariates. No main effect of intensity was observed for pitch or rhythm

accuracy (pitch: $F(1,12) = 0.016$, $p = 0.902$, $eta^2 = 0.001$; rhythm: $F(1,12) = 0.256$, $p = 0.623$, $eta^2 = 0.023$).
Conclusion: Preliminary analysis provides no evidence that HIIT enhances consolidation of piano learning. However, definitive conclusions must be reserved until data collection is complete.

Disclosures: D. Swarbrick: None. **L. Tremblay:** None. **C. Sabiston:** None. **S. Trehub:** None. **D. Brooks:** None. **D. Alter:** None. **J. Chen:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.12/HHH2

Topic: H.02. Human Cognition and Behavior

Support: BMBF Grant 01EO0901
DFG Grant GSC 82-3

Title: Instructor-observer synchronization of BOLD activity mediated by instructive origami videos

Authors: K. KOSTORZ, V. FLANAGIN, *S. GLASAUER
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Abstract: Today's digital society offers diverse possibilities to provide instructive 'how-to' videos and to learn by observing them: video platforms allow uploading of self-made instructive videos, which in turn can be used for watching and learning.We investigated this facet of naturalistic human learning and interaction employing functional MRI: In order to create an instructive origami video we videotaped a highly trained, blindfolded instructor who folded an origami inside the MRI scanner. During the main experiment subjects had three attempts to learn: they viewed the instructive video three times inside the MRI with the task to memorize the foldings; right after each viewing they had to reproduce the sequence of foldings as far as they could. As a control, we videotaped the instructor folding similar but partly repetitive folds. While watching this control video subjects had only to count the number of folds to ensure cognitive processing.
We found high similarity between the (HRF convolved) average optic flow motion of the videos and especially the observers' BOLD activity not only in parietal but also somatosensory and premotor areas, reflecting motion related activity under naturalistic conditions in the Action Observation Network (AON).The broader aim of this study was to investigate voxel-wise similarities and synchronization between the instructor and observers to find common processes for learning, and for mere action identification (the control condition). We found the highest

similarities in all conditions in the AON. Additionally, dorsolateral and medial prefrontal similarities were found esp. for the learning runs. When investigating time lags, a bootstrap procedure showed that while a vast part of the observer activity was either in sync or lag with the instructor, part of the somatosensory and premotor/MTG areas showed advancing observer activity during the initial learning condition. Thus performing a complex naturalistic task and observing it is accompanied by similar brain activity in several brain regions common to both participants, with the naturalistic design offering possibilities to show fine-grained differences between different types of action processing, i.e. memorization and identification.

Disclosures: K. Kostorz: None. **V. Flanagin:** None. **S. Glasauer:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.13/HHH3

Topic: H.02. Human Cognition and Behavior

Support: National Brain Research Program 2017-1.2.1-NKP-2017-00002
Postdoctoral Fellowship, OTKA PD 124148
Janos Bolyai Research Fellowship of the Hungarian Academy of Sciences

Title: How to change automatic behaviors?: The role of inhibitory control and learning processes in overwriting procedural knowledge

Authors: *K. HORVÁTH[1,2], P. SOLYMOSI[3], Á. GERGELY[3], L. PETRENCSIK[3], A. GUTTENGÉBER[3], D. NEMETH[2,4], K. JANACSEK[2,4]
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Abstract: The acquisition of our everyday habits strongly relies on procedural learning. To change these habits, the associations underlying these behaviors need to be overwritten with new ones. Such *rewiring* typically involves inhibiting the old, automatic associations while developing new ones. These processes have mainly been investigated in the context of extinction learning, focusing on reward-related and drug-seeking behaviors, primarily in rodents. However, little research has been done on how rewiring occurs in other habitual behaviors and whether the findings of extinction learning holds for neutral stimuli as well. Here we aimed to investigate the basic neurocognitive functions underlying habit formation and change, independent of reward-related processes. More specifically, we tested the role of inhibitory control and learning new associations during rewiring in a neutral context in humans. Thirty-two healthy young adults

participated in the experiment. Procedural learning was measured by the Alternating Serial Reaction Time (ASRT) task in three sessions. On Day 1, participants acquired probabilistic associations embedded in an ASRT sequence. After 24 hours, a combined version of the Go/No-go paradigm and the ASRT task was administered with a new sequence that partially overlapped with the previously practiced one. Some of the associations changed: highly probable ones became less probable, while less probable ones became highly probable on Day 2. Other associations remained unchanged. Participants were instructed to suppress their automatized responses for some of the originally high-probability associations (No-go trials) that became less probable on Day 2. In contrast, they had to respond to those that became more probable to acquire these new associations. After another 24-hr delay, performance was tested on both the original and the new sequence. Results show that associations learned on Day 1 could not be wiped out by the newly learned associations; instead, participants were able to flexibly switch between and express the knowledge on the associations learned on Day 1 and Day 2 in a context-specific manner. The No-go manipulation seemed to impair the acquisition of the new associations instead of promoting it. These findings are mostly consistent with extinction and inhibitory learning studies showing that newly formed memories compete with the original memories for the control of behavior and suppressing automatic responses may be even detrimental during rewiring. Our study provides further insights into the neurocognitive underpinnings of habit change and can contribute to a better understanding of relapse behavior in addictions.

Disclosures: K. Horváth: None. **P. Solymosi:** None. **Á. Gergely:** None. **L. Petrencsik:** None. **A. Guttengéber:** None. **D. Nemeth:** None. **K. Janacsek:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.14/HHH4

Topic: H.02. Human Cognition and Behavior

Title: Behavioral biases in people at risk for problematic gambling and pornography use

Authors: *S. M. SKLENARIK[1], M. PADUA[2], C. LOVE[2], M. FERNANDEZ[2], R. LIVOTI[2], M. K. GOLA[4], M. POTENZA[5], R. S. ASTUR[3]
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Abstract: Research suggests that automatic cognitive biases and action tendencies exist for addictive stimuli in people with problematic use. For example, Weirs, et al. (2011) found that alcohol-dependent individuals are quicker to approach and slower to avoid pictures of alcohol stimuli compared to neutral stimuli; this cognitive bias is not present in people without

problematic drinking behaviors. Importantly, studies indicate that these cognitive biases can be manipulated to decrease problematic behavior and improve treatment outcomes (Weirs, et al., 2013). The purpose of the current study is to replicate this cognitive bias effect in individuals at risk for problematic gambling behavior.
132 undergraduates were recruited from the University of Connecticut for a 30-minute study. First, participants completed three questionnaires assessing gambling behavior: Massachusetts Gambling Screen (MAGS), South Oaks Gambling Screen (SOGS), and Problem Gambling Severity Index (PGSI). Participants then completed a cognitive bias task, in which they were seated in front of a computer equipped with a standard gaming joystick and headphones. Participants were instructed to pull the joystick in response to an irrelevant property of the stimuli (ie. if the image is tilted to the left), causing the stimuli to enlarge as if it is moving closer, and to push the joystick in response to the opposite irrelevant property (ie. if the image is tilted to the right), causing the image to minimize as if it is moving farther away (instructions for whether to push or pull in response to the tilt of the image depended on the condition the participant was randomly assigned to). Participants completed two test sessions total. Response time and accuracy were recorded by the computer.
Initial analyses do not reveal any significant differences between the two groups, nor significant cognitive biases for gambling stimuli in either group. Future research will compare this lack of cognitive biases for gambling stimuli to cognitive biases for other behavioral addictions, such as pornography. Subsequent studies will also aim to use a cognitive retraining paradigm to reduce automatic cognitive biases and thereby decrease problematic behaviors.

Disclosures: S.M. Sklenarik: None. **M. Padua:** None. **C. Love:** None. **M. Fernandez:** None. **R. Livoti:** None. **M.K. Gola:** None. **M. Potenza:** None. **R.S. Astur:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.15/HHH5

Topic: H.02. Human Cognition and Behavior

Support: Hungarian Scientific Research Fund OTKA PD 124148 (KJ)
Janos Bolyai Research Fellowship of the Hungarian Academy of Sciences (KJ)
National Brain Research Program (project 2017-1.2.1-NKP-2017-00002 (KJ)
NSF BCS 1439290 (MTU)
NIH R21 HD 087088 (MTU)

Title: Revealing the neural basis of sequence learning by a series of coordinate-based activation likelihood estimation meta-analyses

Authors: *K. JANACSEK[1,2], K. F. SHATTUCK[3], K. M. TAGARELLI[3], J. A. G. LUM[5], P. E. TURKELTAUB[4], M. T. ULLMAN[3]
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Abstract: Sequence learning, which often occurs gradually and implicitly, underlies numerous motor, cognitive, and social skills. Previous models and empirical investigations of sequence learning in humans and non-human animals have highlighted cortico-striatal-cerebellar circuitry. To systematically examine the functional neuroanatomy of sequence learning in humans, we conducted a series of neuroanatomical meta-analyses. We used rigorous study selection criteria to control for visual, motor, and other confounds. This allowed us to target sequence learning itself, independent of other factors. With this approach, we found that sequence learning, as well as implicit sequence learning more specifically, yielded consistent activation only in the basal ganglia, across the striatum (caudate nucleus and putamen) and the globus pallidus. In contrast, when visuomotor and other factors were not controlled for, premotor cortical and cerebellar activation were additionally observed. The study provides solid evidence that sequence learning in humans, in particular implicit sequence learning, relies on the basal ganglia, with no evidence from these analyses for cerebellar or premotor contributions. The findings have both basic research and translational implications.

Disclosures: K. Janacsek: None. **K.F. Shattuck:** None. **K.M. Tagarelli:** None. **J.A.G. Lum:** None. **P.E. Turkeltaub:** None. **M.T. Ullman:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.16/HHH6

Topic: H.02. Human Cognition and Behavior

Title: Corticospinal excitability changes after training suggest implicit coding of a bimanual motor skill

Authors: *A. T. MCCULLOCH, I. PARK, J. CHEN, D. L. WRIGHT, J. J. BUCHANAN
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Abstract: The purpose of this study was to determine if training with a bimanual motor task would result in a motor skill memory that was enhanced over wakefulness in a manner consistent with developing an implicit memory for sequencing skills. To examine this idea, corticospinal excitability was measured at three time intervals: 1) in a baseline session 10 minutes before

training, 2) at a 6 minute interval after training, and 3) at a 21 minute interval after training. Previous research with uni-manual sequencing tasks have revealed no decrease as well as increases in corticospinal excitability above baseline at similar and longer post-training intervals for tasks that are characterized by an enhancement of motor memory formation within 2-6 hours after brief bouts of training. In this study, transcranial magnetic stimulation (TMS) over left-hemisphere M1 was used to generate motor evoked potentials (MEPs) in the right-hand first dorsal interosseous (FDI) muscle. Participants abducted-adducted the index fingers on the horizontal plane without seeing their fingers. A visual display of a circle template representing the coordination pattern of 90° and a dot representing the motion of the two fingers was presented on a monitor in front of the participants. Participants (n=15) were trained on the 90° pattern for 20 minutes and instructed that moving the dot around the circle would indicate they were producing the 90° coordination pattern between their fingers. It was predicted that post-training MEPs at 6 and 21 minutes would not decrease compared to baseline and would be larger than baseline MEPs. The above predictions were statistically supported, *ts (14) > 5.1, ps <= .0001*. The training also resulted in performance improvements for the bimanual pattern as evidenced by significant reductions in error and significant increases in coordination stability across practice, *ts (14) < -2.2, ps <= .01*. Thus, brief training with the bimanual task resulted in corticospinal excitability increasing above baseline for an extended period after training, a novel finding for a bimanual task and a finding consistent with excitability levels found after training with sequencing tasks. This suggests that the motor memory for the 90° bimanual pattern was being encoded as an implicit motor task.

Disclosures: A.T. McCulloch: None. **I. Park:** None. **J. Chen:** None. **D.L. Wright:** None. **J.J. Buchanan:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.17/HHH7

Topic: H.02. Human Cognition and Behavior

Support: Michael J. Fox Foundation for Parkinson Research

Title: Therapeutic paths diverging in the brain: Differential changes in behavior and resting state functional connectivity induced by differing transcranial magnetic stimulation targets

Authors: *S. NARAYANA[1], K. SCHILLER[1], B. N. BYDLINSKI[1], C. ROYAL-EVANS[2], M. S. LEDOUX[3]
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Abstract: Transcranial magnetic stimulation (TMS) is a noninvasive neuromodulation tool that shows promise as an adjuvant to skill learning paradigms. TMS can be applied in a myriad of ways, and the effects of changing its parameters, including site of stimulation, are not well understood. Furthermore, measures of behavior alone following TMS may not fully reflect the processes of neurophysiological plasticity that occur. Here we use a standardized voice treatment protocol (LSVT) for individuals with Parkinson disease (IWPD) as a model paradigm for TMS adjuvancy, along with resting state fMRI (RSMRI) connectivity measures, to examine the effect of TMS targeted on the primary laryngeal motor cortex ($M1_{larynx}$) in the left and right hemispheres (affected in IWPD with voice deficits) and respective networks as described by the Directions Into Velocities of Articulators (DIVA) model of speech system. We hypothesized that compared to sham (STMS), TMS applied to the left $M1_{larynx}$ (LTMS) would increase connectivity to the feed forward speech network (FFSN) and behaviorally effect treatment duration, while TMS applied to right $M1_{larynx}$ (RTMS) would increase connectivity to the feedback speech network (FBSN) and impact the rate of learning. Fifteen IWPD (5 female, Hoehn and Yahr stage 2.6 ± 0.8) with voice deficits were enrolled in a double blinded, radomized, sham controlled clinical trial. Voice measures and RSMRI scans were performed at baseline, post treatment, and at 16 week follow up. Three thousand pulses of 5 Hz LTMS, RTMS, or STMS were delivered immediately preceding LSVT for 16 sessions over 4 weeks. Connectivity of LTMS and RTMS targets was measured by correlating LM1 and RM1 time courses to other regions and contrasting results on individual and group levels. Behaviorally, there was no significant difference between groups post-treatment in the primary endpoint of vocal loudness, but the RTMS group improved fastest during treatment (reaching endpoints at only 2 weeks) and the LTMS group showed the best retention of gains at follow up. Post treatment, RSMRI demonstrated greater connectivity of LM1 to FFSN in the LTMS group and of RM1 to FBSN in the RTMS group versus sham. At follow up, the RTMS group had no further changes while the LTMS group had increased FBSN connectivity. This exploratory study is novel in its use of RSMRI to demonstrate how the site of TMS stimulation differentially affected network changes even with similar primary endpoint behaviors. This suggests that a wider array of behavioral measures of learning may be needed when studying TMS adjuvancy and that RSMRI is useful for elucidating how specific TMS parameters affect cognitive changes during skill learning.

Disclosures: S. Narayana: None. **K. Schiller:** None. **B.N. Bydlinski:** None. **C. Royal-Evans:** None. **M.S. LeDoux:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.18/HHH8

Topic: H.02. Human Cognition and Behavior

Support: ONR N00014-16-1-2251

Title: Variability in inter-cue timing slows implicit motor sequence learning

Authors: *K. D. SCHMIDT[1], Y. HAN[2], P. J. REBER[3]
[2]Psychology, [3]Dept Psychol, [1]Northwestern Univ., Evanston, IL

Abstract: Increasing variability in practice schedules has been shown to slow initial learning but lead to improved transfer after a consolidation period (Shea & Morgan, 1979). The underlying mechanisms for this process are not well-understood and there has been limited exploration of methods by which variability can be imposed during practice. The present study increased training variability by introducing random noise in inter-cue timing during learning of a purely implicit motor sequence learning task, the Serial Interception Sequence Learning (SISL) task. In this task, participants make a precisely timed response to a cue moving down a computer screen towards a target in one of four spatial locations. Participants are not told that a repeating 12-cue sequence is embedded within the task. This sequence has a consistent timing pattern of inter-cue intervals split between short (300ms initially) and long (600ms) intervals. The task speeds up with practice adaptively to each participants' performance to keep the overall accuracy at ~80% correct and speed changes are reflected proportionally in the short/long intervals between cues. Variability during practice was created by adding normally distributed noise with a standard deviation of 100ms or 200ms during 6 blocks of training with 36 target sequence repetitions each block. Participants were 54 Northwestern University undergraduates randomly assigned to 1 of the 3 timing conditions during training. Sequence knowledge was assessed during a post-training test with no timing variability in which participants saw 3 sequences (1 trained and 2 novel foils) and sequence knowledge was measured as the increase in accuracy (percent correct) for the practiced sequence compared with foils. A one-way between subjects ANOVA of training variability condition revealed a significant linear effect of variability on test performance, $F(1,52) = 9.6$, $p = .003$. The normal timing condition (M = 17%, SD = 11%) was more accurate than the intermediate timing condition (M = 12%, SD = 8%) which was more accurate than the high variability timing condition (M = 7%, SD = 9%). This suggests that imposing timing variability slows learning of implicit motor sequences, reinforcing the idea that implicit learning is inflexible (Dienes & Berry, 1997; Gobel et al., 2011a, b). Future work will examine the effect of training variability on transfer of skill performance immediately and at a delay to assess if increasing inter-cue timing variability produces effects like contextual interference (Shea & Morgan, 1979) on implicit sequence learning.

Disclosures: K.D. Schmidt: None. **Y. Han:** None. **P.J. Reber:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.19/HHH9

Topic: H.02. Human Cognition and Behavior

Title: Partial transfer of implicit perceptual-motor skill to novel timing structure

Authors: *Y. C. HAN, K. D. SCHMIDT, P. J. REBER
Northwestern Univ., Evanston, IL

Abstract: Implicit learning has been observed to be inflexible, with virtually no knowledge transfer of a covertly embedded perceptual motor sequence when relative inter cue timing was changed (Sanchez, Yarnik, & Reber, 2015; Gobel et al. 2011a, b). In the Serial Interception Sequence Learning (SISL) task, participants observe circular cues moving vertically down a screen towards one of four target zones, which follow an undisclosed 12 item repeating sequence with a timing structure of 6 long (600ms) and 6 short (300ms) inter cue intervals. Correct responses require a precisely-timed press of a key corresponding to cue location. Task speed is adaptively adjusted based on individual performance to maintain ~80% accuracy. Inter-cue timing is adjusted proportionally to maintain the long/short (2:1) timing ratio. Sequence knowledge is measured as accuracy during the repeating sequence minus accuracy on novel sequences, resulting in sequence-specific performance advantage (SSPA) assessment. Participants completed training with 6 blocks (540 trials/block, 216 total sequence repetitions) followed by SSPA assessments in three tests: (1) the same timing structure, (2) inverted long/short cue timings (replicating Gobel et al. 2011a, b), and (3) repeating sequence presented cues at equal fixed inter-cue timing. As seen previously, participants exhibited no sequence knowledge on the inverted timing test, replicating prior results ($M = -2.28\%$, $SE = 1.43\%$). However, performance on the equally-spaced timing was reliably greater than chance ($M = 7.78\%$, $SE = 1.26\%$), $t(53) = 6.19$, $p < 0.01$, reflecting partial transfer of implicit knowledge. Performance on this transfer test was reliably lower than performance on the test with the trained timing structure ($M = 12.42\%$, $SE = 1.43\%$), $t(53) = 2.51$, $p = .015$, indicating some inflexibility. This is the first study to observe partial transfer after implicit learning. Prior studies observed either full expression of sequence knowledge or complete inflexibility, transfer conditions being treated essentially as a novel sequence. Future research will test whether there is a general gradient across magnitude of timing change, which may indicate the precision of implicitly acquired, timed-action sequence neural representations. Alternately, equally spaced timing may reflect a special case that reveals separate representations of cue order information and ISI timing. Because of the limited flexibility seen selectively in implicit learning, the character of the underlying neural representations can be examined via assessing patterns of transfer.

Disclosures: Y.C. Han: None. **K.D. Schmidt:** None. **P.J. Reber:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.20/HHH10

Topic: H.02. Human Cognition and Behavior

Support: DFG GO-8 Re-LOAD
DFG VO-15/1 Re-LOAD

Title: Effects of high intensity acute exercise on motor learning and EEG beta power in a precision grip fine motor task

Authors: L. HUEBNER[1], K. ZWINGMANN[1], B. GODDE[2], *C. VOELCKER-REHAGE[1]
[1]Inst. of Human Movement Sci. and Hlth., Technische Univ. Chemnitz, Chemnitz, Germany; [2]Psychology & Methods, Jacobs Univ., Bremen, Germany

Abstract: A bout of high intensity cardiovascular exercise seems to lead to an enhanced state of arousal as reflected by increased EEG beta (13-30 Hz) power after acute exercise (AE) (Crabbe & Dishman, 2004) and to trigger motor learning 24 h after exercise, i.e., motor memory consolidation, more than a resting control condition (Roig et al., 2012). So far, research on AE and motor learning mainly focused on motor tasks requiring power grips and matching force profiles by continuous wrist movements. EEG correlates after AE during motor performance in young adults have not been examined. Thus, this study aimed to investigate the influence of AE on motor learning in a fine motor task using a precision grip with index finger and thumb. Therefore, thirty high-fit young adults (18-34 years of age) performed a cardiovascular exercise test on a bicycle ergometer and were matched with respect to their cardiovascular fitness level into two groups; a high intensity exercise group (HEG; n=15, female: n=8; AE = warm up: 5 min cycling at 40% max Watt (mW), 3x3 min at 90% mW interspersed with 3x2 min at 60% mW, cool down: 5 min at 20% mW) and a low intensity exercise group (LEG; n=15, female: n=9; AE = 25 min cycling at 20% mW). Motor learning was assessed with a precision grip tracking task. Participants had to track a sine wave with their right dominant hand at baseline (immediately before AE: 8 trials of 15 sec (i.e., 1 block)) and three practice sessions (immediately, 30 min and 24 h after AE: 4 blocks each). Tracking variability was operationalized as the root mean square error (RMSE). EEG was recorded at baseline and practice immediately and 30 min after AE. Beta task-related power (TRPow) was analyzed for frontal, central and centro-parietal electrodes. Data analysis is still in progress. We hypothesize that motor performance of the HEG is better 24 h after AE as compared to the LEG, reflecting improved motor memory consolidation. With respect to the EEG, we expect the HEG to reveal stronger beta TRPow decreases immediately and 30 min after AE than the LEG, indicating enhanced cognitive and motor processing during

motor performance.
Crabbe, JB & Dishman, RK (2004). *Psychophysiol, 41*(4), 563-574.
Roig, M, Skriver, K, Lundbye-Jensen, J, Kiens, B & Nielsen, JB (2012). *PloS One, 7*(9), e44594.

Disclosures: L. Huebner: None. **K. Zwingmann:** None. **B. Godde:** None. **C. Voelcker-Rehage:** None.

Poster

247. Human Cognition and Behavior: Motor Learning and Memory

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 247.21/HHH11

Topic: H.02. Human Cognition and Behavior

Support: DFG GO-8 Re-LOAD
DFG VO-15/1 Re-LOAD

Title: Resting state EEG classification using echo state networks for prediction of motor learning outcome in older adults

Authors: *B. GODDE[1], H. YUAN[1], L. HUEBNER[2], M. HUNTER[1], C. VOELCKER-REHAGE[2]
[1]Psychology & Methods, Jacobs Univ., Bremen, Germany; [2]Inst. of Human Movement Sci. and Hlth., Technische Univ. Chemnitz, Chemnitz, Germany

Abstract: Numerous studies revealed the capacity of older adults (OA) to learn new motor skills. To effectively design personalized motor learning interventions, it is crucial to predict potential learning outcomes and to isolate neural mechanisms that are associated with these predictions. Echo State Networks (ESNs), a variant of Recurrent Neural Networks, are particularly suitable to classify EEG data based on their critical spatiotemporal characteristics. We used ESNs to classify resting state EEG data of young (YA) and OA obtained before training a force modulation tracking (FM) task in precision grip with their right thumb and index finger. 28 YA and 47 OA were trained in the FM task. 32-channel resting EEG was measured before the training. Based on their performance gain, OA were identified as good (OA+) or bad learners (OA-) by median split. Half of the EEG data per participant was used to train two ESNs to classify the other half of the data either as YA or OA, or as OA+ or OA-, respectively. Interestingly, the ESN that was trained to differentiate between YA and OA, classified OA+ to be more like YA but OA- to be like OA. Based on the classification, individual EEG data were split in segments that were classified as either YA, OA+, or OA- per participant. These segments were pooled within groups and are further analyzed with respect to their EEG signatures. These analyses will now provide evidence about the EEG components and therefore potential underlying neural mechanisms predicting good learning outcomes in OA. Analysis of resting

EEG further revealed that OA+ and OA- differed with respect to alpha (8-12 Hz) and beta (13-30 Hz) oscillatory power over several frontal, central, and parietal sites with OA- having more alpha and less beta power than OA+ at rest, even when controlled for baseline performance. YA had even higher alpha and lower beta power than OA-. Results indicate that OA+ compensate for age-related decline in learning capacity by using different processing strategies in the preparatory phase before motor training. Further, EEG data of OA+ contain signatures that are similar to YA but are not reflected in alpha and beta oscillations.

Disclosures: H. Yuan: None. **L. Huebner:** None. **M. Hunter:** None. **C. Voelcker-Rehage:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.01/HHH12

Topic: H.02. Human Cognition and Behavior

Support: Intramural Research Program of the National Institutes of Health (ZIA-MH-002909)

Title: Leveraging thousands of dynamic, daily real-world memories to investigate the neural patterns of memories over time

Authors: *W. A. BAINBRIDGE, C. I. BAKER
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Abstract: Previous work has shown a striking difference in the brain between remembering meaningful, autobiographically-relevant memories versus laboratory-learned stimuli (e.g., Rissman et al., 2016). However, autobiographical memory research has been largely limited to small numbers of self-reported and subjective verbal memories or photographs collected over a short experimental time. Because of these limitations, work in autobiographical memory has been unable to probe the neural correlates of visual memories over a long time scale to look at questions such as how retrieving remote memories may differ from recent memories, and how different content of autobiographic memory is reflected in the brain. In the current study, participants were recruited for a 3T fMRI experiment from the userbase of the app “1 Second Everyday” - a popular social media app where users record a 1-second video every day of events in their lives. While one second is brief, these videos are also information-dense, with dynamic visual content that serves as highly salient cues to specific memories. Participants (N=16) were scanned in an event-related design while they viewed 300 randomly sampled videos across their recorded time span (on average, participants had 724 total recorded videos, or close to 2 years). Importantly, participants were experimentally paired based on similar matched demographics, and in addition to watching their own videos in the scanner, watched 300 videos of the other

participant randomly interspersed with their own. These two matched participants will thus have identical perceptual experiences but opposite memory experiences. From this, we find significantly higher activation in several regions including the medial parietal cortex, medial temporal lobe (including the hippocampus), and the frontal pole when participants viewed their own memories versus another's. Importantly, these same regions show sensitivity to the remoteness of a participant's own memories. We additionally find significant neural patterns related to familiarity of the faces and scenes present within people's memories. In sum, these large-scale real-world memories give us an unprecedented ability to look at detailed questions about the neural correlates of memories over different times and content.

Disclosures: W.A. Bainbridge: None. **C.I. Baker:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.02/HHH13

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant BCS-1461088

Title: Fast sleep spindles associated with improved memory for specific objects

Authors: *S. WITKOWSKI, J. D. CREERY, L. E. DIONISIO, K. A. PALLER
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Abstract: Current theories of sleep postulate that memories can be strengthened through replay. This replay is thought to be engaged spontaneously during sleep, and has tentatively been associated with fast sleep spindles in EEG recordings (brief increases in oscillatory activity at 13.5-15 Hz). In this study, we investigated EEG sleep physiology and memory for visual objects. Participants first learned the locations of 64 objects on a grid. They intentionally learned the locations of these objects, but did not know that they would need to recognize the specific objects later. Each object was presented concurrently with a related sound. After a pre-nap test of this spatial knowledge, participants took a 90-minute nap during which 32 object sounds were presented softly during slow-wave sleep. Upon waking, participants were given a surprise recognition test with 96 objects, including 32 new objects, 32 old objects (identical to those seen before), and 32 similar objects (different from one seen before but within the same category). Participants attempted to identify each object as old, similar, or new, and then took a post-nap spatial recall test. A recognition specificity score was calculated as the sum of correctly recognized old and similar objects from the object-recognition task. Fast spindle density during sleep (number of spindles per 30 seconds) correlated with the specificity score, but not with spatial recall accuracy. Slow oscillation density (number of slow oscillations per 30 seconds) and

delta power during NREM sleep negatively correlated with the specificity score. Cues during sleep produced a relative improvement for top-half learners in spatial recall, as observed in previous studies of targeted memory reactivation (TMR). Recognition specificity was not influenced by TMR. Overall, these results provide further evidence that fast spindles play a role in memory consolidation during sleep, particularly for memory precision with respect to remembering which specific objects were seen previously.

Disclosures: S. Witkowski: None. **J.D. Creery:** None. **L.E. Dionisio:** None. **K.A. Paller:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.03/HHH14

Topic: H.02. Human Cognition and Behavior

Support: NIMH K99/R00MH103401

Title: Brain networks supporting the composition and precision of episodic memory reconstruction

Authors: *R. COOPER, M. RITCHEY
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Abstract: Episodic memories can be highly rich in detail, containing a wealth of multimodal sensory information. In reflection of such qualitative variability, the process of recollection is accompanied by increases in activity and functional connectivity of a widespread network of brain regions. Despite this behavioral and neural complexity, research has only recently begun to distinguish the fidelity of distinct episodic memory features from the overall probability of recollecting a previous experience. As such, it remains largely unknown how neural networks dynamically support qualitative aspects of memory retrieval, including the composition and precision of episodic memory details. It is also unknown how these neurocognitive processes might be modulated by factors such as emotion, which may bias the contents or fidelity of retrieval. To investigate these questions, we developed a novel memory paradigm using complex multimodal events where, in an MRI scanner, 28 participants studied a series of unique objects. Each object was presented in a specific location within a 360 degree panorama scene, in a specific color sampled from a continuous color spectrum, and was accompanied by either an unpleasant or a neutral natural background sound. In a memory test, participants were asked to recollect each object's encoding event and reconstruct its original color and scene location, providing fine-grained measures of memory quality. Univariate analyses revealed that regions within the anterior temporal network and posterior medial network, particularly the angular

gyrus, code for the precision of item and contextual features in memory over and above successful retrieval. Moreover, negative emotion modulated the relationship between posterior medial function and item color memory precision specifically. Planned analyses will use network-level functional connectivity and multivariate techniques to further specify how interactions between brain regions support memory for specific episodic features and the precision with which they are recollected.

Disclosures: R. Cooper: None. **M. Ritchey:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.04/HHH15

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS098981
NIH Grant DC014589

Title: Selectivity for familiar faces in human retrosplenial cortex shown by direct intracranial recordings

Authors: *O. WOOLNOUGH[1], K. FORSETH[1], C. M. KADIPASAOGLU[1,2], N. TANDON[1,2]
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Abstract: Retrosplenial cortex (RSC) is an important node in the human cortical memory network, showing strong anatomical and functional connectivity to the parahippocampal gyrus (PHG). RSC has been well established to be involved in complex scene analysis and the memory of fixed landmarks; however, it has not been investigated whether RSC is involved in processing of other 'unique entities' such as human faces.
Here we studied the responses to human faces from 160 electrodes in RSC with a large patient cohort (n=65) who underwent neurosurgical implantation of intracranial electrodes for treatment of intractable epilepsy. To test activity in this region, we used a famous face identification task. To establish category selectivity, we also investigated responses to famous landmarks, common objects, face parts and scrambled faces. The broadband gamma activity (BGA; 70-150Hz) was measured in these electrodes and later compared to that of the activity in PHG.
Our results show that RSC has distinct spatial regions of selectivity with the inferior aspects showing preferential activation to famous landmarks whereas the region centred around the subparietal sulcus shows a strong selectivity for human faces. Further investigation showed this Retrosplenial Face Area also shows sensitivity to the familiarity of the patients to the faces, with correctly identified faces showing significantly greater BGA. This familiarity effect is also

apparent even when the patients were not performing a naming task but instead performed a visual discrimination task with the faces. We show the responses in RSC precede those in PHG by 45 ms both for discriminating faces from scrambled faces and for the emergence of the familiarity effect.
These results together suggest RSC has an important role in the cortical memory network for identification of other people and may be one of the earliest stages for determination of whether another person is known or not. This finding is significant as RSC is typically the earliest region to show hypometabolism in pre-clinical Alzheimer's and may be the cause of the familiarity deficits seen in the early stages of the disease which are usually attributed to PHG dysfunction.

Disclosures: O. Woolnough: None. **K. Forseth:** None. **C.M. Kadipasaoglu:** None. **N. Tandon:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.05/HHH16

Topic: H.02. Human Cognition and Behavior

Support: the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare (HI15C3175)
the Basic Science Research Program (NRF-2016R1C1B2010726) through the National Research Foundation (NRF) of Korea
the Brain Research Program (NRF-2017M3C7A1031333) through the National Research Foundation (NRF) of Korea

Title: Task-dependent cortical representations during episodic memory retrieval

Authors: *G. KIM, S.-H. LEE
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Abstract: During the retrieval process of episodic memory, top-down control is considered to contribute to reinstatement of the target component of memory that is related to behavioral goal. However, it still remains unclear how top-down signals constrain cortical representations during episodic memory retrieval depending on behavioral goals. To address this issue, we performed an event-related functional magnetic resonance imaging (fMRI) experiment comprising separate learning and retrieval sessions. During the learning session, participants were presented with 6 short movie clips. One day after the learning, the participants conducted the retrieval session inside the scanner. In this session, there were two retrieval tasks: event retrieval task and context retrieval task. During the event retrieval task, the participants were instructed to focus on

recalling the core event while they were asked to attend to the recall of the context in which the event took place. We found that the same cortical regions, including lateral prefrontal, premotor and parietal areas, were activated in both retrieval tasks, and the contrast between the activation maps of the event and context retrieval tasks revealed little significant difference. Consistent with prior neuroimaging studies, which suggest that the posterior parietal cortex is involved in episodic memory retrieval, we found that significant decoding of individual episodic memory traces in the intraparietal sulcus during both retrieval tasks. However, the response patterns of the premotor cortex could be used to decode individual memory traces only during the event retrieval task whereas memory trace decoding was possible in the right planum temporale during the context retrieval task but not during the event retrieval task. These results suggest that while a general retrieval network is engaged in the retrieval process regardless of the nature of the recalled content, top-down signals constrain cortical representations to emphasize the target component of episodic memory.

Disclosures: G. Kim: None. **S. Lee:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.06/HHH17

Topic: H.02. Human Cognition and Behavior

Support: F99 NS105223

Title: Neural encoding of spatial information during visual perception and memory retrieval

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Abstract: Space is a critical dimension on which the neural basis of visual perception is organized, with over 20 maps of the visual field identified in human neocortex. Activity evoked in neocortical areas at the time of perception is thought to be reinstated during later memory retrieval. We used fMRI to investigate the extent to which memory-driven activity preserves the topographic organization of visually-driven activity across many cortical areas. To do this, we first trained human subjects to associate colored fixation dot cues with spatially localized stimuli. Stimuli were four unique radial frequency patterns presented at -3, -1, 1, and 3 degrees on the horizontal meridian. After subjects demonstrated reliable memory for the stimulus features and spatial location paired with each cue, we collected fMRI data while subjects performed matched perception and memory tasks. During perception trials, subjects fixated centrally and viewed a cue followed by the associated spatial stimulus while performing a 1-back task on the stimuli. During memory retrieval trials, subjects fixated centrally and viewed a cue, then recalled the

associated stimulus in its spatial location from memory. Using independent population receptive field (pRF) estimates, we examined the BOLD response as a function of distance from pRF center to the viewed or remembered stimulus location. In early visual areas, we observed that the BOLD response during perception was maximal in voxels with pRF centers close to the stimulus location and dropped off rapidly within a few degrees. Spatial response profiles in these areas were broader during memory retrieval than perception, but memory responses still contained reliable information about stimulus locations. In higher visual areas, spatial response profiles during perception became progressively broader, consistent with estimates of increasing pRF size. However, unlike in early visual areas, parietal response profiles were equivalent during memory and perception. These findings suggest that visual areas differ in their relative sensitivity to externally driven versus internally driven stimulus representations. Planned experiments will manipulate subjects' gaze position during memory encoding to test the hypothesis that retrieval activity reflects the spatiotopic coordinates of a previously viewed stimulus and can thus deviate substantially from retinotopically-organized activity during initial perception.

Disclosures: S.E. Favila: None. **B.A. Kuhl:** None. **J. Winawer:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.07/HHH18

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number JP17H05947

Title: Memory for people whom I told something to: Roles of the ventromedial prefrontal cortex in destination memory

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Abstract: Destination memory (DM) is defined as memory related to people that we told something to, and the concept of this memory is contrasted with that of source memory (SM) which is memory for people whom we were told by. One fMRI study reported that the parahippocampal gyrus showed significant activation in the successful retrieval of DM (Mugikura et al., 2016). However, functional neuroimaging evidence is still unavailable in how the neural mechanisms related to the successful retrieval of DM are different from those of SM. The present study investigated this issue. In the present study, we recruited 25 right-handed and

college-aged healthy participants from the Kyoto University community. All participants performed one encoding and two retrieval tasks, and neural activation was measured only in the retrieval tasks. During encoding, participants were presented with two-letter Japanese kanji words as a target stimulus, and were required to read them orally to persons shown on movie clips in the DM condition, or to listen to them told by persons shown on movie clips in the SM condition. In addition, we prepared two control conditions for each experimental condition of DM and SM, in which participants read two-letter Japanese kanji words orally to an object picture (speaking control: SC) or listened to them sounded by Windows PC (listening control: LC). During retrieval, participants performed two-step retrieval tasks including the direction judgment and paired recognition. In the direction judgment, participants were visually presented with target words one by one, and were required to judge whether each word was what participants had told or had been told. In the paired recognition after the direction judgment, participants were presented with sets of a target word and two faces who had been shown in movie clips during encoding, and were required to choose one face paired with a target word. All trials in the direction judgment were categorized into hits, which included successful retrieval trials in both tasks of the direction judgment and paired recognition, and misses including other trials. Using the categorization of trials, we focused on the analysis of neural activation only in the direction judgment. Behavioral data demonstrated that hit rates in DM were significantly lower than those in SM. In fMRI data, successful retrieval activation in the ventromedial prefrontal cortex (vmPFC) was significantly greater in DM-SC than SM-LC. However, no significant activation was identified in the reverse contrast of SM-LC vs. DM-SC. These findings suggest that the self-referential processes involved in the vmPFC could contribute to the successful retrieval of DM, compared to SM.

Disclosures: Y. Nagasawa: None. **H. Sugimoto:** None. **T. Tsukiura:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.08/HHH19

Topic: H.02. Human Cognition and Behavior

Support: NSERC
OGS

Title: Scrutinizing the grey zones of declarative memory: Does the late positive component (LPC) reflect self-relevance, mental time travel, or proximity of self to other?

Authors: *A. N. TANGUAY[1], D. J. PALOMBO[2], C. ATANCE[1], L. RENOULT[3], P. S. R. DAVIDSON[1]

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Abstract: In the cognitive neuroscience of memory, knowledge of the world (i.e., semantic memory) is often contrasted with the vivid recollection of personal events (i.e., episodic memory). Behavioral and ERP data have dissociated these two forms of declarative memory from self-knowledge (Renoult et al., 2012). In particular, self-knowledge produces a Late Positive Component (LPC), an ERP correlate of episodic processing (Rugg & Curran, 2007), that is intermediate between semantic and episodic memory, whereas thinking of future selves does not differ from episodic memory (Tanguay et al., 2018). Although the LPC is associated with episodic processing, the greater LPC for self-knowledge relative to semantic memory could also reflect greater self-relevance and/or mental time travel. It is unknown how the degree of self-relevance in semantic memory interacts with mental time travel. To disentangle such effects, here participants thought about their own traits in the present and in the future, and did the same for other people. Thus, our atemporal "semantic memory" condition became "temporal" to match the self-knowledge conditions. Additionally, we manipulated the proximity of other people between subject: some thought of the traits of their age group (group other, n = 31), or of a stranger of the same sex and age (generic other, n = 28), or of a close friend (close other, n = 31). Thinking of a close friend should increase self-relevance and possibly also episodic processing, thus decreasing the LPC difference between self and other. We extracted the mean LPC amplitude from 500 to 800 ms post-stimulus onset and entered it in a mixed ANOVA with knowledge type (self, other), temporal perspective (present, future), and parietal electrode (P3/Pz/P4) as within subject factors, and proximity to others (group other, generic other, close other) as a between subject factor. The LPC for self-knowledge was more positive than for other-knowledge, and more positive for future- than present-thinking, as expected, and these effects did not interact. Thus, thinking of future others appears to engage the cognitive processes associated with the LPC in a way that is similar to future self-knowledge. The main effects of knowledge type and temporal perspective did not interact with the proximity to others. Hence, the LPC when thinking of close friends differs from self in a similar fashion to thinking of a group of people or a generic other. Our studies show that the LPC is sensitive to the temporal perspective and self-relevance of semantic aspects of declarative memory, and might not be solely a signature of episodic memory.

Disclosures: A.N. Tanguay: None. **D.J. Palombo:** None. **C. Atance:** None. **L. Renoult:** None. **P.S.R. Davidson:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.09/HHH20

Topic: H.02. Human Cognition and Behavior

Support: JSPS Kakenhi JP17K00220

Title: Effects of vividness during the elaboration of autobiographical memories

Authors: *N. E. NAWA[1], H. ANDO[2]
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Abstract: Autobiographical memory (AM) retrieval, i.e., the remembering and re-experiencing of past personal events, usually begins with the search for an event, followed by a period where episode-specific details are integrated to form a vivid construct (memory elaboration). While the vividness of mental imagery has been linked to activity in early visual areas (e.g., Dijkstra et al. 2017), and laboratory-based memory tasks have indicated a central role of the hippocampus in the sense of memory vividness (Ford & Kensinger, 2016), much less is known about the correlates of AM vividness. AM retrieval processes have been consistently shown to recruit a large network of brain areas located most notably in the prefrontal cortex, medial and lateral temporal structures, including hippocampus and parahippocampal regions, posterior midline regions, and lateral parietal cortex. Healthy participants (N = 26, 14 females, age 20-25 years old) were asked to retrieve AMs of varying types of valence and emotional intensity while their brain activity was recorded using functional MRI. Here, we examined whether activity in the nodes of that brain-wide network was modulated by a composite index of memory vividness collected prior to scanning. The index assessed three aspects of mental imagery: visual, auditory and spatial (Talarico et al. 2004). Inside the scanner, pre-screened verbal cues customized for each participant (e.g., “Trip overseas”) were displayed on the screen (3 s), and participants were instructed to press a button as soon as they were able to start recollecting the event associated with the cue. They were also requested to continuously relive the original experience by retrieving as many details as possible until the end of the trial (14 s). Based on the vividness index, we performed a parametric modulation analysis using SPM 12 (Wellcome Trust Centre for Neuroimaging), controlling for differences in emotional intensity. Regions of interest (ROIs) were defined using masks derived from the Harvard-Oxford atlas made available by the FMRIB Software Library (Jenkinson et al. 2012). Modulatory effects were examined in the voxels within each one of the ROIs (small-volume correction), and statistical significance was assessed using family-wise-error correction for multiple comparisons at a height threshold of $p < 0.05$. While all nodes in the putative AM retrieval network showed enhanced activity for the main effect of memory elaboration, modulatory effects associated with the vividness index were only observed in the right hippocampus. These results indicate that the hippocampus plays a critical role in the sense of vividness evoked during autobiographical memory elaboration.

Disclosures: N.E. Nawa: None. **H. Ando:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.10/HHH21

Topic: H.02. Human Cognition and Behavior

Support: ERC Grant STG-715714
Scholarship from Stiftelsen Olle Engqvist Byggmastare
Scholarship from BBSRC MIBTP

Title: Memory reactivation in EEG patterns fluctuates rhythmically and is locked to a consistent theta phase

Authors: C. KERRÉN[1], J. LINDE-DOMINGO[2], S. HANSLMAYR[2], *M. WIMBER[2]
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Abstract: Computational and animal models suggest that the hippocampal theta rhythm provides time windows that are optimal for memory encoding at one phase of the oscillation, and for memory retrieval at the opposite phase[1]. Evidence in humans supporting these models is very sparse. The current study was aimed at testing whether neural indices of memory retrieval are indeed fluctuating and locked to a specific theta phase.
We recorded scalp EEG (128 channels) while participants (n=24) were asked to study novel verb-object associations during an encoding phase, and to reproduce the object from memory when cued with the verb during a retrieval phase. Objects belonged to two different semantic classes: animate or non-animate. We trained time-resolved multivariate classifiers based on linear discriminant analysis (LDA) to detect memory reactivation in the EEG patterns. Confidence of the classifier in categorizing the retrieved object was used as an index of memory reactivation at each time point after presentation of the reminder.
To test whether this neural index of retrieval was indeed fluctuating within a trial, we first performed a frequency transformation of the classifier outputs. This analysis revealed a power peak at 7-8Hz that was present for the real classifiers, but not for classifiers trained with random labels. We next tested if neural memory reactivation was locked to a specific theta phase, using a classifier-triggered average approach, conceptually similar to spike-triggered averages in the animal literature. We found that the time points of maximal classifier confidence, presumably reflecting successful retrieval in neural terms, occurred 250-300ms after a highly consistent theta phase, again specific to the 7-8Hz frequency range. This phase locked signal originated from medial temporal and late visual regions, areas different from the ones generating successful memory classification. These findings are consistent with a neural processing hierarchy where memory reactivation is initiated as a consistent phase of a (possibly hippocampal) theta oscillation, and the reactivated memory trace can then be detected with a delay of 200-300ms in

neocortical regions.
[1] Hasselmo, M. E. 2005. What is the function of hippocampal theta rhythm?--Linking behavioral data to phasic properties of field potential and unit recording data. *Hippocampus,* 15**,** 936-49.

Disclosures: C. Kerrén: None. **J. Linde-Domingo:** None. **S. Hanslmayr:** None. **M. Wimber:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.11/HHH22

Topic: H.02. Human Cognition and Behavior

Support: NSF CAREER Award (BCS-1752921) to B.A.K.

Title: Organization of content representations and episodic memory signals in human posterior parietal cortex

Authors: *H. LEE[1], S. C. SWEIGART[2], B. A. KUHL[2]
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Abstract: Posterior parietal cortex (PPC) is activated during episodic retrieval across a variety of stimulus types, which has often been interpreted as reflecting content-general memory processes. However, recent neuroimaging studies using pattern-based analyses have indicated that PPC activation patterns reflect specific mnemonic contents during encoding and retrieval. Here using human fMRI, we consider the question of how PPC combines content-specific representations with content-general memory signals. Subjects were first exposed to hundreds of complex scene images containing a wide range of content and were then tested, during fMRI scanning, on their recognition memory for the images. We generated two different voxel-wise encoding models: one that explained voxel activation patterns based on the contents depicted in the images and one that explained voxel activation patterns based on content-general memory signals including confidence and accuracy. This allowed us to compare the relative influence of the two types of information (content and memory) for each voxel in PPC. We first assessed the overall cross-validated accuracy of each model after controlling for the influence of the other model. We found that both the content model and the memory model successfully predicted trial-by-trial activation patterns in PPC. The accuracy was higher for the memory model, suggesting that content-general memory signals explain more variance in PPC activity. We next explored the spatial distribution of voxels that carried information about content vs. memory signals. Of interest was how/whether content representations and memory signals were shared within individual voxels. We found that the degree of overlap between content voxels and memory voxels was not greater than would be expected by chance, suggesting at least some spatial

segregation between content-specific representations and content-general memory signals within PPC. Comparison of activation for old/new conditions across different image categories revealed that content-general old/new signals were generally additive to content-specific signals within the voxels sensitive to both kinds of information. Together, these results suggest that both content-specific and content-general signals can uniquely explain PPC activation during memory tasks, but the two signals are likely to be independent from each other, potentially originating from different sources. Additional analyses will consider sub-regions of PPC and specific relationships between content-specific information and different kinds of memory processes.

Disclosures: H. Lee: None. **S.C. Sweigart:** None. **B.A. Kuhl:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.12/HHH23

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01MH-08721406A1

Title: Tracking spatial source memory reactivation with alpha-band oscillations

Authors: *D. W. SUTTERER[1], E. AWH[2]
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Abstract: An ongoing debate in the field of memory research revolves around the extent to which all features of an object are bound together as an integrated unit. Psychophysical observations suggest that non-spatial features of remembered objects such as their color or orientation can be forgotten independently in both working memory (WM) and long-term memory (LTM). However, an emerging view in the field of WM suggests that spatial representations may be an exception, serving as a mechanism for binding together non-spatial features in WM. In support of this view, recent EEG work finds that the topography of alpha band activity (8-12 Hz) on the scalp spontaneously tracks remembered locations even when they are not relevant for the task at hand, suggesting that spatial representations may serve as a means of maintaining bound object representations in memory. Here we apply this same approach to LTM and test whether or not an object's spatial location is spontaneously reactivated during retrieval of non-spatial features. To answer this question, we conducted an experiment in which observers memorized the position and color of a collection of 24 unique shapes. The color and position of each shape were each randomly selected from a continuous 360 degree color and location space respectively. On Day 1, human observers memorized the color and location of each object. On Day 2, observers repeatedly retrieved the color or location of each shape while EEG were recorded. We used an interleaved block design in which observers alternated between

reporting either the location of each item but not the color, and the color of all items but not the location during each block. Using an inverted encoding model (IEM) and electroencephalography (EEG) alpha-band activity (8-12 Hz), we found that we were able to track the precise spatial location of the cued object on both trials where observers retrieved the remembered location as well as on trials where observers retrieved the color of the remembered representation. These findings provide support for the idea that spatial representations are an integral component of online object memory representations both in WM and LTM.

Disclosures: D.W. Sutterer: None. **E. Awh:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.13/HHH24

Topic: H.02. Human Cognition and Behavior

Title: Construction and elaboration of autobiographical memories from multiple visual perspectives

Authors: H. IRIYE[1], *P. L. ST. JACQUES[1,2]
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Abstract: Visual perspective, recalling events from one's own eyes or from an observer-like viewpoint, is a fundamental aspect of autobiographical memory (AM). Yet, how visual perspective influences the functional mechanisms supporting retrieval is unclear. In the current fMRI study, we used a multivariate neuroimaging analysis technique called partial least squares to characterize the spatiotemporal dynamics supporting AM retrieval from multiple visual perspectives. 20 participants were presented with bespoke spatial location cues and asked to construct specific AMs from a particular perspective and then elaborate by recalling as much detail as possible. Compared to a spatial visualization control task, we found that own eyes and observer perspectives engaged an AM retrieval network (i.e., hippocampus, anterior and posterior midline, lateral frontal and posterior cortices) that peaked during later retrieval periods but was recruited less strongly for observer perspectives. Functional connectivity analyses with a left anterior hippocampal seed region revealed that visual perspective also altered interactions among neural regions and their timing during retrieval. There was stronger hippocampal connectivity with a posterior medial network (i.e., thalamus, precuneus, posterior parahippocampal, retrosplenial, and posterior inferior parietal cortices) during the initial construction of AMs from observer perspectives and stronger connectivity with a medial temporal lobe network (i.e., posterior hippocampus, amygdala, ventromedial prefrontal and visual cortices) during later retrieval periods from own eyes perspectives, suggesting that visual

perspective directs how neocortical systems guide retrieval. Our findings demonstrate that visual perspective influences AM retrieval by altering hippocampal-neocortical interactions and subsequently the strength of neural recruitment in the AM retrieval network during later retrieval periods, thereby supporting the central role of visual perspective in shaping the personal past.

Disclosures: H. Iriye: None. **P.L. St. Jacques:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.14/HHH25

Topic: H.02. Human Cognition and Behavior

Support: Army Research Lab Cooperative Agreement Number W911NF-10-2-0022

Title: Stable representations of a cautious state of mind: An fMRI study of memory and perceptual decision-making

Authors: *T. SANTANDER, E. LAYHER, P. CHAKRAVARTHULA, N. MARINSEK, B. O. TURNER, M. P. ECKSTEIN, M. B. MILLER
Psychological & Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Successful memory judgments rely on both the available memory evidence and an appropriately biased decision criterion. Recent behavioral research suggests that criterion placement is a stable individual trait across various memory and decision-making tasks alike. However, it is unknown whether neural representations of criterion placement are similarly consistent. To test this, 29 healthy young adults performed recognition memory and perceptual decision-making tasks during fMRI scanning. In each task, criterion placement was manipulated by assigning monetary rewards/punishments to decision outcomes. To induce liberal criterion placement, one condition heavily punished misses (e.g. calling a studied stimulus in the memory task 'new'); another condition punished false alarms (e.g. calling an unstudied stimulus 'old') to induce conservative criterion placement. Decision evidence was also manipulated across 'low' and 'moderate' conditions, such that stimuli with moderate memory evidence were repeated multiple times during encoding, and perceptual stimuli had easier/harder targets to detect. As predicted, individuals set decision criteria similarly regardless of task, while discrimination performance (d-prime) was unrelated. We then applied a sparse Bayesian multi-task multi-kernel learning (SBMTMKL) approach to probe whether multivariate neural representations of decision evidence and criterion placement were shared across tasks. Inputs were contrast images (Hits > Correct Rejections) reflecting successful decision-related activity in each task, criterion condition, and low/moderate evidence conditions. Multiple linear kernels were constructed for each input by parcellating the brain according to the 400-region Schaefer atlas. Split-half cross-

validation was used to evaluate cross-task classification accuracy (i.e. training on memory data, testing on perception, and vice-versa). SBMTMKL significantly distinguished between liberal/conservative criterion conditions across tasks, with a network of frontoparietal regions providing the strongest contributions to the model. However, we did not identify consistent patterns of activity underlying low/moderate decision evidence across tasks. This suggests criterion placement may have a stable neural representation invariant to decision task, and moreover, that activity related to successful decisions reflects the extent to which one is monitoring evidence through careful criterion placement, not the strength of evidence itself. This research was sponsored by the Army Research Laboratory and accomplished under Cooperative Agreement Number W911NF-10-2-0022.

Disclosures: T. Santander: None. **E. Layher:** None. **P. Chakravarthula:** None. **N. Marinsek:** None. **B.O. Turner:** None. **M.P. Eckstein:** None. **M.B. Miller:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.15/HHH26

Topic: H.02. Human Cognition and Behavior

Support: The National Institute of Information and Communications Technology entitled, 'Development of network dynamics modeling methods for human brain data simulation systems'
The ImPACT Program of the Council for Science, Technology and Innovation (Cabinet Office, Government of Japan)

Title: Whole-brain propagating activities estimated from resting-state MEG and EEG data

Authors: *Y. TAKEDA, N. HIROE, O. YAMASHITA
ATR Neural Information Analysis Labs., Kyoto, Japan

Abstract: Repetitive spatiotemporal patterns in spontaneous brain activities have been widely reported in nonhuman studies. It is suggested that such patterns reflect propagating activities along connections with various conduction delays and have roles in memory consolidation. In human magnetoencephalography (MEG) and electroencephalography (EEG) studies, however, propagating brain activities emerging in resting-state have not been extensively examined. Here, we reveal whole-brain propagating activities from resting-state MEG and EEG data using a recently proposed method, SpatioTemporal Pattern estimation (STeP, Takeda et al., 2016). Within 0.1 s, the propagating activities transiently showed spatial patterns that slightly but significantly resembled the following resting-state networks (RSNs): executive control, visual, sensorimotor, and default mode. This result suggests that the propagating activities reflected the

cognitive functions the RSNs reflect, such as the self-generated thought based on visual and sensorimotor memories. The propagating activities were composed of multiple frequency components from delta (1-4 Hz) to gamma (30-50 Hz), indicating that these components exhibited fixed temporal patterns at the same time. This result suggests the existence of driving regions that trigger the propagating activities in these frequency bands. These results provide new insights into the resting-state activities of the human brain.

Disclosures: Y. Takeda: None. **N. Hiroe:** None. **O. Yamashita:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.16/HHH27

Topic: H.02. Human Cognition and Behavior

Title: Probing episodic memory reinstatement with continuous stimuli

Authors: *L. SKALABAN[1], C. T. ELLIS[1], J. S. TUREK[2], N. B. TURK-BROWNE[1]
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Abstract: Episodic memory gives us the ability to mentally time travel back to when an experience was encoded and to relive the sensory details of that experience. This kind of retrieval is assessed most commonly using behavioral measures of recall and recognition, along with source, confidence, or familiarity/recollection judgments. However, these measures provide only indirect assessment of a key prediction of episodic memory retrieval, *reinstatement* — i.e., that the brain is returned to the same state it was in at the time of encoding. Moreover, behavioral measures are sometimes unavailable, such as in pre-verbal infants or even older infants and toddlers who may struggle to follow instructions. This limits the field's understanding of episodic memory retrieval in this important age range, when the hippocampus is developing rapidly, and when the memories that are formed later become inaccessible, resulting in infantile amnesia. Here we report a novel paradigm that uses fMRI to assess memory reinstatement automatically and without task demands. We take advantage of intersubject correlation methods developed for data obtained using continuous stimuli (e.g., movies), adapted to be used within rather than across participants. We hypothesized that the dynamics of activity during episodic retrieval — when cued with auditory information but in the absence of visual information — would mirror those from encoding of the corresponding visual information. We showed adult participants 10 pairs of 3-minute long animated movies in the scanner. Each pair consisted of one presentation of the intact movie and one presentation of the movie with audio intact but where the video went blank for 10 seconds several times. For half of the pairs, the intact movie presentation preceded the presentation with video blanks (allowing memory to reinstate the missing visual information from the audio and preceding video), whereas for the other half of

pairs, the presentation with blanks preceded the intact presentation, preventing reinstatement from episodic memory. We assessed whether reinstatement occurred during the blanks of all movies by correlating these periods with the intact presentation of the same periods, either in space (over voxels at one time point) or in time (over volumes in one voxel). Preliminary evidence shows that correlations were greater between blank periods and their corresponding intact video time points when the intact movie was played first, suggesting that participants were able to fill-in missing visual information from episodic memory. This method could be used to measure episodic memory in infants and track how these representations change over development.

Disclosures: L. Skalaban: None. **C.T. Ellis:** None. **J.S. Turek:** None. **N.B. Turk-Browne:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.17/HHH28

Topic: H.02. Human Cognition and Behavior

Support: NSERC-CREATE Grant
NSERC-PGSD
Understanding Human Cognition Scholar Award, James S. McDonnell Foundation

Title: Identifying the neural correlates of music familiarity using a strict training paradigm

Authors: *A. STERNIN[1,2], A. M. OWEN[1,2], J. A. GRAHN[1,2]
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Abstract: Memory for music is reported to be selectively spared in neurodegenerative disorders like Alzheimer's disease. One hypothesis for why this sparing occurs depends on the idea that memory for music is supported by areas of the brain that are only affected in late stages of the disease. Previous studies have investigated the neural correlates of music familiarity by comparing unknown and well-known music. However, well-known and unknown music may also differ in the presence of lyrics, emotional connection of the listener to the music, and preference. In this experiment, we controlled for these differences by familiarizing participants with half the clips from a novel musical and spoken stimulus set, comparing brain responses before and after familiarization, and characterizing how responses differed for musical and verbal material.
Participants passively listened to 10 second long clips from 8 novel songs in the fMRI scanner. Subsequently, they listened to 4 (50%) of these songs (in their entirety) on a daily basis for 2-3 weeks through an online player that tracked listening patterns. After the training period,

participants again passively listened to 10 second clips from all 8 songs in the scanner. To examine differences between language and musical memory, 4 categories of stimuli were used: spoken words, a capella singing, instrumental music (no lyrics), and whole songs (instruments+lyrics). No musical or verbal material was repeated across stimuli. Behaviourally, forced choice memory paradigms probed memory for lyrics and for melodies to assess familiarity.
At the end of training, participants scored 82% correct on the lyric memory task and 92% correct on the melodic memory task. The fMRI data were analyzed in SPM12.
Average BOLD activity to the 10 second long clips was compared across conditions.
Preliminary results from 14 participants show that familiarity (as measured by the number of listens during training) negatively correlated with activity in the superior temporal gyrus, indicating greater auditory activity to less familiar songs. As expected, all songs with lyrics produced activation in typical language networks. The interaction between familiarity and the presence of language showed greater activation in the medial and superior temporal gyri to familiar music with lyrics than to familiar music without lyrics or to unfamiliar music. These data show that familiarity with music alters auditory activity. Further investigation of these data will assess changes in functional connectivity as a result of familiarity to music and language.

Disclosures: A. Sternin: None. **A.M. Owen:** None. **J.A. Grahn:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.18/HHH29

Topic: H.02. Human Cognition and Behavior

Support: Emory FERN Training Grant

Title: FMRI functional connectivity and content analysis of overtly retrieved autobiographical memories

Authors: *C. S. FERRIS[1], C. S. INMAN[2], S. B. HAMANN[3]
[1]Psychology, [2]Neurosurg., Emory Univ., Atlanta, GA; [3]Psychology, Emory Univ. Dept. of Psychology, Atlanta, GA

Abstract: The process of retrieving an autobiographical memory (AM) recruits brain regions into complex networks supporting memory search, access, and content elaboration. Previously, we have characterized patterns of AM-related functional connectivity and temporal dynamics involving the hippocampus, PFC, and other regions during covert (silent) memory retrieval. Here, we extend this research with high temporal (TR = 1 second) and spatial (2mm isotropic) resolution multi-band EPI fMRI, and both covert and overt (spoken) retrieval to test theoretical

accounts of dynamic AM retrieval. Subjects retrieved unrehearsed AMs during extended retrieval periods (approximately 24 seconds). In half of the runs, subjects overtly narrated their memories, which were recorded and transcribed, with each word coded by content category. We identified regions active earlier vs. later in retrieval and used functional connectivity and graph theory analyses to examine dynamic changes in AM retrieval processes. Broadly similar regional activation was observed during both covert and overtly retrieved AMs including activation of the hippocampus, mPFC, and PCC. As expected, overtly retrieved memories elicited greater activity in speech and motor production areas. Graph theory analysis of functional connectivity between overt and covert AM regions was performed to characterize differences in interregional connectivity. Finally, content categories (scene, action, face, object) identified from overtly retrieved speech during AM retrieval were used to characterize neural activity associated with online retrieval of AM content. Several similarities between regions activated during overt retrieval and regions associated with these content categories in previous fMRI studies of imagery and perception were observed. These results suggest that overt and covert AM retrieval in fMRI utilize broadly similar networks of brain regions, and that the time course of overt AM speech content can be used to examine the temporal evolution of content-specific activity during AM memory retrieval.

Disclosures: C.S. Ferris: None. **C.S. Inman:** None. **S.B. Hamann:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.19/HHH30

Topic: H.02. Human Cognition and Behavior

Support: F32AG054116
R01AG034570

Title: Using dynamic, contextually rich video stimuli as a more ecologically valid test of remembering and forgetting

Authors: L. A. FERGUSON, *S. L. LEAL, W. J. JAGUST
Univ. of California, Berkeley, Berkeley, CA

Abstract: Being able to accurately measure memory is important for understanding how episodic memories are remembered and forgotten over time. Most studies use simple stimuli and test memory within the same day. However, our real-world experiences are more contextually-rich than the typical object or word memory paradigms and require recall of memories beyond a single day, as most forgetting occurs after 24 hours. Incorporating these components into an ecologically valid paradigm is crucial for mimicking naturalistic memory processing and for

testing memory impairments in aging. We designed an episodic memory task that utilized video clips to create a more vivid and real-world encoding experience. We showed participants (young: N = 25, mean age = 22; old: N = 32, mean age = 77) short video clips and then tested their memory by examining their recognition of repeated scenes from the videos (targets), similar but different scenes from the videos (lures), and completely new scenes. The inclusion of similar lures taxes hippocampal pattern separation, a computation used to differentiate between very similar experiences. We also included emotional stimuli since the importance of an event strongly influences memory, and tested memory immediately and 24 hours later. Overall, we found that memory for targets and lures was impaired after 24 hours compared to immediately, with diminished ability to discriminate lures compared to recognizing targets. Interestingly, better memory performance immediately was associated with more forgetting over 24 hours. Emotional versus neutral videos were better remembered immediately but were also more likely forgotten over 24 hours. When comparing age groups, we found no major differences in forgetting. However, when older adults were split into age-unimpaired (AU) versus age-impaired (AI) based on a memory composite, we found the AU group was better at immediate recognition of targets compared to the AI group, but was no different after 24 hours. The AU group discriminated more neutral compared to emotional lures after 24 hours, while the AI group showed no difference between conditions. Our findings suggest that memory measures taken at one time point may not fully capture an individual's memory performance. Further, the lack of age differences on this task suggests that using more contextually rich stimuli may better equalize young and older performance. However, the presence of subtle age-related differences in emotional lure discrimination after 24 hours is consistent with a specific impairment in gist versus detail trade-offs in AI individuals compared to young adults and AU individuals.

Disclosures: L.A. Ferguson: None. **S.L. Leal:** None. **W.J. Jagust:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.20/HHH31

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 HD057076-01(BLS)
OHSU Fellowship for Diversity and Inclusion in Research
Portland State University BUILD EXITO program, Grant 5TL4GM118965-03

Title: Unveiling temporal changes in brain activity in task fMRI using connectotyping

Authors: *V. VAZQUEZ-TREJO[1], B. NARDOS[2], B. L. SCHLAGGAR[3], D. A. FAIR[4], O. MIRANDA DOMINGUEZ[5]
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Portland, OR; [3]Dept Neurol, Div. Child Neurol, Washington Univ, Sch. Med., Saint Louis, MO; [4]Oregon Hlth. Sci. Univ., Portland, OR; [5]Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Task functional Magnetic Resonance Imaging (fMRI) enables the identification of specific brain areas associated with particular tasks. While multiple brain areas are involved for performing various tasks, existing methodological approaches with fMRI focus on the magnitude of responses in a given region, rather than how they communicate (i.e., connectivity). Recently we developed a method, termed connectotyping, to efficiently model functional brain connectivity that has the potential to track changes in brain dynamics in individuals. Here our work aims to use connectotyping to reveal the progression of temporal brain connectivity patterns in task fMRI. Twenty-four participants (12 male, mean age 24.8 years, 2.57 std. dev) performed a widely-spaced event-related fMRI word vs. nonword lexical decision task. Stimuli were presented for 2.5 seconds followed by 17.5 seconds of a fixation screen. Imaging data was processed using a slightly modified version of the workflow pipelines from the Human Connectome Project and connectotypes (connectivity matrices) were calculated for each participant, at each time point, per word type. A Repeated Measures ANOVA applied on the connectotypes was used to characterize differences across time for words and nonwords. Exposure to words vs. nonwords resulted in significantly different temporal connectivity patterns between the frontoparietal and cinguloparietal cortices, areas known to be involved in adaptive cognitive control and memory retrieval, respectively. These results support the use of connectotyping as a tool for task fMRI analysis and provide a novel depiction of brain activity which resolves temporal changes in functional connectivity.

Disclosures: V. Vazquez-Trejo: None. **B. Nardos:** None. **B.L. Schlaggar:** None. **D.A. Fair:** None. **O. Miranda Dominguez:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.21/HHH32

Topic: H.02. Human Cognition and Behavior

Title: Neural pattern similarity predicts brand recall

Authors: *F. SHENG, M. L. PLATT
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Memory about a brand is associated with memory about the category of the brand's product. The strength of mental association between a brand (e.g., BMW) and its product category (e.g., car) determines the top-of-mind accessibility of the brand in the product category

and constitutes a fundamental aspect of the consumer-based brand equity. Consequently, when thinking about products of that category, that brand is likely to be recalled by the activation of the associative network and to be considered for choice. Despite its importance, the structure of mental association between a brand and a product category is largely invisible in traditional behavioral measurements. We posit that the mental association between a brand and its product category can be operationally defined as the similarity of the neural representations between the brand and the product category. Furthermore, we hypothesize that neural representational similarity between brand and product category will be predictive of mental accessibility of brand assessed by behavioral measurement such as brand recall. To test our hypothesis, in an fMRI study, we first recorded the process of car brand recall when consumers were cued by the product category "car" outside the scanner, and then recorded their' brain activity in response to a variety of car brands and the concept of car. Results showed that the order of car brand recall was predicted by the similarity of neural representations between car brands and the product category car across a distributed brain network including ventral medial prefrontal cortex, posterior cingulate cortex, and lateral temporal cortex, which overlaps with the neural circuity involved in processing semantic knowledge and personal value. This implies that the degree to which knowledge of a brand is incorporated with the concept of a product category is critical for the mental accessibility of the brand in that product category. We further demonstrated that neural pattern similarity in ventral medial prefrontal cortex between car brands and car was predictive of the market share of car brands. Our measurement of neural similarity between brand and product category has potential to act as a new indicator for brand equity, and suggests a novel application of neuroscientific techniques to business.

Disclosures: F. Sheng: None. **M.L. Platt:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.22/HHH33

Topic: H.02. Human Cognition and Behavior

Support: Intel Labs

Title: Decoding mental walkthroughs of spatial memories in an immersive virtual reality environment

Authors: R. MASIS-OBANDO[1], K. NORMAN[1], *C. BALDASSANO[2,1]
[1]Princeton Univ., Princeton, NJ; [2]Psychology, Columbia Univ., New York, NY

Abstract: When recalling autobiographical memories, we can use our semantic knowledge about the spatial and temporal structure of the world (schemas) to help retrieve and elaborate on

episodic details. One of the most salient features of an event is the spatial environment in which it occurred (Robin et al. 2018); notably, the brain network engaged by recall of naturalistic episodes contains regions critical for spatial navigation (Chen et al. 2016), including parahippocampal cortex (PHC) and retrosplenial cortex (RSC). By having subjects first learn a novel spatial environment and then recall information about objects in that environment, we can study how the reactivation of spatial layout information interacts with the retrieval of specific episodic content.
Using principles borrowed from the method-of-loci mnemonic technique, commonly known as the "memory palace", we custom-built a virtual reality environment made up of 23 distinct rooms, which subjects explored using a head-mounted virtual reality display. On the first day, subjects learned the layout of the environment by playing two foraging games for a total of 1 hour, in which they first had to collect a cube from every room and then had to repeatedly navigate to designated rooms to collect additional cubes. Every 20 minutes, subjects were asked to draw a bird's-eye-view map based on their current knowledge of the environment. Their learning performance was measured based on both their in-game performance (navigation efficiency) as well as the accuracy of their map drawings. On day 2 (1-2 days later), subjects were re-familiarized with the environment and then asked to memorize the locations of 23 distinct objects randomly placed within each of the 23 rooms. Whole-brain fMRI data were recorded from subjects as they freely recalled the objects and the rooms in which they appeared, recalled objects along specific paths, and viewed videos of rooms and random walks through the memory palace.
Preliminary data show that subjects learn the environment across the two days, showing reductions in excess path length during navigation ($p=0.002$) and increased accuracy of map drawings, with the mean Jaccard similarity coefficient between drawn and actual maps (the number of correctly drawn room connections divided by the sum of unique connections in the drawn and actual maps) increasing from 0.09 at initial exposure to 0.84 at the end of the second day. Subjects were also able to recall objects and their locations on day 2 with very high accuracy (99.1%). Planned analyses of the fMRI data include using a Hidden Markov Model to track mental trajectories through the environment based on the reactivation of room-specific activity patterns.

Disclosures: R. Masis-Obando: None. **K. Norman:** None. **C. Baldassano:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.23/HHH34

Topic: H.02. Human Cognition and Behavior

Title: Memory of time: A novel paradigm to assess mnemonic discrimination for event duration

Authors: *N. MUNCY, B. KIRWAN
Psychology, Brigham Young Univ., Provo, UT

Abstract: Behavioral paradigms designed to tax hippocampal-dependent pattern separation processes in humans have largely focused on visual and spatial information. We note that while episodic memories often contain visual, spatial, and temporal information (e.g. the memory of a lecture) few studies have tested for the capacity to discriminate for temporal information, and the studies that have done so have focused only on the temporal order or antecedence of stimuli. We have therefore developed a behavioral paradigm to test the participants' sensitivity to stimulus duration while controlling for attention, as attention is integral in time perception. The experimental paradigm consists of six continuous recognition temporal discrimination blocks and two blocks of a standard Posner attention task. During the temporal discrimination block, participants are presented with a series of images for either one or two seconds. All stimuli are followed by a static mask, after which participants are cued to make a response. For first-trial presentations, participants are prompted with one of three questions in reference to the stimulus. For Targets and Lures, participants were tasked with Target/Lure identification via "Longer, Same, Shorter" response options. Targets and Lures consist of the same stimulus with either the same or shorter (50% reduction) presentation time, respectively. "Longer" responses are used to control for whether participants are responding in reference to the original, or merely the antecedent, stimulus. Forty healthy, young adults participated in a pilot study. Bias-corrected scores indicate that participants are capable of temporal discrimination for stimulus duration, and further, their sensitivity is independent from their performance on the Posner paradigm. Follow-up studies will use functional MRI to (A) identify regions in the medial temporal lobe associated with temporal discrimination and whether they differentiate from mnemonic discrimination for visual features and (B) to identify prefrontal and parietal regions that are differentially engaged in temporal versus attention tasks.

Disclosures: N. Muncy: None. **B. Kirwan:** None.

Poster

248. Human Cognition and Behavior: Human Long-Term Memory: Retrieval I

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 248.24/HHH35

Topic: F.08. Biological Rhythms and Sleep

Support: Grant-in-Aid for Scientific Research, the Japan Society for the Promotion of Science 15K12055
Cooperative Study Program of National Institute for Physiological Sciences
Grant-in-Aid for Researchers from the Hyogo College of Medicine, 2015

Title: Respiratory modulation of cognitive performance during the retrieval process

Authors: *N. H. NAKAMURA[1], M. FUKUNAGA[2], Y. OKU[1]
[1]Hyogo Col. of Med., Nishinomiya, Japan; [2]Natl. Inst. of Physiological Sci., Okazaki, Japan

Abstract: Recent research suggests that cognitive performance might be altered by the respiratory activity generated in the brainstem. Previous human studies, however, have yielded inconsistent results when assessing task performance during distinct respiratory phases (inspiratory phase vs. expiratory phase). We therefore tested whether cognitive performance is regulated based on the timing of breathing components (e.g., expiratory-to-inspiratory (EI) phase transition) during the retrieval process. To determine the role of respiration in performance, the present study employed healthy subjects (n = 18) in a delayed matching-to-sample visual recognition task. Because this effect is assessed by task difficulty, we altered the degree of difficulty by using two sessions, which utilize less and more variable intervals between cue exposure. Here, we demonstrate that the response time (RT) of the task increased by 466 ms (p = 0.003) and accuracy decreased by 21.4% (p = 0.004) when the retrieval process encompassed the EI transition (or onset of inspiration) during nasal breathing. The breathing-dependent changes were revealed during the retrieval process with more variable intervals between the cues, and were particularly prominent when the EI transition occurred during the middle step of the retrieval process. Meanwhile, changes in the RT and accuracy were not observed when the retrieval process encompassed inspiratory-to-expiratory phase transition (or onset of expiration). This is the first time that a certain phase transition in the respiratory cycle has been shown to modulate performance on the time scale of sub-seconds in a cognitive task. We propose that cancellation of these breathing-dependent cognitive fluctuations might be crucial for the maintenance and stability of successful performance in daily life and sports.

Disclosures: N.H. Nakamura: None. **M. Fukunaga:** None. **Y. Oku:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.01/HHH36

Topic: H.02. Human Cognition and Behavior

Title: Episodic simulations reveal the structure of affective representations in ventromedial prefrontal cortex

Authors: *P. C. PAULUS[1,2], I. CHAREST[3], R. G. BENOIT[1]
[1]Max Planck Inst. For Human Cognitive and Brain Sci., Leipzig, Germany; [2]Int. Max Planck Res. Sch. NeuroCom, Leipzig, Germany; [3]Univ. of Birmingham, Birmingham, United Kingdom

Abstract: The ventromedial prefrontal cortex (vmPFC) has been associated with valuation and with memory processes. In particular, recent evidence indicates that it codes for representations

of elements from our everyday life (e.g., familiar people and places). Here, we test the hypothesis that this region does not just code for individual elements but also their associations. These associations build up with increasing experience with a given element and they are weighted by the element's affective value. To test this hypothesis, participants arranged the names of personally familiar people and places on a two-dimensional surface to indicate how strongly they associate each element with the others (indexing associative centrality). Participants also indicated how familiar they are with each person and each place (indexing knowledge), and how much they like them (indexing affective value). A principal component analysis revealed that these three features indeed share a common factor, with an element's value on this factor reflecting its relative importance. We used these importance values to estimate the structure of participants' unique affective associative representations. In a following functional MRI session, participants vividly imagined interacting with each person and place, which allowed us to assess each element's neural representation. Using representational similarity analysis, we examined the strength of the elements' associations with each other as reflected in their neural similarity. The results support our hypothesis: The neural similarity structure in vmPFC (but not in the hippocampus) can best be accounted for by the structure of the estimated affective associative representation.

Disclosures: P.C. Paulus: None. **I. Charest:** None. **R.G. Benoit:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.02/HHH37

Topic: H.02. Human Cognition and Behavior

Title: Tracking the impact of retrieval suppression on neural memory representations

Authors: *A.-K. MEYER[1,2], R. G. BENOIT[1]
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Abstract: When we experience aversive events, these often turn into unwanted memories. Simple reminders can then trigger the involuntary retrieval of these memories. However, prior evidence indicates that we can intentionally suppress the retrieval process to prevent unwanted memories from entering awareness. Such suppression can render memories less vivid and eventually cause forgetting. Here, we test the hypothesis that retrieval suppression weakens memories by compromising their unique neural representations. In an fMRI study, participants learned associations between reminders and aversive scenes. They were then repeatedly presented with the reminders. For some of these, participants were instructed to suppress the retrieval of the associated scene. Suppression was associated with increased activation in the

right dorsolateral prefrontal cortex and a concomitant decrease in hippocampal and parahippocampal activation, a pattern that has been linked to the top-down inhibition of memory retrieval. Critically, we assessed the distributed activity patterns of individual memories (as a proxy for their neural representations) both before and after suppression. Using representational similarity analysis, we could thus track changes in the specificity of the memories' representations. We observed that memories became less vivid after suppression, and that a stronger decline in vividness was associated with a greater reduction in the specificity of their parahippocampal representations. These preliminary results support the hypothesis that suppression deteriorates memories by compromising their unique neural representations.

Disclosures: A. Meyer: None. **R.G. Benoit:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.03/HHH38

Topic: H.02. Human Cognition and Behavior

Support: T32 GM007171

Title: Coupled ripple oscillations between the medial temporal lobe and neocortex retrieve human memory

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Abstract: Hippocampal ripple oscillations are known to be relevant during memory replay and consolidation. These oscillations coordinate with cortical ripples to support a hippocampal-neocortical dialogue in rodents. However, it is unknown if a similar oscillatory mechanism exists in humans and if such a mechanism would be cognitively relevant. Here we examined ripple oscillations in human electrocorticography and found robust coupling of ripples between the medial temporal lobe and association cortices. These ripple events were selectively enhanced during successful memory retrieval in a verbal episodic memory task. Our data provide evidence that coupled ripple oscillations between the medial temporal lobe and neocortex are a neural substrate for memory retrieval in the human brain.

Disclosures: A. Vaz: None. **S. Inati:** None. **N. Brunel:** None. **K.A. Zaghloul:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.04/HHH39

Topic: H.02. Human Cognition and Behavior

Support: NINDS IRP

Title: Human Spiking Neuron and Intracranial EEG signals during semantic processing of words and images

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Abstract: Our memory of semantic information, such as the meaning of the word “pencil” or our knowledge of how we could use a pencil if we saw a picture of one, is hypothesized to be facilitated by communication from the anterior temporal lobe to posterior temporal and parietal regions. In order to test this hypothesis, we have developed a task in which participants must rapidly recognize and categorize either a picture or a word with the same meaning. Here we present preliminary data from seven neurosurgical participants with intractable epilepsy who completed the task while intracranial EEG (iEEG) was being recorded to determine the epileptic focus. In two participants we also recorded spiking neuron activity from a 96-channel Utah array implanted in the anterior temporal lobe. For each participant, we contrast iEEG or microelectrode high-frequency power for two stimulus modalities (images and words) coming from four distinct categories (famous people, landmarks, animals, and tools). We search for electrodes that show item-specific, category-specific, and/or modality-specific differences in high-frequency power, and test whether spatially distributed patterns of activity can reliably predict the semantic meaning of a stimulus.

Disclosures: J.H. Wittig: None. **K.A. Zaghloul:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.05/HHH40

Topic: H.02. Human Cognition and Behavior

Support: ERC Consolidator Grant 647954

Title: Alpha/beta desynchronization tracks pattern reinstatement in episodic memory: A simultaneous EEG-fMRI study

Authors: *B. GRIFFITHS[1], S. D. MAYHEW[1], K. J. MULLINGER[1,2], I. CHAREST[1], M. WIMBER[1], S. HANSLMAYR[1]
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Abstract: Recalling a past event induces vivid reinstatement of information about the episode, which is echoed in the reactivation of neural activity present during encoding. The information-via-desynchronization hypothesis suggests that this information reinstatement is facilitated by desynchronized alpha/beta frequency activity (8-20Hz; prevalent during episodic memory retrieval) as these oscillatory dynamics are ideal for the representation of information in neocortex. Here, we test this hypothesis by investigating whether an increase in pattern reinstatement correlates with a decrease in alpha/beta power (an index of neural desynchronization) during memory retrieval. Twenty-four participants took part in a paired associates memory task while undergoing simultaneous EEG-fMRI at 3T. While in the MR scanner, they learnt a series of words (n=192; across 4 blocks), paired with either a video or sound, and were later cued with the words and asked to identify the associated videos/sounds. Representational similarity analysis (RSA) revealed significantly greater encoding-retrieval similarity in the BOLD signal for videos of the same content relative to those of differing content, and searchlight analysis localized this pattern reinstatement to the fusiform gyrus. Critically, the degree of pattern reinstatement within the fusiform gyrus negatively correlated with EEG alpha/beta power. These results support a recently proposed computational model[1,2] wherein alpha/beta power decreases during memory retrieval play a very specific role, which is enabling the reinstatement of information-rich neural patterns coding the sensory content of a memory trace.
1. Parish, G., Hanslmayr, S., Bowman, H. (2018) The Sync/de-Sync Model: How a synchronized hippocampus and a de-synchronized neocortex code memories. J Neurosci, 38 (14) 3428-3440.
2. Hanslmayr, S., Staresina, B., Bowman, H. (2016) Oscillations and episodic memory - Addressing the synchronization / desynchronization conundrum. Trends Neurosci, 39, 16-25.

Disclosures: B. Griffiths: None. **S.D. Mayhew:** None. **K.J. Mullinger:** None. **I. Charest:** None. **M. Wimber:** None. **S. Hanslmayr:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.06/HHH41

Topic: H.02. Human Cognition and Behavior

Support: ERC Grant

Title: Simultaneous EEG-fMRI measurements reveal the spatio-temporal trajectories of episodic memories during retrieval

Authors: *J. LIFANOV, B. J. GRIFFITHS, J. LINDE-DOMINGO, C. S. FERREIRA, M. WILSON, S. D. MAYHEW, M. WIMBER
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Abstract: During object perception, the neural representation of a stimulus is known to become increasingly abstract as the information travels forward along the visual processing hierarchy. Retrieving an object from episodic memory is known to involve the reactivation of the same neural patterns present during the earlier encoding of an event. However, our understanding of how information travels through the brain when we recall information from memory remains limited. We here test whether reactivated activity patterns are predominantly perceptual or semantic in nature, and when in time and where in the brain the different components re-emerge during retrieval.
Participants studied novel associations between objects and action verbs in an encoding phase, and subsequently recalled the objects upon presentation of the corresponding verb. Importantly, objects were categorized into two perceptual and two semantic classes, which allowed us to explore the source of perceptual and semantic processes during retrieval. Multivariate representational similarity analyses allowed us to map the reactivation of spatial fMRI patterns onto the EEG time courses. At the hemodynamic level, we found similarity in neural activity patterns in posterior brain regions between encoding and retrieval. We also found spatial distinctions between the semantic and perceptual categories that were overlapping at encoding and retrieval. At the electrophysiological level, we found that semantic information was represented earlier and more robustly than perceptual information during recall, showing a reversed order relative to encoding. Finally, using second-order correlations to compare representational similarities between fMRI and EEG activity patterns, we were able to map these semantic components onto late visual and frontal brain areas. For the first time, we were able to zoom into the spatio-temporal neural patterns during retrieval, and to map the brain sources of memory-related electrophysiological activation patterns.

Disclosures: J. Lifanov: None. **B.J. Griffiths:** None. **J. Linde-Domingo:** None. **C.S. Ferreira:** None. **M. Wilson:** None. **S.D. Mayhew:** None. **M. Wimber:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.07/HHH42

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust/Royal Society Sir Henry Dale Fellowship

Title: The role of cross-frequency coupling during sleep for episodic-like memory consolidation

Authors: *M. PETZKA[1], I. CHAREST[2], A. CHATBURN[2], G. BALANOS[3], B. STARESINA[2]
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Abstract: Our ability to remember past events and experiences relies on the transition of labile memory traces into stable long-term representations, a process referred to as memory consolidation. Memory consolidation is facilitated by sleep, and it has been proposed that sleep spindles (10-16 Hz) and slow oscillations (< 1 Hz, SOs) play an essential mechanistic role. Importantly, recent studies suggest that it is particularly the precise timing between SOs and spindles, rather than the isolated events themselves, which facilitates memory consolidation. One intriguing hypothesis emerging from this is that newly formed memory traces are more likely to be reactivated during the co-occurrence of SOs and spindles than during any of these events in isolation.

To test this idea, we first designed a new non-navigational spatial-temporal memory paradigm (the Memory Arena), geared at being sensitive to the beneficial effects of sleep on memory stabilisation. In the first (behavioural) study, a 2 (wake vs. sleep) x 2 (interference vs. no interference) between-subject design (N = 56) was used to test sleep effects on performance on the Memory Arena task. Indeed, we observed that the sleep group reliably outperformed the wake group on both spatial and temporal memory measures, especially in their resistance to retroactive interference. This result is in good agreement with previous findings showing that sleep stabilizes new memory traces.

In the second study, high-density Electroencephalography (EEG) was used to test the particular role of SO-spindle coupling for memory consolidation in this paradigm. Participants (N = 22) performed the learning part of the Memory Arena and were tested after spending 2 hours napping in the sleep lab with full polysomnography. Intriguingly, we found a topographical distribution of SO-spindle coupling that differed from the topography of SO or spindle density per se. This difference was most pronounced at frontoparietal sites, thought to underlie successful learning in the Memory Arena task.

Together, our data raise the possibility that sleep-dependent memory consolidation is driven by targeted deployment of SO-spindle complexes to learning-related cortical sites.

Disclosures: M. Petzka: None. **I. Charest:** None. **A. Chatburn:** None. **G. Balanos:** None. **B. Staresina:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.08/HHH43

Topic: H.02. Human Cognition and Behavior

Support: European Research Council Starting Grant ERC-2016-STG-715714 (STREAM)

Title: Exploring the 'what', 'when' and 'where' of memory reinstatement in human intracranial EEG recordings

Authors: *M. TER WAL[1], J. LINDE-DOMINGO[1], F. ROUX[1], B. STARESINA[1], D. ROLLINGS[2], V. SAWLANI[2], R. CHELVARAJAH[2], M. WIMBER[1]
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Abstract: Memory retrieval involves the reconstruction of a previous experience, sometimes with great detail and from an only marginally related cue. In recent years it has emerged that successful memory retrieval involves reinstatement of activity in the hippocampus, as well as in the cortical sensory and association areas that were involved in processing the original episode. However, little is known about how this reinstatement unfolds in time, i.e. what information becomes available at what point in time. A recent EEG study in our lab provides evidence for a reversal of the original information flow during reinstatement [1]: while sensory processing starts with simple perceptual features that are subsequently bound into complex semantic concepts, memory retrieval first accesses this higher level semantic information before reinstating low level perceptual details.
Here, we address both the 'where' and the 'when' of memory reinstatement simultaneously and at a high resolution by using invasive recordings from epilepsy patients. Due to the implantation of Behnke-Fried micro electrodes, the intracranial recordings yielded both unit activity and local field potentials in the hippocampus, in addition to local field potentials from several cortical regions. The patients performed a memory task in which they learned to associate unique verb-object pairs. In a later retrieval phase, patients recalled the object when cued with the verb. Objects differed in low level perceptual information (line drawings or photos) and/or higher level semantic information (animals or non-animals), allowing us to track the representation of perceptual and semantic information in the same set of stimuli.
We report task-related single unit activity in the hippocampus and compare spike trains and population activity between the encoding and retrieval of the same object. In addition, using linear classifiers and Representational Similarity Analysis, we track the perceptual and semantic information in local field potentials across the brain and over time. Extending our previous results, we localise perceptual and semantic information to the relevant sensory and association

areas and report reversed information flow during reinstatement in brain areas involved with high level processing.
[1] Linde-Domingo et al. (16 April 2018). bioRXiv. doi: https://doi.org/10.1101/300913

Disclosures: M. Ter Wal: None. **J. Linde-Domingo:** None. **F. Roux:** None. **B. Staresina:** None. **D. Rollings:** None. **V. Sawlani:** None. **R. Chelvarajah:** None. **M. Wimber:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.09/HHH44

Topic: H.02. Human Cognition and Behavior

Support: MSCA-IF-2015, under grant agreement Nº702530

Title: Empathy draws on autobiographical memories. EEG pattern classifier reveals memory reactivation in empathy for pain

Authors: *F. MECONI, I. APPERLY, S. HANSLMAYR
Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Empathy relies on the ability to mirror and to explicitly infer others' inner states. Accumulating evidence supports the idea that our memories interact with empathy when building a representation of others' inner states. However, direct evidence of a reactivation of autobiographical memories when it comes to empathizing with others' inner states is yet to be shown. We collected electroencephalographic activity from 28 participants while performing an empathy (i.e., the pain decision task) and a retrieval task. For each trial, participants viewed pictures of faces and were required to imagine that individual in a context described by a written sentence representing either non-autobiographical or autobiographical experiences of painful and neutral events. Participants judged how much empathy they felt for each individual depicted in the specified context. The success of these manipulations was confirmed by participants' higher self-reported empathy for faces depicted in autobiographical compared to non-autobiographical contexts. In the retrieval task participants were cued to imagine the painful and neutral contexts "in their mind's eye", and these data became the training set for a pattern classifier, which was then applied to data from the empathy task to test for evidence that the same memories were activated. The results showed evidence for the reactivation of autobiographical memories in preparation for the empathy judgement independent of the emotional content of the memory. These findings demonstrate that autobiographical memories are involved in drawing our empathy.

Disclosures: F. Meconi: None. **I. Apperly:** None. **S. Hanslmayr:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.10/HHH45

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust/Royal Society Sir Henry Dale Fellowship to B.P.S. (107672/Z/15/Z)

Title: Dissociation of associative retrieval processes across the human medial temporal lobe

Authors: *H. SCHULTZ[1], R. TIBON[2], K. F. LAROCQUE[3], S. A. GAGNON[3], A. D. WAGNER[3], B. P. STARESINA[1]
[1]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom; [2]MRC Cognition and Brain Sci. Unit, Cambridge, United Kingdom; [3]Dept. of Psychology, Stanford Univ., Stanford, CA

Abstract: The medial temporal lobe (MTL) is central to human episodic memory. Its anatomical connectivity pattern suggests that different subregions may support domain-specific and domain-general aspects of memory. In particular, the perirhinal cortex (PrC) and parahippocampal cortex (PhC) are anatomically connected to ventral and dorsal visual regions, respectively. They are therefore well-suited to process object-related and spatial memory content in a domain-specific fashion. At the top of the MTL hierarchy, the hippocampus interacts with both PrC and PhC, thus thought to support memory independent of memory content (domain-generality). Here, we test the central prediction that retrieval of objects and scenes is supported by domain-specific contributions of PrC and PhC, and by domain-general retrieval in the hippocampus. Healthy volunteers (n=18) engaged in an associative memory task while undergoing fMRI (GE 3T, 2.5mm isotropic voxels, TR=1s, 48 slices, multiband factor 3). The task was presented as a slow event-related design, consisting of two object and two scene runs. In each run, participants encoded a list of adjectives, each paired with an image of an object or scene. After a short rest phase, they were cued with the adjectives and asked to retrieve the associated object or scene from memory. We assessed brain activity averaged within bilateral MTL subregions hand-drawn in each participant's native space. Consistent with our prediction, we found that the hippocampus was engaged during successful vs. unsuccessful recollection of both objects and scenes. Conversely, there was a double dissociation in the contributions of MTL cortical regions: While PrC was preferentially engaged during successful object recollection, PhC was preferentially engaged during successful scene recollection. Moreover, we show that within PrC, object recollection effects were driven by voxels that were object-selective during perception. Similarly, within PhC, scene recollection effects were driven by voxels that were scene-selective during perception. Our results support and extend previous findings, showing that the MTL supports episodic memory through both domain-specific and domain-general retrieval processes,

and further demonstrating that domain-specific retrieval of objects and scenes is supported by the same voxels that are object- and scene-selective during perception.

Disclosures: H. Schultz: None. **R. Tibon:** None. **K.F. Larocque:** None. **S.A. Gagnon:** None. **A.D. Wagner:** None. **B.P. Staresina:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.11/HHH46

Topic: H.02. Human Cognition and Behavior

Support: ESRC Grant ES/M001644/1

Title: Testing the fast consolidation hypothesis of retrieval-mediated learning using pattern fMRI

Authors: *A. C. SANCHES FERREIRA, I. CHAREST, M. WIMBER
Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: It is well known that actively and repeatedly retrieving information produces more durable memories than repeatedly studying that same information. On a neural level, it is still unclear why retrieval has such beneficial effects on long-term retention. Attempting to fill this gap, we here tested some key predictions derived from a recent framework proposing that retrieval acts as a fast consolidation mechanism, stabilizing memories through online reactivation, similar to memory replay during offline (e.g. sleep) consolidation. In this fMRI study, participants encoded scene-object pairs, and repeatedly retrieved or restudied the objects over two different sessions, two days apart. We analysed univariate and multivariate changes in brain activity specific to retrieval but not restudy, and tested whether the predicted changes occur rapidly (i.e., within a session) or evolve slowly, across the two days. If retrieval rapidly creates consolidated, integrated neocortical memory traces, we expected to observe categorical (semantic) pattern changes within the first session, along with an increase in neocortical and decrease in hippocampal activity. Results showed that ventromedial prefrontal cortex activation increased across retrieval trials within one session, consistent with a fast consolidation account. Hippocampal activity decreased not within but across sessions, suggesting a slower mechanism. Moreover, Representational Similarity Analyses (RSA) showed that consecutive retrieval attempts strengthen both higher-level semantic and episode-specific information in parietal areas, again across but not within sessions. Our results suggest that retrieval does support the creation of an additional neocortical trace, which becomes increasingly relevant at long delays when hippocampus-dependent episodic details would otherwise have faded.

Disclosures: A.C. Sanches Ferreira: None. **I. Charest:** None. **M. Wimber:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.12/HHH47

Topic: H.02. Human Cognition and Behavior

Support: James S McDonnell Foundation
NSERC

Title: Temporal context effects of digital memory augmentation on episodic free recall

Authors: *R. N. NEWSOME, C. B. MARTIN, M. D. BARENSE
Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Successful memory for an event requires information about not only the content of the event (what happened) but also the temporal information about the event (when it happened, and the context of what happened before and afterwards). Digital memory augmentation (DMA) is a promising approach to improve memory for episodic details. We have developed a novel DMA application for both smartphone and web-based use, where one can record and review content. Indeed, we have recently found that by replaying event information using DMA, event-specific autobiographical memory content improved after one week, relative to non-replayed autobiographical information. However, we still know very little regarding the exact mechanism of replay as it relates to improving mnemonic performance. One open question is how replay affects memory for events sharing a temporal context. For example, does replay for one event boost memory for events that happened immediately before or immediately after, in line with the Temporal Context Model? Or does replaying one event actually block memory for temporally related events, in line with research investigating retrieval-induced forgetting? What is the optimal replay schedule, specifically in terms of the timing of the first replay relative to the original event? In the present study, we systematically investigated episodic memory for a naturalistic stimulus - Agatha Christie's "Poirot". After initial viewing in the lab, participants were administered a replay session using our web-based DMA, where they viewed 6 scenes from the episode, after either a short or long delay, and continued to view a pseudorandomized subset of those scenes up to 12 times over the course of the week between study and test. At the end of the week, we examined their memory for details of the episode using a free recall test. Control participants had the same initial encoding and 7-day delayed free recall test, but viewed no replay sessions. We asked whether number of details recalled was higher for replayed scenes, and for temporally adjacent scenes. Initial pilot data shows that memory was boosted for the replayed scenes relative to non-replayed scenes, and relative to scenes occurring immediately before or after the replayed scene. Future analyses will investigate if it is necessary to replay a

memory within hours of the initial viewing, or whether replay occurring after natural consolidation is sufficient to boost memory.

Disclosures: R.N. Newsome: None. **C.B. Martin:** None. **M.D. Barense:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.13/HHH48

Topic: H.02. Human Cognition and Behavior

Support: James S McDonnell Foundation
NSERC

Title: Using a novel digital memory augmentation device to improve episodic detail recall for autobiographical memory in older adults

Authors: *B. HONG[1], C. B. MARTIN[1], R. N. NEWSOME[1], A. XIA[1], C. J. HONEY[2], M. D. BARENSE[1,3]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Johns Hopkins Univ., Baltimore, MD; [3]Rotman Res. Inst., Toronto, ON, Canada

Abstract: Autobiographical memory (AM) is memory about one's self, and may contain both episodic and semantic content. Episodic AM information has been found to be more vulnerable to age-related memory decline, compared with semantic AM information. A promising approach to minimizing episodic AM decline is digital memory augmentation (DMA), in which a portable device is used to record daily events for later review. In the current study, we developed a novel DMA application for smartphone devices which allows users to create and review dynamic audiovisual memory cues. This novel DMA application is based on principles from the cognitive neuroscience literature outlining how to optimally learn and remember events. Thirty-three older adult participants (23 females; mean age = 70.67) used the DMA application for two weeks to create and review AM cues for real-world events. Importantly, these cues were assigned to either a "replayed" or "hidden" condition, with "replayed" events being reviewed using the DMA application and "hidden" events being never reviewed. This allowed for a within-subjects comparison to test the benefit of reviewing AM cues using our DMA application on AM recall. Using a cued recall task, we found that recall of "replayed" events contained significantly more event-specific AM details, compared with "hidden" events. At the same time, event-nonspecific AM details were recalled equally between "replayed" and "hidden" event. Also, we found that the boost in episodic detail from using our DMA application was specifically driven by enhanced recall for unique episodes, rather than for events that occurred daily, weekly, monthly, or annually. These results demonstrate that our DMA intervention selectively targets the episodic

AM deficit seen with aging, opening up the possibility of an inexpensive, efficient, and scientifically-tested means of improving the quality of life of those affected by memory loss.

Disclosures: B. Hong: None. **C.B. Martin:** None. **R.N. Newsome:** None. **A. Xia:** None. **C.J. Honey:** None. **M.D. Barense:** None.

Poster

249. Human Cognition and Behavior: Human Long-Term Memory: Retrieval II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 249.14/HHH49

Topic: H.02. Human Cognition and Behavior

Support: James S McDonnell Foundation
NSERC

Title: Digital memory augmentation in older adults promotes distinctive hippocampal coding of autobiographical memory

Authors: *C. B. MARTIN[1], B. HONG[1], R. N. NEWSOME[1], A. XIA[1], C. J. HONEY[2], M. D. BARENSE[1,3]
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Abstract: Age-related memory decline is characterized by decreased recall of the details of unique autobiographical events. Digital memory augmentation (DMA) is one promising approach to mitigating memory decline. In DMA, portable devices are used to capture information about everyday episodes, making them available for later review. Although this approach has been shown to benefit autobiographical memory in older adults, the neural basis of these effects remains unclear. We addressed this issue by developing a novel, smartphone-based DMA application that allowed older adults (Mean age = 68.25) to create and review rich autobiographical memory cues. Importantly, memory review sessions were distributed both within and across days. Using a within-subjects design, autobiographical cues were randomly assigned to one of two conditions: replayed or hidden. Over a two-week period, participants created an average of 67.83 autobiographical cues, approximately half of which were reviewed an average of 8.47 times each. Content in the hidden condition was never replayed. We then used a cued recall test to measure behavioral memory performance. In addition, following a one-week delay, we used fMRI to probe for differences in neural representations related to retrieval of previously replayed and hidden autobiographical memories. Using a cued-recall test, we revealed a 30% boost in the number of event-specific autobiographical details retrieved in the replayed as compared to the hidden condition, while holding event significance, event frequency, and memory age constant. Replayed memories exhibited more distinct neural representations. A

representational similarity analysis focused on the hippocampus revealed that voxel patterns of replayed memories were more dissimilar during retrieval than were voxel patterns of hidden memories. A whole-brain searchlight analysis revealed reliable differences in activity patterns between when retrieving hidden and replayed events within the core episodic memory network: posterior medial regions, angular gyrus, medial temporal, and ventromedial prefrontal cortex. Taken together, these findings indicate that reviewing rich autobiographical memory cues can boost retrieval of event-specific detail and promote orthogonal coding of pertinent information in the hippocampus. More generally, they provide novel insight into the neurocognitive effects of DMA, and they highlight the real-world value of translational memory research.

Disclosures: C.B. Martin: None. **B. Hong:** None. **R.N. Newsome:** None. **A. Xia:** None. **C.J. Honey:** None. **M.D. Barense:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.01/HHH50

Topic: H.02. Human Cognition and Behavior

Support: DFG Grant SE 2771/1-1
ERC-2012-StG_20111124
Veni Grant 451-15-010

Title: Neural correlates of trigger failures in the stop-signal task: A model-based analysis

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Abstract: Flexibly adapting our behavior to changing environments is crucial for goal-directed behavior. Response inhibition is required when the goals of our actions are no longer adequate or even harmful. The stop-signal task is widely used to study response inhibition [1]. Participants perform a two-choice response time (“go”) task. Occasionally, a stop-signal instructs participants to inhibit their response. Stop-signal performance is typically formalized as a race between two independent processes, a go and a stop process; if the stop process finishes first, the response is successfully inhibited; otherwise it is erroneously executed [1]. A fronto-basal ganglia stopping network has been identified comprising right inferior frontal gyrus (rIFG), pre-supplemental motor area, and the basal ganglia [2,3]. Individual differences in stopping performance may not only be reflected in the latency of successfully stopping a response (i.e., stop-signal RT, SSRT), but also in the probability of triggering the stop process (i.e., trigger failures). A recently developed Bayesian method enables researchers to to estimate the entire SSRT distribution, as

well as a trigger failure parameter which represents the individual propensity for failing to react to the stop-signal [4]. Here, we used a model-based approach to study how the propensity for trigger failures is related to the neural signature of stopping.
Thirty healthy participants (36.1 ± 14.7 years, 19 females) performed a visual stop-signal task during functional magnetic resonance imaging. We estimated the trigger failure parameter [4] and correlated it with brain activation during unsuccessful stop trials as compared to correct go trials. This revealed a negative correlation of the propensity for trigger failures with right inferior frontal gyrus activity (r=-.451, p=.006, BF_{-0}=8.92). In an ongoing study we aim to replicate this finding in a large-scale data set.
Our results show that right inferior frontal gyrus is critically involved in successfully triggering a stop process. The finding is well in line with the notion that a fast and efficient stop process is associated with strong activation of the stopping network including the right inferior frontal gyrus [5]. In summary, by using a complimentary model-based approach the present study provides insights into neural underpinnings of individual differences in stop-signal performance.

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Disclosures: A. Sebastian: None. **B.U. Forstmann:** None. **D. Matzke:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.02/HHH51

Topic: H.02. Human Cognition and Behavior

Support: NIGMS Grant T32 NS007421
R01 NS10220

Title: A fairer race between going and stopping: Neural signatures of motor inhibition in a redesigned stop-signal task

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Abstract: The stop-signal task (SST) is a gold standard for assessing motor inhibition in the laboratory. In the classic SST, participants respond to “go” signals on every trial and attempt to

withhold responses when presented with “stop” signals that sometimes follow the go signal. The action-stopping literature conceptualizes the interaction between go and stop processes as a race whose outcome depends on speed and relative onset of the two processes. Researchers study the neural underpinnings of stopping by quantifying differences between stop and go trials. However, assessment of these differences is complicated by the presence of an additional, infrequent signal during stop trials – the stop signal. So, purported neural indices of inhibition may be confounded by a requirement to detect an oddball stimulus. To address this, we designed a version of the SST where the stop signal was presented on all trials.
Thirty participants completed two tasks during EEG recording: a visual SST where a stop signal was present on one-third of trials and a redesigned SST with an audio stop signal on every trial. In the second task, they were awarded 200 points for “beating” the stop-signal, 100 points for stopping successfully after the stop signal was presented, and penalized 100 points for failing to withhold their response following the stop signal. Thus, participants attempted both to respond before the stop signal and to stop following the stop signal.
EEG data were cleaned and subjected to independent component analysis. For each participant, the independent component (IC) best representing the stopping P3 was selected based on the following criteria: a) earlier onset in successful versus failed stops and b) correlation of onset with participant stop signal reaction time. This independent component showed increased activity even in the version of the task that had stop-signals on every trial. This suggests the stopping P3 is indeed a “pure” index of inhibition, present even when stop-signals are not rare ‘oddballs’. The use of a redesigned SST to investigate the interplay between going and stopping processes without the influence of infrequent events may inform basic theory and assist in understanding inhibitory deficits in clinical cases such as Parkinson’s Disease or ADHD.

Disclosures: T. Dykstra: None. **E. Hazeltine:** None. **J.R. Wessel:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.03/HHH52

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1554105
NIH R01MH110831
NIH P50MH094258

Title: Neuronal correlates of post-action conflict monitoring

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Abstract: Goal-directed behaviors require monitoring of ongoing actions and evaluation of their outcomes, processes critically involving the primate medial frontal cortex (MFC). Specifically, previous studies have demonstrated MFC responses in tasks where stimuli contained conflicting information that corresponds to incompatible behavioral responses and the goal is to suppress one in favor of the other response option. This MFC activation induced by conflict, reflected in BOLD signal in human fMRI studies, is stimulus-onset triggered and could thus be involved in online control of the ongoing action.The MFC has also been shown to register self-generated errors and errors communicated by external feedback, and this error signal appears only after an erroneous action has been committed, suggesting that this area is capable of computing an evaluative signal triggered by actions. Does the MFC also monitor conflicts after a goal-directed action has been made? Such an internally generated signal, if exists, would be correlated with the subjective measure of action difficulty caused by conflicts in task-relevant information.
Here we report single neurons in human dorsal anterior cingulate cortex (dACC) and pre-supplementary motor area (pre-SMA), two major components of the MFC, that signal conflicts after action completion. We recorded single neuron activity from epilepsy patients while they performed the Stroop task and the multi-source interference (MSIT) task, both classical tasks for inducing cognitive conflicts. We confirmed the existence of conflict signals triggered by stimulus onset in both tasks as previously reported. We also found a significant proportion of MFC neurons that signaled conflict immediately before action onset. However, the post-action conflict neurons constitute a different class of neurons than conflict neurons with pre-action activation. The post-action conflict signal could not be explained simply by a continuation of stimulus-onset-triggered conflict. Preliminary analyses also suggested that these post-action conflict neurons could distinguish between the three levels of interference introduced in the MSIT task. Importantly, the ability of these post-action conflict neurons to distinguish between different levels of interference could not be explained by correlation with reaction time (which differed significantly between inference levels), as this spike rate difference remained significant even after controlling for the effect of reaction time. This signal thus represents a metacognitive mechanism that serves a putative role in evaluating the difficulty encountered during action performance due to conflict.

Disclosures: Z. Fu: None. **U. Rutishauser:** None. **R. Adolphs:** None. **A. Mamelak:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.04/HHH53

Topic: H.02. Human Cognition and Behavior

Title: Motivation and emotion elicited accidental rewards on action inhibition

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Abstract: Research has implicated motivation and reward in action inhibitory control, i.e., to implement a balance between proactive and reactive control. In this study, we used fMRI together with a stop-signal task to investigate neural correlates of (1) effects of positive and negative accidental rewards (i.e. PR and NR) and (2) interaction between motivation with PR and NR upon inhibition of an upcoming action. Two groups of participants were recruited for experiments under different contexts. *For the first group of the participants,* right before the occurrence of each stop trial, they received various accidental rewards (i.e., PR, NR, or a neutral one) which were randomly assigned to denote performance of the preceding go trial. We found that, compared to the neutral condition, both PR and NR significantly shortened the processing time of a stop-signal (i.e., the stop-signal reaction time, SSRT). In the BOLD data, although brain activities associated with PR and NR were widely spread, functional segregation in the dorsal and ventral medial striatum was revealed. While the ventral part encodes reward valences, the dorsal part represents more for the current task demands. *For the second group of the participants*, in addition to the trial-based reward manipulation, we included another factor to motivate the participants. That is, the participants could get a lump-sum monetary bonus by speeding up their go responses and stopping as accurate as possible. In this second case, the SSRT was shortened only for the PR condition. In the BOLD data, it was found, when compared to BOLD data of the first group participants, enhanced activities in the pre-SMA and right inferior frontal junction for processing the stop-signal when the participants were motivated. However, we found no significant effect for PR and NR for processing the stop-signal between the two groups, suggesting that motivation has an impact on the underlying mechanism induced by accidental reward. *In summary,* the accidental reward seems to boost inhibition control reactively, and motivation exerts its influence by adjusting the mechanism of reactive control.

Disclosures: H. Lee: None. **F. Lin:** None. **W. Kuo:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.05/HHH54

Topic: H.02. Human Cognition and Behavior

Title: Speed vs. accuracy priority and conflict during the flanker task

Authors: *K. B. BEYER, W. E. MCILROY
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Abstract: Cognitive control tasks, such as the flanker task, employ irrelevant distractor stimuli to introduce behavioural conflict during speeded choice responses. Despite consistent instructions, individual participants may choose to prioritize speed or accuracy. This choice will influence their overall performance in each of these domains relative to other participants but may also influence which performance domain is more influenced by conflict and what adaptations are made following conflict to improve future performance. The purpose of this study was to examine how individual flanker task performance in the speed and accuracy domains was associated with the influence of conflict on each of these domains. For each flanker trial, we measured reaction time, accuracy (correct vs. error), and correct-related negativity (CRN) amplitude, an EEG measure of conflict-related brain activity. Initial results show that individuals vary in the degree to which their overall performance is influenced by conflict (i.e., conflict effect on reaction time and accuracy combined) as well as what aspect of performance is more influenced by conflict (i.e., conflict effect on reaction time vs. accuracy). Within individuals, reaction time and accuracy relative to other individuals on both congruent and incongruent trials separately predicts which of these variables is more influenced by conflict and which variable is adapted following conflict. For example, better accuracy, even on congruent trials, predicts a greater conflict effect for reaction time than accuracy and an improvement in accuracy but not reaction time following high conflict trials. These findings indicate that the prioritization of speed or accuracy determines which domain is more influenced by conflict and how performance is adapted when conflict increases. The combined conflict effect on reaction time and accuracy predicts the conflict effect on CRN amplitude better than reaction time or accuracy conflict effect separately. This finding indicates that both speed and accuracy performance are associated with the conflict monitored by the CRN, but it remains unclear how this conflict-related activity may be related to the prioritization of speed or accuracy. Ongoing research is, therefore, examining how CRN amplitude is associated with performance depending on indicators of the strategy to prioritize speed or accuracy.

Disclosures: K.B. Beyer: None. **W.E. McIlroy:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.06/HHH55

Topic: H.02. Human Cognition and Behavior

Support: CIHR Doctoral Award to SLR
NSERC Discovery Grant to GRT

Title: Neural basis of sustained and transient control processes during task switching

Authors: *E. R. CONNELL, S. LEMIRE-RODGER, W. D. STEVENS, G. R. TURNER
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Abstract: Task switching involves the flexible allocation of attention between different stimuli or tasks by maintaining a sustained task-set and monitoring responses on a trial-by-trial basis. Here we used a mixed block and event-related analysis formerly reported by Braver et al. (2003) to isolate brain activity associated with the sustained and transient control processes during task switching. We extend previous work by examining event-related activity associated with mixing costs (comparing individual repeat trials during dual-task blocks to individual trials during single-task blocks). Young adults (N=21, 8 male, M_{age} = 19.43) completed a task-switching paradigm, the number-letter task, during fMRI scanning. Events and blocks were modeled separately to identify patterns of brain activity according to time scale (trial-by-trial vs. sustained) for both dual-task blocks and single-task blocks. We identified sustained activity in the right anterior prefrontal cortex (PFC) during the dual-task blocks when contrasted with single-task blocks, consistent with a role for this region in maintaining an active task-set in the context of switching (Braver et al., 2003). We also identified event-related activity associated with the switching events in left superior parietal cortex, left supplementary motor area, and the left anterior orbitofrontal cortex, similar to those previously reported by Braver et al (2003). Finally, our mixing costs analysis revealed transient activity in the anterior cingulate cortex (ACC) associated with repeat trials within the dual-task block when contrasted with events within the single-task block. We also found increased activity in the ACC during incorrect trials over correct trials, consistent with a role for this region in conflict monitoring. Mixing costs may not only be due to the sustained state of switching, but also to moment-to-moment processing implemented by ACC. The current results highlight the selective modulation of this region in relationship to mixing costs, suggesting the ACC is involved in conflict monitoring on a trial-by-trial basis while the brain is maintaining a flexible switching task-set.

Disclosures: E.R. Connell: None. **S. Lemire-Rodger:** None. **W.D. Stevens:** None. **G.R. Turner:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.07/HHH56

Topic: H.02. Human Cognition and Behavior

Support: NIH NIDA DA026452

Title: Withholding an action during heat pain invokes brain signatures of motor suppression and conflict: Dissecting the components of urge

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Abstract: Whether it be battling the impulse to grab an extra cookie or refraining from scratching a wound, we have all experienced an urge to act. Conceptual models of "urge" characterize the experience as moments in which there is a simultaneous drive to act and a need to withhold (Jackson, Parkinson, Kim, Schüermann, & Eickhoff, 2011). The mechanisms that underlie the withholding of urge, however, are largely unknown. We hypothesize that one component is a motor suppressive process. Further, because an urge is thought to consist of two incompatible motor intentions (to move, but to also withhold), we expect that it may evoke a state of conflict analogous to that observed in response conflict tasks. To test this, we designed a task that used heat to invoke an urge. Specifically, subjects had heat applied to the left arm and were given a button that could be pressed with the right hand to turn off the heat. Importantly, they were required to endure the heat and refrain from pressing for 9, 10 or 11 seconds. We used scalp EEG to test whether i) there was a sensorimotor suppressive process related to action-withholding, ii) there was a neural response to the heat pain, iii) there was a dorsomedial conflict response, and iv) the suppressive or conflict processes would relate to the pain signature. Using independent component analysis, we identified a left sensorimotor component contralateral to the hand capable of pressing for relief. For this component, during the heat withholding period, there was greater beta band power compared to control conditions (p's$<.01$). We interpret this as evidence for a motor suppressive process that is engaged during the urge to press. There was also a "pain signature" contralateral to the arm where the heat was applied, showing a stronger beta band desynchronization relative to control conditions. Strikingly, across subjects, those who "suppressed" more also demonstrated less of a putative "pain" response ($r=.517$, $p<.05$). Lastly, we showed that heat urge evoked a similar neural response to that observed in a response conflict task. Therefore, a state of conflict may be a core symptom of urge and might contribute to the challenge of withholding. Overall, these data suggest that conflict, akin to response conflict, does occur during urge, and further, that a motor suppressive process may be used to withhold during urge, and that the degree of recruitment of this process may relate to changes in sensory processing.

Disclosures: K.K. Sundby: None. **J. Wagner:** None. **A.A. Aron:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.08/HHH57

Topic: H.02. Human Cognition and Behavior

Support: National Defense Science Engineering Fellowship

John Templeton Foundation
Intel

Title: Why we struggle to multitask: Converging evidence from computational modeling, human behavior, and neuroimaging

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Abstract: Why are humans bad at multitasking? Model simulations, human behavior, and neuroimaging provide converging evidence that interference between task-relevant representations limits multitasking.
Model simulations show that networks learn new task representations by exploiting existing representations that share relevant input or output dimensions (Musslick et al., 2016; 2017). The degree of overlap between two task representations predicts whether the tasks can be performed simultaneously, with more overlap (i.e. shared hidden units) predicting worse multitasking performance. Training the network to multitask leads to separation of representations, with more separation predictive of better multitasking performance.
Human behavior is consistent with model predictions; while humans are able to multitask tasks with different relevant input and output features, they initially fail to multitask with two tasks that both require color processing (12 subjects, 7 days of training each). Training on performing these tasks together leads to significant behavioral improvements that cannot be explained by improvement in performing the tasks in isolation. Performance on a related transfer task suggests multitasking training does not globally improve multitasking performance; in fact, training could change representations in ways that impair performance on other tasks.
Preliminary neuroimaging findings reveal how neural representations of task-relevant representations change with training (1 subject, 5 fMRI scanning sessions, 5000 trials of multitasking training). Over the course of five days of training, multitasking performance improves while correlations decrease between task representations that initially overlapped.

Disclosures: A. Novick: None. **S. Musslick:** None. **M. Iordan:** None. **J.D. Cohen:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.09/HHH58

Topic: H.02. Human Cognition and Behavior

Support: NWO Vici 453-14-015

Title: Quantifying the cost of cognitive stability and flexibility

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Abstract: Cognitive control refers to the ability to 'focus' on a task. Exerting cognitive control is well known to be accompanied by a subjective effort cost and people are generally biased to avoid it. However, the mechanisms underlying this effort cost of cognitive control are currently unclear. To begin to address this question, we build on recent theorizing suggesting that the cost of cognitive effort represents a motivational signal that facilitates switching to alternative tasks, hence promoting flexibility (Cools, 2016; Kurzban, Duckworth, Kable, & Myers, 2013). Inspired by these observations, we asked whether the effort cost of cognitive stability is higher than that of cognitive flexibility. Specifically, we tested this prediction in the domain of working memory by using (i) a delayed response paradigm that allows us to quantify the stability (distractor resistance) and flexibility (flexible updating) of working memory representations (as in Fallon et al. 2017), as well as (ii) a subsequent cognitive effort discounting paradigm that allows us to quantify the subjective effort costs assigned to performing the delayed response paradigm (as in Westbrook et al. 2013). We show strong evidence, in two different samples (28 and 62 participants respectively) that subjective value decreases as a function of demand. Moreover, we demonstrate that the subjective cost of performing a task requiring cognitive stability (distracter resistance) is higher than that requiring flexible updating. This finding supports recent theorizing that the cost of control might represent a solution to the stability-flexibility dilemma (Musslick, Jang, Shvartsman, Shenhav, & Cohen, 2017). In ongoing work with this paradigm, we are assessing the role of brain dopamine in the tradeoff between stability and flexibility and associated effort costs. We also aim to adapt this paradigm to assess another key implication of this proposal, namely whether the cost of control varies with current task demands for stability versus flexibility, with higher costs in environment with greater demands for flexibility.

Disclosures: D. Papadopetraki: None. **M.I. Froböse:** None. **B.B. Zandbelt:** None. **A. Westbrook:** None. **R. Cools:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.10/HHH59

Topic: H.02. Human Cognition and Behavior

Support: NINDS Grant R37NS21135
NSF Graduate Research Fellowship

Netherlands Organization for Scientific Research. Grant Number: 446-13-009

Title: Intracranial Stroop recordings reveal parallel conflict processing in networks distributed across frontal and insular regions

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Abstract: Real life scenarios often involve a choice between multiple responses, and control networks in the brain must mediate between these options to implement adaptive behavior. Conflict refers to the competition between simultaneously activated responses that must be resolved to select the appropriate option. Previous literature has identified medial prefrontal cortex (MPFC) and lateral prefrontal cortex (LPFC) as key brain regions involved in conflict processing, and classical theories of conflict processing posit serial computations in which MPFC detects conflict before recruiting LPFC resources to resolve the conflict and execute the correct response. These theories are largely based on EEG and fMRI research examining temporal and spatial profiles of conflict resolution separately. A few intracranial studies in humans have confirmed the involvement of MPFC and LPFC, but the spatiotemporal dynamics of these regions and their relationships during conflict processing remain undefined. Notably, few studies have addressed the role of the insula (INS) in conflict tasks, despite its strong anatomical and functional connections with MPFC. We utilized the spatiotemporal resolution of intracranial recordings in epilepsy patients (iEEG; n = 11) performing a verbal color-word Stroop task to describe the activity profiles of local activity in MPFC, LPFC, and INS and to capture their interactions through connectivity analyses. Data preprocessing included removing epileptic and excessively noisy channels and epochs, bipolar re-referencing, and band-stop filtering line noise. The data were then filtered to 70-150 Hz to isolate high frequency activity (HFA) known to correspond to local population spiking. Although similar proportions of sites with conflict sensitive HFA (cluster-based permutations, $p<0.05$ FDR corrected) were observed in MPFC, LPFC, and INS, individual electrode sites revealed heterogeneous HFA time courses within each region, suggesting distributed functional networks were forming across regions at varying stages of conflict processing. These functional networks were then identified using pair-wise correlations in HFA. Contrasting connectivity strength across conditions to determine relevance to conflict processing revealed that the greatest proportion of sites with significantly different correlations (null distribution via condition labels permutations, $p<0.05$ FDR corrected) were between pairs within INS and within MPFC, followed by pairs between MPFC-INS and LPFC-INS. These findings emphasize the role of the insula and of distributed network interactions in facilitating conflict processing and cognitive control.

Disclosures: C. Hoy: None. **K.L. Anderson:** None. **V. Piai:** None. **J.L. Lin:** None. **R.T. Knight:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.11/HHH60

Topic: H.02. Human Cognition and Behavior

Support: Ministry of Health & Welfare, Korea (HI15C2578)
Ministry of Science and ICT(MSIT)(2017M3C7A1030750)

Title: A fNIRS investigation of interference resolution and response inhibition in amodified Stroop task

Authors: S.-E. CHOI[1], H. LEE[1], D.-J. YI[2], *S. EOM[1]
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Abstract: Objective:
The present study investigated functional brain activation patterns in adults using functional Near Infrared Spectroscopy (fNIRS) during an event-related, Stroop task and neuropsychological tests of executive functioning as a more cost-effective tool measuring cortical hemodynamics and a behavioral paradigm.
Methods:
Eighteen adults were included in the study with a mean age of 31.0±3.5 years (range 26-37; 12 female), and a mean education of 18.7±2.2 years (range 16-22). We adapted the color-word matching Stroop task in an event-related version which might suggest executive processes such as interference resolution and response inhibition, and measured prefrontal activity during task performance. Relating neuropsychological tests of other version of Stroop, verbal/design fluency, working memory and processing speed were also performed. The fNIRS data analysis was conducted on the concentration associated with the activation of each condition. Modified Beer-Lambert law (MBLL) is the main governing equation for NIRS, which extracts the concentrations of oxy-and deoxyhemoglobin by usinglight signals with two wavelengths. fNIRS data and behavioral measure were analyzed with repeated measure ANOVA including condition (congruent vs. incongruent) as a within-subjects factor. And correlation analysis was conducted among fNIRS, behavioral and neuropsychological data.
Results:
The results of the ANOVA analyses demonstrated a significant task-related activation of the PFC.
It specially evoked cortical activations regarding Stroop interference on the dorsolateral prefrontal cortex and some anterior frontal area(Figure 1&2). Behavioral data including reaction time, accuracy, and interference ratio demonstrated the effect of cognitive interference during

Stoop
tasks and also different pattern of groups which might come from different cognitive strategy by individuals even in same task.
Conclusion:
Our results suggest that interference resolution and response inhibition are associated with different functional activation patterns in the frontal subregions. fNIRS could be a potential measure as an effective tool to investigate the contributions of prefontal function including DLPFC and aPFC to executive functioning.

Disclosures: S. Choi: None. **H. Lee:** None. **D. Yi:** None. **S. Eom:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.12/HHH61

Topic: H.02. Human Cognition and Behavior

Title: The impact of repetitive low-level blast exposures on cognitive-motor integration in Canadian Armed Forces breachers

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Abstract: Introduction: Breachers are a specialized group of military personnel trained to use controlled explosions to blast holes through walls and doors to gain rapid entry. Breacher instructors are exposed to hundreds of low-level blast events, during their years of teaching assignments. The relationship between long-term occupational exposure to low-level blasts and human health is unknown, but data collected from professional breachers revealed that they suffer symptoms similar to individuals diagnosed with a concussion. This raises concerns that repetitive exposure to even low-levels of blast may produce adverse neurological effects. Using a novel visuomotor task that involves conditions where the individual has to think and move at the same time, Sergio and colleagues reported cognitive-motor integration (CMI) deficits in varsity athletes with a history of concussion even when they were asymptomatic[1]. In this study, we examined the impact of repetitive low-level blast exposures on CMI in a group of Canadian Armed Forces (CAF) breachers. **Methods:** Data were collected from 19 breaching instructors/range staff and 19 sex- and age-matched CAF controls. Study participants were tested on different eye-hand coordination tasks. While wearing a touch-screen glove, participants were

instructed to place their finger on a central spot on the horizontally placed computer tablet and direct the cursor towards the target by sliding their finger on the touchscreen. In two of the four conditions, participants viewed the targets directly on the tablet while sliding their finger in the same (direct) or opposite direction (direct/feedback reversal) to move the cursor towards the target. In the other two conditions, participants viewed the targets and cursor on an external monitor in the vertical upright position while moving their finger in the same (plane change/direct) or opposite direction (plane change/feedback reversal). **Results:** Of the ten different outcome measures assessed from this task, breachers showed a greater variability in reaction time under all conditions except for when the target was presented in the plane change/direct condition. In addition, the breacher group tended to perform much slower on most of the visuomotor task conditions. **Conclusion:** The slower reaction times observed in the breacher group are consistent with previous reports on varsity athletes with a history of concussion. While there were no differences between the groups in all other outcome measures, we suspect breachers are highly trained individuals and are able to compensate for potential CMI deficits. [1]Brown et al. (2015) BMC Sports Sci Med Rehab 7:25

Disclosures: C.C. Tenn: None. **O. Vartanian:** None. **L.E. Sergio:** None. **D. Gorbet:** None. **A. Nakashima:** None. **S.G. Rhind:** None. **K. Blackler:** None. **D. Saunders:** None. **N. Caddy:** None. **M. Garrett:** None. **R. Jetly:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.13/III1

Topic: H.02. Human Cognition and Behavior

Support: Medical Research Council (UK) Intramural Program MC-A060-5PQ10
Royal Society Dorothy Hodgkin Fellowship (DH130100) to YE
Gates Fellowship to SS

Title: Reward modulates representation of behaviorally-relevant information across the frontoparietal cortex

Authors: *S. SHASHIDHARA, Y. EREZ
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Abstract: Cognitive control has been associated with a distributed network of frontal and parietal regions. In a previous study, we have shown that, across this network, task-related information is represented based on its behavioral relevance (Erez & Duncan, 2015). Previous studies have demonstrated that reward modulates multiple aspects of cognitive control, for example by improving behavioral performance and monitoring in various cognitive tasks. We

and others have shown that overall activity across multiple brain regions increases when reward is introduced. In particular, it was demonstrated that reward leads to enhanced representation of task rules across the frontoparietal network (Etzel et al., 2016). Here we build on these findings and test for the effect of reward on the representation of behaviorally-relevant task content using a functional magnetic resonance imaging (fMRI) study (N=24, healthy adults). In a cued category detection task, displays contained an image from one of three semantic categories, and participants detected whether it was from a cued category or not. In each trial, the cued category served as a target (T). Of the two non-target categories, one was a target on other trials (inconsistent non-target, NI), and the other was never cued (consistent non-target, NC), thus creating three behavioral categories (T, NI, NC). On half of all trials, participants were offered a possibility of substantial monetary reward on correct completion of the trial within a time limit. Behavioral results showed decreased reaction times for the reward trials as compared to the non-reward trials without a change in accuracy. Univariate whole-brain random effects analysis showed increased activity for reward trials compared to no-reward trials across multiple frontal and parietal regions. Multivariate pattern analysis (MVPA) showed representation of the task-relevant behavioral categories, and particularly target vs. non-target, across the frontoparietal network. This pattern of response was modulated by reward, making the target category more distinguishable from the non-target categories. Our results support the view of reward as a facilitator of control processes by enhancing representation of behaviorally-relevant task information.

Disclosures: S. Shashidhara: None. **Y. Erez:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.14/III2

Topic: H.02. Human Cognition and Behavior

Support: JSMF Grant HQR00220
Rutherford Foundation
William Georgetti Trust

Title: Understanding why rewards improve cognitive performance using representational similarity analysis

Authors: *S. HALL-MCMASTER, N. MYERS, P. S. MUHLE-KARBE, M. G. STOKES
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Abstract: Research studying the interaction between motivation and cognition has amassed a substantial body of evidence that rewards tend to enhance cognitive performance. While this

finding has been represented in many cognitive domains, including selective attention, inhibitory control, and task switching, it remains unclear how rewards impact neural coding to bring about performance benefits. One proposal is that rewards boost task representations in prefrontal cortex, under which one would predict greater neural dissimilarity between task representations under high reward conditions. A competing proposal is that rewards boost sensory processing of stimulus features. Under this account, one would predict greater dissimilarity between feature representations in high reward scenarios. Here we present results from an experiment aiming to test these two hypotheses. Thirty participants (11 female, mean age = 23 years) made simple cognitive judgements about the colour and shape of stimuli, while rewards for fast and accurate responses were manipulated dynamically, on a trial-by-trial basis. While participants performed the task, their neural activity was measured using electroencephalography. Behaviourally, we found that our experimental manipulation was effective in modulating cognitive performance, eliciting faster reaction times (~20ms) and greater accuracy (~2%) under high reward conditions. We then used Representational Similarity Analysis to quantify the impact of reward on neural coding patterns. By fitting a selection of coding models to dissimilarity matrices over time, we found that reward coding, task coding, feature coding, and motor coding dominated neural activity patterns sequentially within trials. When comparing cells in the matrices that differed only as a function of task, we found no difference in the dissimilarity of task representations between high and low reward conditions. By contrast, we found that high reward increased the magnitude of feature coding and neural dissimilarity between relevant features during the response phase. In addition, we found that the magnitude of feature coding was significantly correlated with participants' task performance. While preliminary, these results may suggest that rewards can improve cognitive performance by modulating feature representations needed for appropriate behavioural output.

Disclosures: S. Hall-Mcmaster: None. **N. Myers:** None. **P.S. Muhle-Karbe:** None. **M.G. Stokes:** None.

Poster

250. Human Cognition and Behavior: Executive Function: Interference and Flexibility

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 250.15/III3

Topic: H.02. Human Cognition and Behavior

Title: Assessment of pediatric response inhibition via go/no-go tasks with electrocorticography

Authors: *C.-H. KUO[1,6], K. CASIMO[2], J. WU[2], P. RICE[3], A. STOCCO[3], E. J. NOVOTNY, Jr.[4], K. E. WEAVER[5], J. G. OJEMANN[1]
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Abstract: Introduction
Response inhibition is the ability to suppress actions that are inappropriate in a given context or that interfere with goal-driven behavior. One method of assessing response inhibition is via a go/no-go task. Prior studies have implicated the inferior frontal gyrus (IFG) in executive control and inhibition of motor cortex. Although the neuroanatomy of response inhibition is well described in the fMRI literature, precise electrophysiological properties are still unclear, especially in the pediatric population. In particular, neural timing cannot be effectively investigated with fMRI, thus requiring electrophysiological methods. We recorded neural activity with subdural electrocorticography (ECoG) in pediatric patients during a go/no-go task to investigate response inhibition function associated with IFG and primary motor cortex (M1).
Methods
Six right-handed patients undergoing subdural ECoG for seizure localization were included in this study (7-16 years old, mean age 11.5, three with right hemisphere ECoG placement). The go/no-go tasks were optimized for children: the subject was asked to respond as quickly and accurately as possible on the appearance of a go signal (a lion), and not respond for no-go signal (a bear), with simultaneously ECoG recording. Representative electrodes from IFG and M1 were selected on the basis of peak high gamma (HG, 70- 200 Hz) activation. We extracted power spectrum using the square of the analytical amplitude output of the wavelet transform from 2-200 Hz for each behavioral trial. We compared mean power and peak amplitude in theta (4-8 Hz) and high gamma (70-200 Hz) range in both IFG and M1 between go and no-go conditions but identifying statistically significant power values with a standardized permutation test.
Results
We observed higher HG activation in no-go trials relative to go trials within the IFG, regardless of hand used (3 of 6 patients, $p < 0.05$). However, IFG power of the low frequency band (4-8 Hz), was higher in no-go trials than in go trials, but this pattern was not consistent and depended on contra- or ipsilateral hand use. Additionally, HG power in M1 contralateral to the hand used was significantly higher in go trials than in no-go trials (4 of 6 patients, $p < 0.05$).
Conclusion
We observe that HG, and to a lesser extent theta, power in IFG is higher in no-go than in go trials particularly for older participants. Our results indicate that bilateral IFG based on high frequency power responses may have a role in response inhibition. Further studies may investigate the interactions between IFG and M1, as well as the development of power and interactions over age.

Disclosures: C. Kuo: None. **K. Casimo:** None. **J. Wu:** None. **P. Rice:** None. **A. Stocco:** None. **E.J. Novotny:** None. **K.E. Weaver:** None. **J.G. Ojemann:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.01/III4

Topic: H.02. Human Cognition and Behavior

Support: ANR IDEFIX
ANR APEX

Title: Age-specific functional, anatomical and connectivity changes following inhibitory control training in children and adolescents

Authors: *A. CACHIA[1,2,3], L. DELALANDE[2], S. CHARRON[3], M. MOYON[2], C. TISSIER[2], E. SALVIA[2], K. MEVEL[2], N. POIREL[2], J. VIDAL[2], C. OPPENHEIM[3], O. HOUDÉ[2], G. BORST[2]
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Abstract: Executive functions, and particularly inhibitory control (i.e.,the ability to withhold a prepotent response), play a critical role in academic success. While the effect of cognitive training on IC efficiency improvement has been studied either in children or in adults, the neurocognitive effects of IC training from childhood to adolescence is understudied. This is surprising given that childhood and adolescence is a developmental period defined by a high brain plasticity and environmental sensitivity during which the IC neural network become more specialized and integrated. We used anatomical, diffusion and functional magnetic resonance imaging on a 3T MRI scanner and a longitudinal design to test the effects of an intensive (25 sessions, 15 min a day, 5 weeks) and individualized IC computerized adaptive training on tactile devices. 64 healthy children (27 males, 9 to 11- year-old) and 59 healthy adolescents (20 males, 16 to 17-year-old) were randomly assigned to receive either IC (parametric Stroop and Stop-signal tasks, SST) or active control (AC) (knowledge-based task) training. IC efficiency (assessed by SST performance) improved more in the IC than in the AC group. This behavioral change was paralleled by group- and age-specific morphometric changes in regional cortical thickness in prefrontal regions, in functional activations in the bilateral insula for 'Successful *vs* Failed inhibition' contrast in SST and in the white matter microstructure in cingulum bundle. Taken together, the results provided evidence of age-specific functional, anatomical and connectivity changes in the IC network pre- and post-training.

Disclosures: A. Cachia: None. **L. Delalande:** None. **S. Charron:** None. **M. Moyon:** None. **C. Tissier:** None. **E. Salvia:** None. **K. Mevel:** None. **N. Poirel:** None. **J. Vidal:** None. **C. Oppenheim:** None. **O. Houdé:** None. **G. Borst:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.02/III5

Topic: H.02. Human Cognition and Behavior

Title: Multivariate pattern analysis shows distributed representation of cognitive task contents in striatum

Authors: *P. STIERS[1], A. GOULAS[2]
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Abstract: fMRI studies on the dynamic representation of task contents exclusively focus on the cerebral cortex. However, neurophysiological studies also report coding of task-relevant features by striatal neurons (e.g., Ito & Doya, 2015, J Neurosci. 35:3499), fueling theories of basal ganglia involvement in cognitive decision making (eg., Hélie ea., 2015, Cortex 64:123). To investigate the feasibility of including basal ganglia in the non-invasive study of dynamic cognitive coding, we applied multivariate pattern analysis (MVPA) to individual, trial-wise fMRI data (n=12) collected during execution of 3 cognitive tasks (Erikson flanker, 2-back matching, response scheme switching) to establish if different task contents can be decoded from striatum.
Participants completed 6 runs with 6 blocks per task in each run. Trial-wise activity was computed as the average cleaned BOLD signal over volumes 3 and 4 after trial onset. Analysis voxels were individually defined as grey matter voxels within specific ROI masks. Per ROI a pair-wise task classification was performed using support vector machine learning with leave-one-run out cross-validation and recursive feature elimination. Statistical significance was assessed over 125 label randomizations in an otherwise identical procedure.
Classification accuracy over the three tasks in bilateral lateral prefrontal cortex was 76.1±4.4% ($p<0.001$). Accuracy in bilateral striatum was lower, but still significant (59.9±4.1%, $p<0.001$). Similar results were obtained for other MVPA parameters and with a logistic regression algorithm. There were no subregion differences in classification. Accuracies were equal and significant ($p <0.001$) for left or right side striatum and for the three major subregions: ventral striatum (57.3±2.2%), and non-ventral putamen (57.4±2.8%) and caudate nucleus (58.9±3.4%). The lower accuracy in the striatum compared to cortex was not due to a dynamic regional shift with time on task, as the classifier trained on data from runs 1 and 2 generalized equally well to the last two runs 5 and 6 as to intermediate runs 3 and 4. There was also no evidence that the discrimination appeared earlier in ventral striatum than in the other subregions (Ito & Doya, 2015), since decoding the upcoming task from activity induced by the cue preceding each task block was equally effective in all three subregions.

We conclude that cognitive tasks invoke reliably distinctive activity patterns in all three major subregions of the striatum. This finding is consistent with the hypothesis that the basal ganglia contribute to the dynamic representation of cognitive task contents in the telencephalic brain.

Disclosures: P. Stiers: None. **A. Goulas:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.03/III6

Topic: H.02. Human Cognition and Behavior

Support: R01 HD079520
R01 HD086085
Science Foundation Arizona

Title: Associations between KIBRA gene methylation and executive performance in a childhood monozygotic twin difference design

Authors: *C. LEWIS[1,2], A. HENDERSON-SMITH[2], R. S. BREITENSTEIN[1], K. LEMERY-CHALFANT[1], L. D. DOANE[1], M. J. HUENTELMAN[2]
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Abstract: Executive functioning, such as sustained attention, response inhibition, and working memory, is necessary for flexible and adaptive human cognitions, emotions, and behavior. Much research suggests individual differences in executive functioning are strongly driven by genetic variation. For example, twelve years ago our group and collaborators established an association between variation in the KIBRA gene (*WWC1)* and episodic memory in healthy young and middle aged volunteers, which was independently replicated in an elderly group (Papassotiropoulos et al., 2006; Schaper et al., 2008). However, an emerging body of empirical research suggests that environmental factors are also influencing complex phenotypes by affecting the epigenome. We used a monozygotic (MZ) twin difference design to examine cotwin differences in methylation of CpG sites near *WWC1* in relation to cotwin differences in executive functioning. The sample included 48 MZ twin pairs (51% male; 50% Non-Hispanic White, 14.6% Hispanic/Latinx, 8.3% African American, 4.2% Asian American), mean age = 8.5 years, drawn from the Arizona Twin Project (Lemery-Chalfant et al., 2013). Comparing MZ twins allowed us to assess if environmentally driven differences in methylation affected phenotypes while controlling for the influence of genotype on methylation and task performance. We collected buccal cell samples and conducted tasks during home visits. DNA methylation was quantified using the Infinium MethylationEPIC BeadChip. Executive attention was assessed with

the Flanker Task (Linear Integration Speed Accuracy Score [LISAS] for congruent and incongruent trials) and short-term memory (STM) was assessed with Digit Span (Total Forward and Backward). We extracted the first principal component from % methylation of 82 CpG sites near *WWC1* after removing all sites with a < .3 loading (45 sites remained and variance explained was 43.29%). Next, we computed MZ difference scores representing % methylation and task performance for linear regression analysis controlling for sex. We found MZ differences in *WWC1* methylation were not associated with STM but did predict executive attention performance. MZ differences in *WWC1* methylation were negatively associated with executive attention performance on the Flanker Task (higher values indicate lower efficiency; LISA Congruent: $b = 0.367$, $p = 0.022$). Our findings suggest that methylation status of executive functioning genes may influence executive attention over and above genotype. Our results highlight the importance of the epigenome for executive control and memory processes central to cognitions, emotions, and behavior.

Disclosures: C. Lewis: None. **A. Henderson-Smith:** None. **R.S. Breitenstein:** None. **K. Lemery-Chalfant:** None. **L.D. Doane:** None. **M.J. Huentelman:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.04/III7

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant UH2DA041713

Title: Uncovering mental and neural structure through data-driven ontology discovery

Authors: *I. EISENBERG[1], P. G. BISSETT[2], A. Z. ENKAVI[2], J. LI[2], R. A. POLDRACK[3]
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Abstract: Cognitive neuroscience has linked neural activity to a wealth of cognitive processes, yet struggles to produce a cumulative account of neural function. This slow progress has many causes, but is partially explained by the lack of systematic ontologies describing brain structure and mental function. While integrative brain atlases have been steadily improving, commensurate efforts to improve cognitive ontologies have been limited.
We address this by developing a data-driven cognitive ontology derived from individual differences across a broad range of behavioral tasks, self-report surveys, and real-world outcomes. 522 participants completed 63 different measures on Mechanical Turk related to decision-making, working memory, cognitive control, impulsivity, and personality, amongst other psychological constructs. Interestingly, though subsets of the tasks and surveys putatively

reflect similar constructs, we find that they bifurcate in the ontology. Using exploratory factor analysis, we identify two low-dimensional cognitive spaces that separately capture behavioral tasks and surveys. Hierarchical clustering within these spaces identify sensible clusters which capture psychological "kinds", related to, but separate, from the dimensions identified with factor analysis. Overall, this structure discovery reveals a simpler cognitive ontology than typically employed in the psychological sciences.
As real-world relevance is an essential feature of theoretical constructs, we also evaluated whether tasks and surveys can predict real-world outcomes. We reduced the self-reported real-world outcomes to 9 "target" factors (e.g. mental health, binge drinking), computed individual factor scores, and assessed predictive ability using cross-validated ridge regression. While surveys performed moderately well, tasks showed almost no predictive ability.
Using a genetic algorithm, we identified a smaller number of behavioral tasks and survey questions that best captured the entire ontological space to use in an fMRI study. 100 participants completed 10 tasks and resting-state scans, from which we calculate ~40 unique contrasts. Contrasts were subjected to dimensionality reduction and clustered to reveal a neural similarity space that complements that derived from behavioral individual differences.
Cognitive ontologies describe the psychological constructs through which most human neuroscience is understood. We demonstrate that data-driven structure discovery techniques can profitably improve these ontologies, and that doing so helps to contextualize brain states identified using fMRI.

Disclosures: I. Eisenberg: None. **P.G. Bissett:** None. **A.Z. Enkavi:** None. **J. Li:** None. **R.A. Poldrack:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.05/III8

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1UG30D023313
16.14.NRC. Nestec Ltd.

Title: Development of novel tablet-based measures of early learning and developing cognitive skills in early childhood: Preliminary feasibility and validity

Authors: *R. MCLEAN[1], N. SCHNEIDER[2], S. SHOLDS[1], E. MERCER[1], J. BECK[1], V. A. D'SA[3], S. DEONI[1]
[1]Women and Infants Hosp., Pawtucket, RI; [2]Nestlé Res. Ctr., Lausanne, Switzerland; [3]Brown Univ., Attleboro, MA

Abstract: Research objective and rationale: Early executive functioning (EF) skills relate to and predict later outcomes. Given limited availability of tasks measuring processing speed, inhibition and early learning in children ages 18-70 months, we developed tablet-based tasks to study the development of these cognitive skills. Study aim: Test feasibility and associations of investigator created tasks assessing EF with existing measures of cognitive functioning. Methods: 65 participants (40 male, 25 female), ages 18-70 months. Given interest in developing these tasks for toddlers, a subset of children ages 18-26 months was examined. Reaction Time Task: Child clicks on a stimulus as soon as it appears.Inhibition Task: Child clicks on a stimulus as soon as it appears, but avoids responding to another stimulus. Object Reversal Task for Infants (ORTi): Age-adapted based on principles of the probabilistic object reversal task. Cognitive measures: Mullen Scales of Early Learning, Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition. Parent report of EF assessed by the Behavior Rating Inventory of Executive Functioning-Preschool Version (BRIEF-P). Results*: Correlations between iPad measures, age and cognitive measures*

Task	Age (n=64)	MSEL Early Learning Composite (n=36)	WPPSI-IV Full Scale IQ (n=23)	BRIEF-P Global Executive Composite (n=33)
Reaction Time Task				
reaction time	*rs* = -.694, *p*=.000	*rs* = -.023, $p \geq .05$	*rs* = -.116, $p \geq .05$	*rs* = .133, $p \geq .05$
omission errors	*rs* = -.391, *p*=.001	*rs* = .202, $p \geq .05$	*rs* = -.348, $p \geq .05$	*rs* = .054, $p \geq .05$
Inhibition Task				
correct responses	*rs* = .604, *p*=.000	*rs* = .054, $p \geq .05$	*rs* = .276, $p \geq .05$	*rs* = -.257, $p \geq .05$
omission errors	*rs* = -.498, *p*=.000	*rs* = -.073, $p \geq .05$	*rs* = -.099, $p \geq .05$	*rs* = .087, $p \geq .05$
commission errors	*rs* = -.400, *p*=.001	*rs* = -.020, $p \geq .05$	*rs* = -.332, $p \geq .05$	*rs* = .-087, $p \geq .05$
reaction time	*rs* =-.624, *p*=.000	*rs* = -.006, $p \geq .05$	*rs* = -.090, , $p \geq .05$	*rs* = -.202, , $p \geq .05$
ORTi				
number of sets achieved	*rs* =.411, p=.001	*rs* = .034, $p \geq .05$	*rs* = .164, $p \geq .05$	*rs* = -.137, $p \geq .05$
perseverative errors	*rs* =-.671, *p*=.000	*rs* = .215, $p \geq .05$	*rs* = -.140, $p \geq .05$	*rs* = .196, $p \geq .05$
set loss errors	*rs* = -.211, $p \geq .05$	*rs* = .164, $p \geq .05$	*rs* = -.177, $p \geq .05$	*rs* = .109, $p \geq .05$

Toddler Performance

	n	Mean	SD	Range
Reaction Time omission errors	9	5.22	4.92	0-13 (max possible=20)
Inhibition Task omission errors	9	5.00	5.29	0-14 (max possible=24)
Inhibition Task commission errors	9	3.11	3.33	0-10 (max possible=16)
ORTi number of sets achieved (in 30 trials)	8	1.88	1.25	0-4 (1 child was unable to achieve any sets, 2 children achieved 1 set, 5 children achieved 2 or more sets)
ORTi perseverative errors	8	6.63	6.14	1-19
ORTi set loss errors	8	1.38	.916	0-3

Conclusions: Relationships between tablet-based tasks assessing developing cognitive skills (i.e. early learning, EF) and age, but not other cognitive variables (i.e. IQ, parent assessment of EF), suggest that these tasks measure a skill that is developing over time but is not well captured by current measures of global intellectual functioning or parent-reported EF, suggesting differential validity. Successful use of these tasks in young children indicates feasibility in this age range, with variability in performance that is potentially meaningful in terms of mapping early skill development.

Disclosures: R. McLean: None. **N. Schneider:** None. **S. Sholds:** None. **E. Mercer:** None. **J. Beck:** None. **V.A. D'Sa:** None. **S. Deoni:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.06/III9

Topic: H.02. Human Cognition and Behavior

Title: A possible role of childhood sibling aggression in the development of decision making functional networks and decisions made in adulthood

Authors: *S. BEDWELL[1], N. HARRISON[2]
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Abstract: The human prefrontal cortex is known to be associated with many complex high order cognitive functions and is implicated in a range of neurological and psychological disorders, thought to involve abnormal network structure. It is widely accepted that prefrontal connectivity and organisation undergoes a prolonged period of development and can be influenced by external factors experienced during developmental phases. It is also understood that prefrontal cortex connectivity is more complex than other cortical regions. Although it is known that experiences of sibling aggression in childhood influence cognitive functions exhibited in adulthood, it remains unclear how commonly experienced childhood aggression can contribute to the development of complex prefrontal cortical networks and therefore differences in high-order processes exhibited in adulthood, specifically in terms of the role of sibling aggression in complex decision making processes.
Utilising retrospective reports of sibling aggression and measures of current decision making style in 142 adult participants (>25 years), we revealed a previously undescribed link of using sibling aggression to maintain dominance in childhood with avoidant and spontaneous decision making styles exhibited in adulthood ($p<.05$). We also identified a significantly higher degree of avoidant decision making in mutual victims and perpetrators of sibling aggression when compared to those who had been sole victims ($p<.05$). The findings reported here indicate a possible role of sibling aggression in the development of avoidant decision making styles, thus implying an influence on underlying network structure. Notably, the relationship between perpetrators of sibling aggression and avoidant decision making is a surprising finding, given that avoidance is often considered a result of abusive childhood environments, which one might naturally associate with being a victim of sibling aggression over a perpetrator.
These findings form an important basis on which to build further investigations into the structural development of decision making networks and the role of childhood experiences in this. Ultimately, an improved understanding of high order functional development, specifically decision making, will provide vital information from which the understanding of neurological and psychological disorders associated with decision making deficit e.g. schizophrenia, depression and autism, can be improved.

Disclosures: S. Bedwell: None. **N. Harrison:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.07/III10

Topic: H.02. Human Cognition and Behavior

Title: Cognitive benefits of one bout of open- and closed-skill exercise in children, adolescents and young adults

Authors: *A. SETTI, J. M. O'BRIEN, J. GILSENAN, E. HAYES, J. CHAN
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Abstract: Despite a plethora of research documenting the benefits of physical activity on different cognitive abilities, whether one can obtain immediate benefits from one session of exercise is still a debated topic. The potential mediating role of exercise type on these specific benefits also deserves further investigation. This series of studies examined the effect of a single exercise session of open- and closed-skill exercise on working memory and attention. In study 1, 67 children (aged 6-8) were tested in a semi-randomised pre-post design, divided in 4 groups: open skill (soccer, basketball), closed skill (running races, circuit training, skipping), GoNoodleTM ('Indoor Recess' videos ('Sport and Exercise' category), selected for their moderate-to-vigorous exercise intensity), and no exercise. Digit span, Corsi Block Tapping test and motor span were tested, only the latter showed improvement after exercise. In Study 2 the same design was used to test 56 adolescents assigned to two groups: open-skill (table tennis) and closed-skill (skipping in pairs) on the Trail Making Test (TMT) 1 and 2. Results indicated a significant benefit of exercise, with greater improvement in the open-skill group in TMT2. A within participants design was used for Study 3, 21 young adults (18-29 years old) were tested on the Corsi Block Tapping test and the Enumeration test, assessing visual attention. Participants performed open-skill (table tennis), closed-skill (walking in pairs on treadmills) a week apart in counterbalanced order. A significant improvement was found only the visual attention, not modulated by exercise type. In conclusion, this series of studies shows some evidence for improvements after one bout of exercise in different age groups, however the need for standardization of methods is highlighted.

Disclosures: A. Setti: None. **J.M. O'Brien:** None. **J. Gilsenan:** None. **E. Hayes:** None. **J. Chan:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.08/III11

Topic: H.02. Human Cognition and Behavior

Support: DFG SPP 1772 grant BO 649/22-1
DFG SPP 1772 grant VO 1432/19-1

Title: Age-related effects on multitasking in an ecologically valid scenario

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Abstract: Multitasking is typically studied by presenting two abstract tasks concurrently, e.g., parity judgements and tone discriminations. It is well known that under laboratory conditions, performance on such task combinations deteriorates with advancing age. However, it still is largely unknown whether a similar age-related decay occurs in everyday life. Indeed, everyday scenarios typically differ from laboratory conditions in that more than two concurrent tasks are present, and that those tasks are meaningful rather than abstract. We therefore decided to study age-related deficits of multitasking in a scenario that mimics the above characteristics of everyday life. 63 young (20-30) and 61 older (65-75) healthy persons used a driving simulator to follow a lead car that travelled at constant speed but occasionally slowed down for a short time. Participants also executed a mixed series of loading tasks (memory retrieval, reasoning, typing), presented visually or auditorily. Driving and loading tasks were administered separately as well as concurrently, to determine the costs of multitasking (MTC). In addition, participants completed eight standardized laboratory tests which assessed the executive functions updating, inhibition, task switching and dual-tasking. Complete data sets were obtained from 59 young and 46 older persons. MTC of driving were significantly higher in the older group. Performance on executive function tests deteriorated in older age even if age-related slowing was accounted for. The age-related increase of driving MTC was fully attributable to the age-related decay of executive functions.We conclude that multitasking deteriorates in older age even in an ecologically valid scenario, and that training of executive functions may ameliorate this decay.

Disclosures: O.L. Bock: None. **U. Drescher:** None. **M. Haeger:** None. **C. Janouch:** None. **K. Wechsler:** None. **C. Voelcker-Rehage:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.09/III12

Topic: H.02. Human Cognition and Behavior

Support: German Insurance Association (GDV)
Federal Ministry of Labour and Social Affairs (BMAS)

Title: Interference control across the lifespan: Comparison between young, middle-aged and low-, middle- and high-performing old adults. Behavioral and erp evidence

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Abstract: Susceptibility to interference increases with age. However, there is large inter-individual variability in interference processing in older adults due to a number of biological and environmental factors. Surprisingly, only few studies evaluated interference processing across the lifespan. The present study aims at filling the gap by analyzing behavior and brain activity using ERPs in a Stroop interference task in young (*n* = 36, mean age 25 years), middle-aged (*n* = 58, 46 years) and old (*n* = 152, 70 years) participants in three variants of the Stroop task with increasing difficulty. The old age group was divided into three subgroups based on individual drift rates as obtained by a drift-diffusion model. The drift rate reflects individual accumulation of evidence about the stimulus to make a correct decision and serves as valid indicator of performance. The results showed stepwise reduction of performance and an increase of Stoop interference with age. These behavioral effects were accompanied by an increase of the frontal P2 and a reduction of the N2 amplitude with increasing age which are associated with retrieval of stimulus-response mappings and interference resolution during response selection. Importantly, old high performers showed similar performance and ERP patterns like middle-aged or even young adults, suggesting large inter-individual variability in interference processing and neuronal activity beyond the age of seventy.

Disclosures: P.D. Gajewski: None. **M. Falkenstein:** None. **S. Thoenes:** None. **E. Wascher:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.10/III13

Topic: H.02. Human Cognition and Behavior

Support: SEAMO Innovation Fund 365350
CIHR Grant MOP-FDN-148418

Title: Characterizing response inhibition deficits in adolescents showing early signs of borderline personality disorder using an oculomotor task

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Abstract: Adults with Borderline Personality Disorder (BPD) - a severe psychiatric illness that begins in adolescence - show impaired saccadic control in response inhibition tasks. To test whether this pattern also exists in adolescents showing early signs of BPD, we measured saccade performance in female adolescents with BPD traits (ages 14-18) and age-matched female healthy controls while they performed an interleaved pro- and anti-saccade task. This task requires

participants to generate anti-saccades (voluntary saccade away from salient target) or pro-saccades (automatic saccade toward target) depending upon a central color instruction. This task is a sensitive marker of normal and pathological cognitive development. Adolescents with BPD generated more anticipatory saccades (saccade reaction time (SRT): <90 ms) on anti-saccade trials compared to controls, indicating dysfunction of saccadic preparatory suppression signals within the oculomotor network. Direction errors (i.e., a saccade was executed to the incorrect target stimulus), express saccades (SRT: 91-139 ms), and regular latency saccades (SRT: >140 ms) did not differ between groups, suggesting intact functioning of visually-guided oculomotor signaling in BPD patients. These results depict the same behavior recorded in adults with BPD, suggesting that inhibitory dysfunction - specifically a failure to adequately *prepare* for an inhibitory command - develops early in disease progression. This result is distinct from other psychiatric disorders characterized by impulsivity in youth (i.e., ADHD) where dysfunction is evident by increased prevalence of direction errors during the propagation of express saccades and regular latency saccades. We hypothesize that impulsivity across clinical disorders in youth may correspond to distinct impaired signaling circuits within the frontostriatal regions of the oculomotor network. These findings could help identify biomarkers of distinct impulsive behaviors observed in clinic (i.e., difficulty planning versus risk-taking behaviors) and inform early intervention strategies for at-risk youth.

Disclosures: O.G. Calancie: None. **A.C. Parr:** None. **L. Booij:** None. **D. Brien:** None. **B.C. Coe:** None. **S. Khalid-Khan:** None. **D.P. Munoz:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.11/III14

Topic: H.02. Human Cognition and Behavior

Support: NIH UG3 OD023313

Title: Early executive function: Tracking neuroanatomical development

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Abstract: Research objective and rationale: Executive functioning (EF) skills, fundamental to child development, refers to a set of neurologically-based processes responsible for coordinating

aspects of cognitive activity and behavioral/emotional regulation. Given limited data on precise neuroanatomy of EF in early childhood, this study aims to determine developmental trajectory of neural correlates with EF skills in early childhood in typically developing children.
Methods: 119 typically developing participants (70 male, 49 female), ages 30-72 months; participants divided into 4 groups (12-month age intervals; 27-32 participants in each group).
Executive Function: Parent report - assessed by the Global Executive Composite (GEC) of the Behavior Rating Inventory of Executive Functioning-Preschool version (BRIEF-P).
Imaging: Siemens 3T Tim Trio (3D T1-weighted images of brain obtained using: TR/TE/FS=14/5.9/3, 15^0 flip angle, 128x128 acquisition matrix, 1.5mm slab thickness). Scanning completed on the day of BRIEF-P report.
Image analyses - *Voxel Based Morphometry (VBM)* Each child's map non-linearly aligned to study specific template (Deoni et al., 2012) using Advanced Normalization Tools software package (Avants et al., 2008). Images then normalized to MNI space and second-group analyses applied using SPM8 with Matlab 2016b. To determine developmental gain, a BRIEF correlation matrix was created for each group and contrasted the BRIEF matrix of each older group against the younger (following 12-month age increments). All analyses were corrected for age and gender for each group and included intracranial brain volume for global normalization.
Results*:*

Developmental Gain (significantly higher brain-BRIEF correlation with age)

Age groups compared	**Brain Regions with stronger association with BRIEF in older age group**
BRIEF group 2 (38-48 mo) vs BRIEF group 1 (30-36 mo)	Left superior frontal gyrus Right temporal occipital fusiform gyrus Left occipital fusiform gyrus
BRIEF group 3 (50-60 mo) vs BRIEF group 2 (38-48 mo)	Left middle frontal gyrus Left superior temporal gyrus
BRIEF group 4 (61-72 mo) vs BRIEF group 3 (50-60 mo)	Left middle frontal gyrus

All results are at $p<.05$ and were family wise error (FWE) corrected for multiple comparisons.

Conclusions: Progression of brain-BRIEF correlation with increasing age, from multi-regional (younger) to more focused (predominantly frontal lobe in older) demonstrates a pattern to development of EF circuits in typically developing children. This is one of the few studies demonstrating the role of the developing frontal lobe in a neurotypical preschooler's use of executive function.

Disclosures: V.A. D'Sa: None. **R. Lockridge:** None. **M. Bruchhage:** None. **S. Sholds:** None. **S. Joelson:** None. **C. Loiselle:** None. **C. Casnar:** None. **R. McLean:** None. **S. Deoni:** 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.; Nestec Ltd (PI).

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.12/III15

Topic: H.02. Human Cognition and Behavior

Support: This research was funded by the Department of Kinesiology and Community Heath at the University of Illinois at Urbana-Champaign.
This research was funded by the National Dairy Council.

Title: Sub-aerobic fitness is related to the neuroelectric indices of attention in early childhood

Authors: *A. M. WALK, G. MCLOUGHLIN, C. CANNAVALE, S. IWINSKI, R. LIU, L. STEINBERG, N. KHAN
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Abstract: A substantial body of work has shown that aerobic fitness is related to the neuroelectric mechanisms that underlie attentional control in adults and preadolescent children. Specifically, higher aerobic fitness has been associated with increases in the amplitude of the P3 component of the event-related potential (ERP) waveform, and with decreases in the amplitude of the N2 component. P3 amplitude has been indicated as a marker of attentional resource allocation, whereas N2 amplitude has been indicated as an index of attentional inhibition, in the oddball task. In the present study, we investigated the relationship between fitness and the neuroelectric indices underlying attention in an early childhood population. Preschool and Kindergarten children (N = 16, 4 and 5 years old) underwent a 6-minute walking task to assess sub-aerobic fitness. During the task, children walked as quickly as they could for six minutes while wearing an accelerometer. Distance walked and the percent of time spent in moderate to vigorous physical activity during the task (%MVPA) were assessed, as well as resting heart rate pre- and post- task. On a non-consecutive testing day, participants completed an auditory oddball task during which event-related potentials were recorded at midline electrodes. Morphology of the P3 and N2 components of the ERP waveform was examined. Bivariate and partial correlation analyses indicated that the distance walked during the 6-minute walking task was positively associated with P3 and N2 amplitude for target stimuli, even after accounting for sex and age, but was not related to latency. Larger P3 amplitudes and smaller N2 amplitudes were elicited for higher fit, compared to lower fit children, suggesting that higher fit children extended more attentional control and less inhibitory control to relevant stimuli. However, higher sub-aerobic fitness was not associated with the speed of neural processing as measured by P3 and N2 latency. %MVPA was positively correlated with P3 amplitude, but this relationship did not persist after accounting for the variance due to age and sex. These data are consistent with prior work

conducted in preadolescent children and suggest that the beneficial effects of aerobic fitness are established earlier in childhood than had been previously indicated.

Disclosures: A.M. Walk: None. **G. McLoughlin:** None. **C. Cannavale:** None. **S. Iwinski:** None. **R. Liu:** None. **L. Steinberg:** None. **N. Khan:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.13/III16

Topic: H.02. Human Cognition and Behavior

Title: Visuospatial attentive capabilities and saccadic inhibitory control in children with spastic cerebral palsy

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Abstract: Cerebral palsy (CP) is a non-progressive syndrome due to a pre- or perinatal brain injury. Although CP is defined as a movement disorder, it frequently involves attentional and executive impairments, as well as specific learning disabilities. Seven children (5 males and 2 females aged 9-16 years) with spastic CP (CPC) and 13 typically developing children (TDC) (6 males and 7 females aged 9-16 years) participated in the study. Six CPC suffered from right-sided hemiplegia, one was diplegic. Participants had normal IQ and normal or corrected-to-normal visual acuity. CPC did not show visual field defects within ± 10° of visual angle, had normal verbal comprehension and were able to sit independently. Eye movements were recorded by an infrared eye-tracking system (Tobii X120, Sweden), while subjects performed a visually-guided saccade task and a Posner cueing task. A square-shaped grey placeholder was displayed in each quadrant of the visual field at 7° of eccentricity from a central cross, on a black background of a pc screen placed at 80 cm in front of the subject. Participants had to make a saccade as fast as possible to a green target occurring inside one of the placeholders. In the cueing task, a non-informative cue (brief place-holder flash) unpredictably occurred 150 ms before the imperative target, either at the same (valid condition) or at a different (invalid condition) location. No differences in latency and amplitude were found between visually-guided saccades of both groups. By contrast, CPC had a great difficulty to suppress saccades towards task-irrelevant targets both during fixation and in the cuing task. Thus, the expectancy of a relevant target during central fixation elicited in 4 CPC saccades towards a place-holder in 20-60% of the trials (<15% in TDC). Furthermore, while TDC made inappropriate saccades to the

cue in only 0-30% of the trials, 5 of 6 CPC did so in a much larger percentage of trials (up to 89%), with a remarkable preponderance for a specific quadrant or hemifield. Interestingly, we found no relationship between the hemifield of prevalent saccadic intrusions and the affected limbs by CP. In addition, in CPC we observed a significant correlation between the mean latency of visually-guided saccades and the percentage of trials in which saccades were erroneously made to the cue. Finally, by taking into account only the correct trials in the Posner task, in both groups saccade latencies were faster in the valid than in the invalid condition. This study shows that in CP, even in presence of a mild symptomatology, prefrontal inhibitory executive control is frequently impaired, in the absence of deficits in the low-level visuospatial attentive capabilities.

Disclosures: L. Falciati: None. **J. Galli:** None. **S. Micheletti:** None. **L. Turetti:** None. **M. Balconi:** None. **E. Fazzi:** None. **C. Maioli:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.14/III17

Topic: H.02. Human Cognition and Behavior

Support: CONACYT 238313
CONACYT 221092
PROMEP NPTC 236855

Title: General anesthesia effects on preschoolers' cognitive flexibility and geometric language processing

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Abstract: Since the 2016 FDA's warning on the negative effects of the use of general anesthetics over the children's brain development, a global effort has been made to investigate the possible effects of these drugs on different cognitive domains. It is known that brain development and cognitive domains has sensitive periods that can be affected by drug exposure. Executive function refers to abilities that facilitate the formulation of goals, planning and organization of thoughts and actions, regulated by the prefrontal cortex. The slow development of this area makes it more sensitive to external conditions, either positive (e.g. early stimulation) or negative (e.g. toxins) at later stages. Here, we evaluated the effect of general anesthesia in the cognitive functioning of Mexican preschoolers exposed whether a single procedure or multiple anesthetic procedures. To do so, we applied a standardized neuropsychological battery (BANPE) and an eye-tracking language processing protocol before and after the exposure to anesthetics. Until

now, we have encountered that children exposed to anesthesia exhibit changes in overall performance of cognitive tasks demanding executive functions. Changes seem to be more pronounced in subtests involving cognitive flexibility. Moreover, exposed children appear to take longer times to see a figure after a verbal prompt. Based on these preliminary results, we believe that children at ages older than 3 years may also be considered vulnerable to general anesthetics since executive functions are still under development.

Disclosures: J.P. Trillo: None. **I. Vargas De La Cruz:** None. **Y. Ruvalcaba-Delgadillo:** None. **F. Jauregui-Huerta:** None.

Poster

251. Human Cognition and Executive Function: Development

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 251.15/III18

Topic: H.02. Human Cognition and Behavior

Title: How interindividual differences in IPS sulcal morphology shape number estimation fluency in children

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Abstract: Functional brain imaging studies - including position emission tomography (Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Pesenti, Thioux, Seron, & De Volder, 2000), functional magnetic resonance imaging (Bugden, Price, McLean, & Ansari, 2012; Dehaene, Piazza, Pinel, & Cohen, 2003; Holloway & Ansari, 2010) and event-related potential (Szűcs, Nobes, Devine, Gabriel, & Gebuis, 2013) studies in normal and pathological conditions - have provided evidence that the intra-parietal sulcus (IPS) plays a critical role in complex mathematical competences . Whilst most research has focused on which brain regions support numerical processing. The aim of the present study was to investigate the inverse issue, whether individual differences in neuroanatomy may have an influence on numerical abilities. To evaluate such early cerebral constraints on mathematical achievements it is important to examine neuroanatomical characteristics robust to neuroplastic effects, not affected by brain maturation nor learning. Sulcal morphology is a good candidate as it is determined *in utero* (; Mangin, Jouvent, & Cachia, 2010) and not affected by brain maturation and learning (Cachia et al., 2016; Tissier et al., 2018). Using such an approach, we have recently shown that early brain development contribute to cognitive efficiency in children, including inhibitory control (Borst et al., 2014; Cachia et al., 2016; Tissier et al., 2018) and reading abilities (Borst et al., 2016; Cachia, Roell et al., 2017). In the current study we investigated whether difference in the IPS

morphology may explain part of the variability observed in mathematical abilities in children. Fifty nine right-handed typically developing children (mean age=9.89 ± 0.5 years; 34 females) were recruited from a public school in Caen (France). Analysis of the IPS sulcal morphology was performed using BrainVISA 4.2 software (http://brainvisa.info/). Linear models, with sex and age as covariates, revealed that the sulcal pattern of the IPS in both hemispheres predicted number estimation efficiency. In particular, participants with perpendicular branches segmenting the IPS required more time to perform a numerical estimation than participants without perpendicular segmenting branches ($p<0.05$). Interestingly, we found a cumulative effect, i.e. the greater the number of perpendicular branches segmenting the IPS in both hemispheres the longer the participant's response times. Of note, we found no effect of IPS sulcal pattern on a simple visual recognition task. Our findings provide the first evidence that interindividual differences in mathematical abilities in children partly trace back to prenatal processes.

Disclosures: M. Roell: None. **A. Viarouge:** None. **K. Mevel:** None. **L. Delalande:** None. **M. Moyon:** None. **O. Houdé:** None. **G. Borst:** None. **A. Cachia:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.01/III19

Topic: H.03. Schizophrenia

Support: The NeuroTime Erasmus+ Programme of the EU 2015-2020
Inserm 2013-
The Université de Strasbourg 2013-

Title: The psychotomimetic ketamine abolishes thalamocortical spindle-like oscillations

Authors: *D. PINAULT[1], A. MAHDAVI[1,2], Y. QIN[1,3], M. BERTSCHY[1], D. CORNEC[1], C. N. LEVELT[3], S. ROTTER[2]
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Abstract: In schizophrenia, sleep disturbances are observed, and cortical EEG investigations reveal a deficit in sleep-related, thalamocortical (TC) spindle (sigma-frequency: 10-16Hz) oscillations. The underlying neural mechanisms are unknown. The thalamus is a key structure for attention-related sensorimotor and cognitive integration processes and for the generation of TC spindle oscillations, which would play a role in plasticity, learning, and memory. In the GABAergic thalamic reticular nucleus (TRN) neurons, NMDA receptors are essential in the generation of spindle rhythmic burst firing, which cyclically hyperpolarizes the postsynaptic TC

neurons through the activation of GABA receptors. OBJECTIVE: We hypothesized that the deficit in sleep spindles recorded in schizophrenia involves a reduced function of NMDA receptors in TC-TRN systems. METHODS: Multisite electrophysiological cell-to-network recordings were used to investigate the psychotogenic effects of a single administration, at a psychosis-relevant dose (2.5 mg/kg), of the NMDA receptor antagonist ketamine in the somatosensory TC system of pentobarbital-sedated, adult male rats. RESULTS: Under the control condition, spontaneously-occurring sigma-frequency oscillations were simultaneously recorded in the cortical EEG, the extracellular field potential of the somatosensory thalamus, and in juxtacellularly recorded TRN cells (N=16). They all rhythmically exhibited, at the sigma-frequency, robust high-frequency (300-500 AP/s) bursts of action potentials. Remarkably, in all experiments (N=16), ketamine consistently (relative to vehicle condition) abolished TC network spindle-like oscillations and switched the firing pattern of TRN cells from burst mode to tonic mode. These ketamine effects were accompanied by a significant increase in the power of ongoing TC gamma-frequency (30-80 Hz) oscillations. The cholinesterase inhibitor physostigmine (0.5 mg/kg) abolished TC spindle-like oscillations and, simultaneously, decreased the power of gamma oscillations. CONCLUSION: The present original findings support the hypothesis that the schizophrenia-related deficit in sleep spindles involves NMDA receptor hypofunction at least in TC-TRN systems.

Disclosures: D. Pinault: None. **A. Mahdavi:** None. **Y. Qin:** None. **M. Bertschy:** None. **D. Cornec:** None. **C.N. Levelt:** None. **S. Rotter:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.02/III20

Topic: H.03. Schizophrenia

Support: BBHI-COBRE 12-100899-HSC

Title: Exposure to phencyclidine alters the relationship between functional network connectivity, spatial behavior performance, and mRNA expression

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Abstract: Chronic administration of phencyclidine (PCP) generates neurobiological and behavioral changes that mimic symptoms and micro-levels changes found in schizophrenia (sz).

PCP impairs spatial learning and memory performance and flexibility of learning in addition to decreasing mRNA expression of markers including parvalbumin, NR2B, and $GAD_{65/67}$. The neuropathology responsible for the onset of sz is still unknown. Thus, establishing valid animals models plays a vital role in characterizing the processes involved. A growing interest in quantifying functional network connectivity (FNC) has yielded clinical studies, which have identified abnormal activation in sz patients. The current study aims to evaluate the effects of chronic PCP exposure on resting state FNC in the rat.
Adult male rats were pre-trained in the Morris Water Task (MWT) prior to a 4-week injection regimen. Rats received 14 intraperitoneal injections of either PCP (2.58 mg/kg) or 0.9% saline solution. Rats were anesthetized 72-hrs after their final injection & imaged in a 4.7T Bruker Biospin MRI scanner. Resting state fMRI BOLD data were collected after which rats were retested in the MWT to investigate long-term spatial memory and behavioral flexibility. Tissue punches from the medial and ventral frontal cortex, and parietal cortex were collected following the MWT retest. RT-PCRs were performed in order to examine gene expression for parvalbumin, calbindin, GAD67, ErbB4, NR2A, and NR2B. Group independent component analysis implemented in Group ICA of fMRI Toolbox (GIFT) was used to identify resting state networks. A total of 21 non-artifactual components were retained and consisted of 10 cortical, 4 hippocampal, 1 thalamic, 3 striatal, 1 cerebellar, and 2 midbrain components. Initially, PCP exposed animals displayed increased FNC in striatal-cortical and cortical-cortical correlations. After the 1 week wash out period, PCP exposed animals displayed increased negative FNC in striatal-striatal, thalamic-hippocampal, striatal-hippocampal, and cortical-midbrain correlations. Performance during the MWT retesting phase indicated that PCP exposure induced a long-term spatial memory deficit but did not impair subsequent spatial learning. RT-PCR analysis determined that rats exposed to PCP show decreased expression for GAD67 in the ventral frontal cortex and increased calbindin expression in the medial frontal cortex. These results indicate that sub-chronic PCP exposure causes widespread alterations in FNC and mRNA expression in subcortical and cortical regions implicated in sz.

Disclosures: C.M. Magcalas: None. **N. Perrone-Bizzozero:** None. **V. Calhoun:** None. **J. Bustillo:** None. **D.A. Hamilton:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.03/III21

Topic: H.03. Schizophrenia

Support: Work supported by Fundação para a Ciência e a Tecnologia (PD/BD/128091/2016)
GAPIC project No 20180014

SynaNet which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 692340 LISBOA-01-0145-FEDER-007391, project cofunded by FEDER, through POR Lisboa 2020 - Programa Operacional Regional de Lisboa, PORTUGAL 2020, and Fundação para a Ciência e a Tecnologia

Title: Interplay between the loss of BDNF signalling and cognitive dysfunction in the subchronic phencyclidine model of schizophrenia

Authors: *S. R. TANQUEIRO[1,2], G. ALMEIDA-SILVA[2,1], F. M. MOURO[1,2], N. DAWSON[3], M. J. DIÓGENES[1,2], A. M. SEBASTIÃO[1,2]
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Abstract: Patients with schizophrenia, despite positive and negative symptoms, suffer from untreated cognitive deficits that have an enormous impact on their daily lives. Alterations in BDNF levels, which has a crucial role in synaptic function and plasticity through the activation of TrkB-full length (FL) receptor, may have a role in the molecular mechanisms underlying cognitive dysfunction in schizophrenia. Thus, this work aimed to characterize BDNF signalling in the subchronic phencyclidine (PCP) mouse model of schizophrenia. After subchronic treatment with PCP·HCl (10 mg/kg, i.p.) or vehicle, male C57BL/6 mice (10 week old) were subjected to behavioural tests (Open Field, Novel Object Recognition and Y-Maze Spontaneous Alternation tests) to confirm cognitive dysfunction. After behaviour, animals were sacrificed and samples from different brain areas were collected for molecular analysis.We observed impaired recognition memory ($p^{***}<0.001$, n=6-7, student's t-test) and decreased spontaneous alternation behaviour ($p^{*}<0.5$, n=5-7, student's t-test) in PCP-treated mice. Importantly, we found decreased protein levels of TrkB-FL ($p^{**}<0.01$, n=8, student's t-test) and increased truncated TrkB, a negative modulator of TrkB-FL ($p^{***}<0.001$, n=8, student's t-test), in the prefrontal cortex (PFC) of PCP-treated mice. Moreover, we found a tendency for increased levels of truncated TrkB in the hippocampus of PCP-treated mice. Overall, data support BDNF signalling dysfunction in the PFC and hippocampus of the subchronic PCP model, brain areas involved in memory processes and known to be affected in schizophrenic patients. These results encouraged us to continue scrutinizing BDNF signalling in this pathology to evaluate whether its modulation could be part of a promising strategy in schizophrenia treatment.

Disclosures: S.R. Tanqueiro: None. **G. Almeida-Silva:** None. **F.M. Mouro:** None. **N. Dawson:** None. **M.J. Diógenes:** None. **A.M. Sebastião:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.04/III22

Topic: H.03. Schizophrenia

Title: Auditory steady state response as a translational EEG biomarker in the PCP rat model of schizophrenia

Authors: *C. DRIEU LA ROCHELLE[1], E. CAYRE[2], G. VIARDOT[3], B. RION[2], A.-S. DENIBAUD[2], B. MÉOT[2], H. WING YOUNG[2], S. LOIODICE[2]
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Abstract: Successful drug discovery for schizophrenia relies on the development of more predictive animal models to better assess the efficacy at the preclinical stage. Clinical data have shown that the Auditory Steady-State Response (ASSR) which relies on the integrity of cortical pathways, was usually impaired in schizophrenia. Furthermore, preclinical studies suggested that ASSR could be also assessed in the rat. Therefore, we sought to investigate whether ASSR could be used as an efficacy biomarker in a rat model of schizophrenia using telemetry recording of EEG.
A cohort of 24 rats was operated for implantation of electrodes at the surface of the primary motor cortex (leads fixed on the skull in contact with the dura) to allow telemetry recording of EEG. The body of the telemetry device was inserted subcutaneously in the flank. Animals were sub-chronically treated with phencyclidine (PCP) (5 mg/kg, ip, bid) or its vehicle during 7 days. After a wash-out period of 7 days, animals received a single injection of clozapine (0.3 mg/kg, sc) or its vehicle before undergoing a 1.5h sessions of auditory stimuli (25 clicks at 50 Hz) with EEG recording (analysis on [45-55Hz] band) to investigate ASSR. Memory performances were also assessed on the following days using the novel object recognition (NOR).
The data revealed a significant impairment of the ASSR with a 208% deficit in evoked power and a 300% deficit in phase locking factor in PCP-treated rats compared to vehicle. A 22% deficit was also observed in the NOR in PCP-treated rats. Interestingly, clozapine was able to reverse the deficit observed in the NOR but not the impairment of ASSR.
The discrepancy in the effect of clozapine in ASSR and NOR should be further investigated. However, our study suggests that the sub-chronic treatment with PCP impaired the integrity of cortical pathways and a deficit in their capacity to produce a synchronous activity. This highlights the value of ASSR as a translational efficacy biomarker during drug discovery.

Disclosures: C. Drieu La Rochelle: None. **E. Cayre:** None. **G. Viardot:** None. **B. Rion:** None. **A. Denibaud:** None. **B. Méot:** None. **H. Wing Young:** None. **S. Loiodice:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.05/III23

Topic: H.03. Schizophrenia

Support: JSPS KAKENHI Grant Numbers 26860942
JSPS KAKENHI Grant Numbers 17K16397

Title: Abnormal neural activation patterns underlying working memory impairment in chronic phencyclidine-treated mice

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Abstract: Working memory impairment is a hallmark feature of schizophrenia and is thought be caused by dysfunctions in the prefrontal cortex (PFC) and associated brain regions.However, the neural circuit anomalies underlying this impairment are poorly understood. The aim of this study is to assess working memoryperformance in the chronic phencyclidine (PCP) mouse model of schizophrenia, and to identify the neural substrates of working memory. To address this issue, we conducted the following experiments for mice afterwithdrawal from chronic administration (14 days) of either saline or PCP (10 mg/kg): (1) a discrete paired-trial variable-delay task in T-maze to assess working memory, and (2) brain-wide c-Fos mapping to identify activated brain regions relevant to this task performance either 90 min or 0 min after the completion of the task, with each time point examined under working memory effort and basal conditions. Correct responses in the test phase of the task were significantly reducedacross delays (5, 15, and 30 s)in chronic PCP-treated mice compared with chronic saline-treated controls, suggesting delay-independent impairments in working memory in the PCP group. In layer 2-3 of the prelimbic cortex, the number of working memory effort-elicited c-Fos+ cells was significantly higher in the chronic PCP group than in the chronic saline group. The main effect of working memory effort relative to basal conditions was to induce significantly increased c-Fos+ cells in the other layers of prelimbic cortex and the anterior cingulate and infralimbic cortex regardless of the different chronic regimens. Conversely, this working memory effort had a negative effect (fewer c-Fos+ cells) in the ventral hippocampus. These results shed light on some putative neural networks relevant to working memory impairments in mice chronically treated with PCP, and emphasize the importance of the layer 2-3 of the prelimbic cortex of the PFC.

Disclosures: Y. Arime: None. **K. Akiyama:** F. Consulting Fees (e.g., advisory boards); Taisho Toyama Pharmaceutical Co., Ltd..

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.06/III24

Topic: H.03. Schizophrenia

Support: NIH Grant P50MH094268

Title: Adolescent exposure to a cannabinoid receptor agonist in mice reduces psychomotor responses and enhances working memory in adulthood

Authors: *M. KOH, A. SHERWOOD, P. AHRENS, R. W. MCMAHAN, M. GALLAGHER
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Abstract: Synthetic cannabinoids such as Spice and K2 have become increasingly popular among teenagers, with increase psychotic symptoms and cognitive dysfunction thought to be among some of the deleterious long-term side effects. To test that prevailing thought, we exposed mice subchronically to a synthetic cannabinoid during adolescence and tested them for psychosis-like behavior and cognitive function during adulthood. Starting at 40 days old, male C57/BL6 mice were injected daily with a synthetic cannabinoid receptor agonist, WIN55,212-2 (2 mg/kg, IP), or vehicle for three weeks, and behaviorally tested drug-free after 70 days old. When challenged with amphetamine (2 mg/kg) to assess dopamine-mediated responses, mice with a history of synthetic cannabinoid exposure showed reduced locomotor activity compared to vehicle controls, and normal responses to the reinforcing property of the dopamine agonist as measured by conditioned place preference. Our data therefore indicate that adolescent cannabinoid exposure did not lead to hyperdopaminergic function that underlies psychotic-like symptoms. The same mice were also tested for their cognitive function with a delayed matching-to-sample task that assessed working memory. The mice exposed to the cannabinoid agonist performed surprisingly better than control mice, showing higher overall correct responses on a range of short retention delays. Together, these unexpected outcomes suggest that adolescent exposure to synthetic cannabinoids by itself is not sufficient to produce long term cognitive deficit or increase psychosis-like behavior; whether genetic makeups such as those that increased the risk for schizophrenia interact differently with cannabinoid exposure is currently under investigation.

Disclosures: M. Koh: None. **A. Sherwood:** None. **P. Ahrens:** None. **R.W. McMahan:** None. **M. Gallagher:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.07/III25

Topic: H.03. Schizophrenia

Title: Efficacy of antipsychotic treatments in rodent models of social recognition and social interaction

Authors: *Q. CHANG, S. DAVIS, M. LANG, T. HANANIA
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Abstract: Social withdrawal and impaired cognitive function have been associated with the negative symptoms of schizophrenia. Individuals with schizophrenia and depression show evident deficits in social interaction and social recognition. The social recognition or social memory task is an ethologically relevant learning and memory test used in lab animals, especial in rodents. This test is mostly based on the rat's olfactory discriminative capacities and it takes advantage of animal's innate desire to investigate its conspecifics. In rodents, social recognition has been used to evaluate the efficacy of antidepressants and antipsychotics. Rats treated with the NMDA receptor antagonist Phencyclidine (PCP) showed deficits in social interaction and social recognition. In the reciprocal social interaction paradigm, atypical antipsychotic treatments showed efficacy in reversing PCP-induced deficits and increased interaction time following acute administration. In the social recognition test in which rats were given 4 trials of exploration of a familiar stimulant rat and a 5^{th} trial where they are exposed to a novel stimulant rat, PCP-treated rats showed no recognition of the novel rat and their interaction time was significantly reduced compared to saline-treated rats. Treatment with either clozapine or olanzapine significantly reversed PCP-induced deficit of recognition memory. These results confirm that assays can serve preclinical models for the negative symptoms of schizophrenia and can be used to screen novel therapeutics.

Disclosures: Q. Chang: None. **S. Davis:** None. **M. Lang:** None. **T. Hanania:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.08/III26

Topic: H.03. Schizophrenia

Support: RGC/ECS 27103715
NFSC 31571031
HMRF 03143096
RGC/GRF 17128816

Title: Effects of environmental enrichment in a mouse NMDA receptor hypofunction model

Authors: *C. S. LAI[1,2], Y. HUANG[1], X. LI[1]
[1]Sch. of Biomed. Sci., [2]State Key Lab. of Brain and Cognitive Sci., The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Schizophrenia is a neurodevelopmental psychiatric disorder with an age of onset in late adolescence and early adulthood. Although the precise pathogenesis and etiologies of the disease are remaining elusive, hypofunction of N-methyl-D-aspartate receptor (NMDAR) has been proposed to underlie the emergence of symptoms. NMDAR antagonists, such as MK-801, phencyclidine and ketamine, have been shown not only to induce schizophrenia-like symptoms in healthy subjects. These antagonists can also exacerbate existing psychosis in schizophrenia patients, suggesting they can be used as appropriate agents to study schizophrenic symptoms. NMDAR antagonists may produce aberrant behavioral phenotypes via several mechanisms, including disinhibition of glutamate release, disruption of synaptic plasticity, and disturbance of functional connectivity. Structural imaging studies show a decrease of dendritic spine density on pyramidal neurons (PNs), a structure for receiving the majority of excitatory synaptic input, in the prefrontal cortex of schizophrenia patients. Dendritic spines undergo activity-dependent morphological changes over the lifetime and subtle changes in dendritic spines may have marked effects on synaptic function and connectivity in neuronal circuits and even cognition and behavior. The exposure to enriched environments (EE) during early life influences brain development and leads to altered behavior. EE paradigm through increased stimulation induces experience dependent-plasticity, which increase the number of dendritic spines, the size of synapses on PNs, and enhance sensory and cognitive function. In animal studies, EE has been demonstrated to reverse key schizophrenia-like behaviors such as hyperactivity and sensorimotor gating deficits. However, the effect of EE on dendritic spine plasticity in animal schizophrenic models is still unclear. In this study, we aim to use *in vivo* two-photon transcranial imaging of adolescence fluorescent mice to investigate the structural plasticity of PNs' dendritic spine in a chronic MK-801-treated schizophrenic mouse model. We found that repeated exposure to the NMDA receptor antagonist MK-801 induced schizophrenia-like behaviors and deficits of dendritic spine plasticity; while chronic treatment of EE ameliorated the synaptic and behavioral deficits. Further studies will focus on better understanding environmental modulation and NMDAR-mediated glutamatergic system interactions on synaptic and behavioral levels through manipulation of neuronal activity.

Disclosures: C.S. Lai: None. **Y. Huang:** None. **X. Li:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.09/III27

Topic: H.03. Schizophrenia

Title: Predictive validity of antipsychotics using NMDA receptor antagonist induced behavioral and neurophysiological abnormalities

Authors: M. FOWLER, A. SUGIYAMA, K. TAMAKI, J. HILL, S. HONDA, *M. ADACHI
CNS, Astellas Res. Inst. of America, San Diego, CA

Abstract: Schizophrenia is a severe mental disorder affecting ~1% of the population that is characterized by hallucinations, delusions, negative symptoms (emotional disturbances), and cognitive dysfunction. While the antipsychotics currently on the market show some clinical efficacy for treating the psychosis associated with schizophrenia, they show only marginal efficacy in treating negative symptoms and cognitive impairments. In addition, these drugs also come with many unwelcome side effects, such as tardive dyskinesia and metabolic disturbances, which limits their use for many patients. We seek to identify novel therapeutics for treating schizophrenia that are both more effective and have less side effects when compared to existing drugs on the market.

Here we examine the efficacy of the atypical antipsychotic, olanzapine, in behavioral tests for cognitive and sensorimotor functions using a classical rodent model of schizophrenia that is induced by a blockade of NMDA receptor with a psychostimulant, MK-801. Acute administration of olanzapine (1 mg/kg) blocked the hyper locomotor effects of MK-801. However, while olanzapine ameliorated the MK-801 induced deficit in the y-maze spontaneous alternation task, it failed to mitigate the MK-801 induced deficit in the novel objection recognition task. Furthermore, olanzapine exhibited no effect on MK-801 induced impairment in prepulse inhibition of the startle reflex. This suggests that olanzapine has limited therapeutic efficacy for treating cognitive dysfunction and aberrant sensorimotor gating processes. We continue to build data sets for a variety of antipsychotics in the above behavioral paradigms. In addition, we investigated the antipsychotics' efficacy in neurophysiological parameters by measuring electroencephalogram (EEG) responses as these can serve as biomarkers and are frequently utilized to assess a proof of pharmacology in clinical trials. The results of these studies will be used as a benchmark for identifying novel drugs that are more effective in treating schizophrenia than the drugs currently available.

Disclosures: M. Fowler: A. Employment/Salary (full or part-time):; Astellas Research Inst of America. **A. Sugiyama:** A. Employment/Salary (full or part-time):; Astellas Research Inst of America. **K. Tamaki:** A. Employment/Salary (full or part-time):; Astellas Research Inst of

America. **J. Hill:** A. Employment/Salary (full or part-time):; Astellas Research Inst of America. **S. Honda:** A. Employment/Salary (full or part-time):; Astellas Research Inst of America. **M. Adachi:** A. Employment/Salary (full or part-time):; Astellas Research Institute of America.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.10/III28

Topic: H.03. Schizophrenia

Title: The NMDAr positive allosteric modulator CAD-8688 reverses mismatch negativity impairments in the rat sub-chronic PCP model of schizophrenia

Authors: S. KANTOR[1], S. C. LEISER[2], D. ANDERSON[3], R. VOLKMANN[3], *N. UPTON[1], T. PISER[3]
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Abstract: Background: Converging lines of clinical evidence suggest that hypofunction of the glutamatergic N-methyl-D-aspartate receptor (NMDAr) is implicated in the pathogenesis of schizophrenia. NMDAr antagonists such as phencyclidine (PCP) exacerbate psychotic symptoms in schizophrenic patients, and mimic schizophrenia in healthy volunteers. Auditory novelty-detection is an NMDAr-dependent process that is associated with an auditory-evoked potential (AEP), the mismatch negativity (MMN). MMN is reduced in schizophrenic patients and may represent a biomarker of NMDAr hypofunction in schizophrenia. The aim of this study was to determine whether sub-chronic PCP treatment impairs MMN in rodents and, if so, whether these deficits can be reversed by an NMDAr positive allosteric modulator (PAM: CAD-8688).
Methods: 28 adult (200-250 g) male LH rats (Envigo, UK) were surgically implanted with telemetry transmitters (F40-EET; DSI, USA) for fronto-parietal EEG and EMG recordings. MMN was elicited in awake, freely-behaving rats by an auditory oddball paradigm in which a deviant ('oddball'; DEV) tone occurred randomly within a sequence of identical tones ('standards', STD). AEP components were measured in difference (DIFF) waves that were generated by subtracting STD waves from DEV waves. After recording baseline MMN, rats were treated with PCP (5 mg/kg, i.p.) twice daily for seven days. MMN was tested after the first and last treatment with PCP, as well as after a seven days washout period. Rats were then treated acutely with vehicle (5 ml/kg, p.o.; n=12) or CAD-8688 (1 mg/kg, p.o.; n=12).
Results: We found that, compared to baseline, sub-chronic treatment with PCP significantly reduced AEP amplitude in DIFF waves, thereby demonstrating impaired MMN in rats. Specifically, we found that MMN was already disrupted after the first PCP treatment and it was abnormal at the end of the treatment period. Furthermore, the deficits in MMN induced by PCP

were maintained for at least seven days after the last treatment. Treatment with CAD-8688 (1 mg/kg, p.o.), but not with vehicle, fully reversed the MMN deficits in PCP-treated rats. **Conclusion:** Our data demonstrate that schizophrenia-like MMN deficits are induced in the rat sub-chronic PCP model with deficits lasting after drug washout. Therefore, this model provides a powerful translational tool for testing novel therapeutics targeting schizophrenia. Reversal of sub-chronic PCP-induced MMN deficits in rats by the potent, drug-like NMDAr PAM, CAD-8688, suggests a therapeutic potential to restore early auditory processing and cognitive function impaired by putative NMDAr hypofunction in patients with schizophrenia.

Disclosures: S. Kantor: A. Employment/Salary (full or part-time):; TRANSPHARMATION LTD. **S.C. Leiser:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **D. Anderson:** A. Employment/Salary (full or part-time):; Cadent Ther. Inc. **R. Volkmann:** A. Employment/Salary (full or part-time):; Cadent Ther. Inc. **N. Upton:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **T. Piser:** A. Employment/Salary (full or part-time):; Cadent Ther. Inc..

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.11/III29

Topic: H.03. Schizophrenia

Support: NIH 111R21MH111609
NIH R01MH085666
NARSAD Independent Award 2015 to Wen-Jun Gao
Helen S. Vernik Schizophrenia Pilot Research Project Grant, 2017

Title: Leveraging prefrontal parvalbumin interneurons to restore cognitive function in schizophrenia

Authors: *L. CHAMBERLIN[1], B. R. FERGUSON[2], E. P. MCEACHERN[1], Y. MOHABBAT[3], W.-J. GAO[1]
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Abstract: Schizophrenia is a severe psychiatric illness most known for its psychotic symptoms, yet the associated cognitive deficits are more predictive of functional outcome and less responsive to treatment. The prefrontal cortex of schizophrenia patients contains fewer parvalbumin (PV)-expressing interneurons; such a loss of inhibitory GABAergic cells could disrupt the balance between excitation and inhibition in ways that affect cognition. This idea is supported by the role of PV cells in gamma oscillations, which increase in amplitude during

working memory tasks in healthy people, but not in people with schizophrenia. Here, we examine the potential of prefrontal PV cells as a target for treating cognitive deficits. We administer an NMDA antagonist (MK801) to adolescent rats, which has been shown to reduce PV cells and recapitulate many of the endophenotypes seen in schizophrenia. Our electrophysiological data indicates an altered prefrontal excitation/inhibition balance in MK801-treated rats, which is brought back to control levels by activation with CNO of a novel PV-promoter driven excitatory hM3Dq DREADD in females, but not males. These changes are reflected in performance on a working memory task, wherein female rats treated with MK801 perform worse than saline-treated females at the shortest delay interval, and improve performance if transfected with a virus carrying the PV-hM3Dq-DREADD and administered CNO, suggesting that upregulating the activity of remaining PV cells may be sufficient to rescue cognition. To further characterize these sex differences, we compare PV cell counts in MK801- and saline-treated male and female rats, and compare PV expression with task performance.

Disclosures: L. Chamberlin: None. **B.R. Ferguson:** None. **E.P. McEachern:** None. **Y. Mohabbat:** None. **W. Gao:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.12/III30

Topic: H.03. Schizophrenia

Support: Sumitomo Dainippon Pharma Co., Ltd, Japan

Title: TPA-023 and pregnenolone sulfate attenuate subchronic phencyclidine-induced declarative and executive functioning deficits via GABAAR mechanism: Possible therapeutic target for cognitive deficit in schizophrenia

Authors: *L. RAJAGOPAL[1], M. HUANG[2], H. Y. MELTZER[3]
[1]Psychiatry and Behavioral Sci., [2]Psychiatry and Behavior Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [3]Northwestern Univ. Sch. of Med., Chicago, IL

Abstract: GABAergic drugs contribute to the treatment of anxiety, depression, bipolar disorder, and have potential to treat the cognitive impairment associated with schizophrenia (CIAS), psychosis, and negative symptoms of schizophrenia. There are conflicting clinical data regarding the efficacy of TPA-023/MK-0777(7-(1,1-Dimethylethyl)-6-(2-ethyl-2H-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b] pyridazine), a benzodiazepine-like $GABA_A$ $\alpha_{2,3}$ subtype-selective $GABA_A$ partial agonist and $\alpha_{1/5}$ antagonist, and the neurosteroid, pregnenolone sulfate (PregS), a $GABA_A$ negative modulator and an N-methyl-D-aspartate receptor (NMDAR) positive modulator, to improve CIAS. The goals of this study were to

investigate the effects of TPA-023 and PregS in mice, after acute or subchronic (sc) treatment with phencyclidine (PCP), followed by washout, on episodic memory, executive functioning, negative symptoms, and psychosis. We also investigated the effect of TPA-023 in combination with lurasidone (Lur), an atypical antipsychotic drugs (AAPD) or PCP, on neurotransmitter efflux (NT) in medial prefrontal cortex (mPFC) and dorsal striatum (dSTR) to identify NTs involved in the action of TPA023. We assessed the effects of TPA-023 on NOR, RL, SI, and LMA in scPCP-treated mice, and on cortical and striatal NT efflux using in vivo microdialysis in awake freely moving mice. Acute TPA-023 and PregS significantly reversed sc PCP-induced NOR, RL, and SI deficits. Co-administration of sub-effective dose (SEDs) of TPA-023 or PregS with Lur, reversed scPCP-induced NOR and RL deficits. Further, scTPA-023 significantly *prevented* scPCP-induced NOR deficit for *five* weeks. Also, TPA-023 given for 7 days following scPCP withdrawal reversed NOR deficit for one week. Co-administration of SEDs of TPA-023 or PregS+Lur also rescued scPCP-induced SI deficit. However, neither TPA-023 nor PregS blunted acute PCP-induced hyperactivity. Systemic TPA-023 in mPFC and dSTR significantly blocked Lur-induced increases in cortical acetylcholine (ACh), dopamine (DA), and glutamate (Glu) and had minimal effect on basal release of these NTs. TPA-023 significantly inhibited PCP-induced cortical and striatal DA, 5-HT, NE, and Glu efflux. These and other findings suggest both TPA-023 and PregS diminish cortical activation and enhance neuroplasticity. These preclinical studies suggest both TPA-023 and PregS may be of benefit to treat some aspects of schizophrenia in patients where cortical hyperactivity is prominent. Further study is needed to determine if they may have potential for adjunctive treatment of psychosis, negative symptoms, and CIAS.

Disclosures: L. Rajagopal: None. **M. Huang:** None. **H.Y. Meltzer:** 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.; Sumitomo Dainippon Pharma Co., Ltd, Japan.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.13/III31

Topic: H.03. Schizophrenia

Title: SUVN-M8036, a differentiated serotonergic and dopaminergic modulator for the treatment of psychiatric disorders

Authors: R. KALLEPALLI, A. VUYYURU, S. YATHAVAKILLA, J. FERNANDES, J. TADIPARTHI, N. BOGARAJU, P. SINGH, A. MOHAMMED, *A. K. SHINDE, V. KAMUJU,

S. GANDIPUDI, S. PETLU, N. PRAVEENA, V. MEKALA, R. SUBRAMANIAN, R. NIROGI
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Abstract: Schizophrenia is a debilitating disorder that affects nearly 1% of the global population. For the goal of controlling symptoms, several new treatments are available for initial and maintenance therapy. However, most of the treatments cause a plethora of side effects. Thus, there is an un-met medical need for a therapy which alleviates neuropsychiatric symptoms with no or minimal side effects. SUVN-M8036 is a multimodal molecule having affinity for 5-HT/dopamine receptors. SUVN-M8036 was evaluated in open field task using MK-801 and amphetamine challenge. The pro-cognitive potential was studied using object recognition task. Antidepressant potential was evaluated using forced swim assay. SUVN-M8036 was tested in brain microdialysis for modulation of dopamine, norepinephrine in prefrontal cortex and striatum. Rota-rod and catalepsy assays were used to study the effect of SUVN-M8036 on the motor system. SUVN-M8036 reversed hyperlocomotor effects of MK-801 and amphetamine. It also blocked the amnesic effects of MK-801. Dose dependent antidepressant effects were observed in the forced swim assay. SUVN-M8036 produced significant increase in dopamine and norepinephrine levels in prefrontal cortex with non-significant effects in striatum. The efficacy doses were devoid of motor impairment i.e., a clear separation was observed between the doses which produced efficacy and side effects. SUVN-M8036, a modulator of 5-HT/dopamine systems could be a promising medication for psychiatric disorders.

Disclosures: R. Kallepalli: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Vuyyuru:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Yathavakilla:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Fernandes:** 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. Bogaraju:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Singh:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A.K. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Kamuju:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Gandipudi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Petlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Praveena:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Mekala:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Subramanian:** 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

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.14/III32

Topic: H.03. Schizophrenia

Support: NIH Grant R01MH084894
NIH Grant R01MH111940

Title: Role of 5-HT_{2A}R in the mGluR2 receptor-dependent antipsychotic-related activity of LY379268 in mice

Authors: *J. M. SAUNDERS, J. GONZALEZ-MAESO
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Abstract: The serotonin 5-HT_{2A} receptor (5-HT_{2A}R) is an important target of atypical antipsychotics, such as clozapine and risperidone, and metabotropic glutamate receptor 2 (mGluR2) agonists have been proposed as a novel class of antipsychotics. Crosstalk between mGluR2 and 5-HT_{2A}R has been shown in both heterologous systems and rodent behavior models. Previous findings suggested increased 5-HT_{2A}R and decreased mGluR2 density in postmortem frontal cortex samples of untreated schizophrenic subjects. A 5-HT_{2A}R-mGluR2 receptor heterocomplex has been proposed, and crosstalk between these receptors has been hypothesized to be a crucial element of antipsychotic effect. Use of pharmacologic agents with different targets, such as the NMDA receptor antagonist MK-801 or the dopamine transporter blocker amphetamine, can be used to determine the implications of this crosstalk for various neurotransmitter systems. We therefore used pharmacologically induced psychosis-related phenotypes in rodents to evaluate 5-HT_{2A}R-mGluR2 crosstalk by determining the ability of an mGluR2/3 agonist, LY3792698 (LY37), to suppress hyperlocomotion in the presence or absence of 5-HT_{2A}R-dependent signaling. Locomotion experiments were conducted in wild type and 5-HT_{2A}R knockout male and female littermates in a 129Sv background. Following a 90 minute habituation to an Omnitech locomotor response arena and 5 minute pretreatment with the mGlu2/3 agonist LY37 (5 mg/kg), or vehicle as a control, adult mice were treated with 0.5 mg/kg MK-801 or 6mg/kg amphetamine to induce hyperlocomotion. The locomotor response was recorded for 120 minutes using infrared beams within the chamber and data were analyzed as total horizontal activity during the testing period. It was found that LY37 pretreatment is able to prevent MK-801-induced hyperlocomotion in wild type, but not 5-HT_{2A} knockout mice. It was also found that amphetamine produces a greater degree of locomotor activity in 5-HT_{2A} receptor knockout than wild type mice and that LY37 prevents amphetamine-induced hyperlocomotion in wild type mice. The automated nature of the recording system precluded the need for blinding. These findings further confirm crosstalk between the 5-HT_{2A} and mGlu2 receptors and

demonstrate differential influence of this crosstalk on the behavioral effects of pharmacologic agents targeting different neurotransmitter systems.

Disclosures: J.M. Saunders: None. **J. Gonzalez-Maeso:** None.

Poster

252. Schizophrenia: Animal Models: Pharmacological

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 252.15/III33

Topic: H.03. Schizophrenia

Support: CIHR Grant 125984
CIHR Grant 153111

Title: Antipsychotic-like effects of the T-type calcium channel antagonist, Z944, on behaviours characteristic of a schizophrenic-like phenotype in rats

Authors: *W. N. MARKS[1], A. J. ROEBUCK[1], M. C. LIU[1], N. B. TAHIR[1], N. K. ZABDER[1], S. M. CAIN[2], T. P. SNUTCH[2], J. G. HOWLAND[1]
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Abstract: The therapeutic action of antipsychotics is thought to largely arise from their role as D2 dopamine receptor antagonists. However, a number of classes of antipsychotics also act as T-type calcium channel blockers. T-type calcium channels are heavily expressed in brain areas implicated in schizophrenia, therefore, it is possible that the therapeutic efficacy of antipsychotics may in part be associated with their activity on T-type calcium channels. Preclinical data suggests that T-type calcium channel antagonists may be effective for the treatment of the positive symptoms of schizophrenia; however, it is unknown whether these effects extend to the cognitive and social symptoms associated with the disorder. The purpose of the current study was to examine the effects of the novel and highly selective T-type calcium channel antagonist, Z944, on behaviours thought to be indicative of a schizophrenic-like phenotype in rats. We examined the effects of acute, systemic Z944 (5mg/kg; i.p.) on social aggression, MK-801-induced hyperlocomotion, and MK-801-induced impairments in a touchscreen-based paired associates learning task. Z944 significantly reduced social aggression in an open field social interaction task in male Wistar rats. Z944 also significantly reduced hyperlocomotion produced by MK-801 in male Long-Evans rats. Z944 failed to reverse the visuospatial associative memory impairments introduced by MK-801 in paired associates learning in male Long-Evans rats. These results suggest that further investigation into the regulation of T-type calcium channel activity may be useful towards developing new therapeutic

approaches for the treatment of the positive and social symptoms characteristic of disorders such as schizophrenia.

Disclosures: W.N. Marks: None. **A.J. Roebuck:** None. **M.C. Liu:** None. **N.B. Tahir:** None. **N.K. Zabder:** None. **S.M. Cain:** None. **T.P. Snutch:** None. **J.G. Howland:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.01/III34

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: JSPS KAKENHI Grant Number JP17H02088
Grant by Foundation for Promotion of Material Science and Technology of Japan

Title: Synthesis of serotonin-imprinted polymer nanoparticle as highly selective fluorescent probe for neurotransmitter-imaging

Authors: Y. KATSUMATA[1], N. OSAWA[1], R. MORI[1], *Y. YOSHIMI[2]
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Abstract: Analysis of the action of neurotransmitters in nervous system is important for elucidating the mechanism of neural network in nervous system. Then development of a probe which can track a specified neurotransmitter in real time with high selectivity has been required. Molecularly imprinted polymer (MIP), which is a molecular recognition material obtained by polymerization with a template-effect of the target molecule may be applicable for the probe. In this study, nanoparticle of MIP including fluorescent group (fMIP-NP) were developed as the probe of serotonin. The serotonin, as the template, was immobilized on glass beads by using mixed anchor of 3-aminopropyltrimethoxysilane (shorter anchor) and 3- (2-aminoethylamino) propyltrimethoxysilane (longer anchor) (1:1 in weight) with glutaraldehyde. The template-immobilized beads were fluidized in a mixed solution of a fluorescent monomer, a template-affinity monomer, and a crosslinking monomer under UV irradiation. The colloidal fMIP-NP was collected from the surface of the beads by washing with *N*,*N*-dimethylformamide at 60℃. And the dispersion medium of the colloidal fMIP-NP was replaced with 0.15 M phosphate buffer. The fluorescent intensity and the radius of the fMIP-NP was increased by addition of serotonin but was insensitive to L-tryptophan. The another fMIP-NP prepared with unmixed anchor (shorter anchor only, or longer one only) was also sensitive to serotonin and L-tryptophan. The fluorescent nanoparticle prepared without the template was insensitive to both of serotonin and tryptophan. Those results indicate that the specific interaction between the serotonin and the serotonin-imprinted cavity in the enhances the fluorescent intensity and the size of fMIP-NP. The relative change in the fluorescent intensity of the fMIP-NP is 0.13% to the

serotonin concentration of 0.25 μM which corresponds to the concentration of serotonin in the brain fluid and plasma. Thus, the serotonin secretion in nervous system can be detected by fluorescent voltage sensitive dye imaging system (e.g. MiCAM series in Brain Vision Inc.), which can detect relative change of 0.05% in fluorescent intensity.

Disclosures: Y. Katsumata: None. **N. Osawa:** None. **R. Mori:** None. **Y. Yoshimi:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.02/III35

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1U01NS090455-01
NRF 2017R1A2B2006896

Title: *In vivo* measurements of basal dopamine levels using multiple cyclic square wave voltammetry

Authors: *Y. OH[1], M. L. HEIEN[4], S. B. DE SOUZA[2], C. PARK[5], D. JANG[5], K. E. BENNET[3], K. H. LEE[1]
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Abstract: Real-time recording of basal dopamine concentrations in the brain would enhance our understanding neurotransmittion mechanisms and neuropsychiatric diseases. Conventionally, microdialysis is the most commonly used method for neurotransmitter monitoring, but weaknesses of this method are that it requires considerable sampling quantities, causes tissue damage, and has low spatiotemporal resolution. Fast-scan cyclic voltammetry has served as suitable technique for recording dopamine release in vivo because of its high spatiotemporal resolutiona and minimal tissue damege. However, fast-scan cyclic voltammetry is not able to measure basal dopamine concentrations because the technique is based on a differential method which can observe phasic (rapid) changes. Here, we describe the application of a new type of voltammetric technique, multiple cyclic square wave voltammetry (M-CSWV), for a robust analytical quantification of basal dopamine concentrations in vivo with high temporal resolution (every 10 seconds). We show that, M-CSWV enriches the electrochemical information which leads to higher sensitivity (Limit of detection, 0.17nM) and selectivity (against ascorbic, and 3,4-dihydroxyphenylacetic acid and pH changes) by generating a two dimentional voltammogram. We also show robust basal dopamine quantification using two dimensional principle component analysis. We report that basal dopamine concentration in the anethetized rat striatum was 122.1±0.14 nM (n = 7 rats, ± SEM). Pharmacological manipulation confirmed the technique's

selectivity for in vivo dopamine detection. Then, we applied our technique to measure basal dopamine level in the pig as a model of deep brain stimulation study. Our novel technique offers the potential to quantify basal dopamine level robustly in the brain which would be a critical clue for understanding neuropsychiatric dieases.

Acknowledgement
This research was supported by a NIH 1U01NS090455-01 award and the National Research Foundation of Korea NRF-2017R1A2B2006896.

Disclosures: Y. Oh: None. **M.L. Heien:** None. **S.B. De Souza:** None. **C. Park:** None. **D. Jang:** None. **K.E. Bennet:** None. **K.H. Lee:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.03/III36

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: FCT Fellowship PD/BD/114278/2016
FCT Fellowship SFRH/BPD/81627/2011
Mind-Brain College of University of Lisbon
SynaNet – Twinning Action funded by H2020 (GA-692340)
Aarhus University Research Foundation
LISBOA-01-0145-FEDER-007391, project cofunded by FEDER, through POR Lisboa 2020 - Programa Operacional Regional de Lisboa, PORTUGAL 2020, and Fundação para a Ciência e a Tecnologia

Title: Organic and inorganic-based microreactors as a therapeutic approach against excitotoxicity

Authors: *A. ARMADA-MOREIRA[1,2,3], E. TAIPALEENMÄKI[3], M. BAEKGAARD-LAURSEN[3], P. S. SCHATTLING[3], B. THINGHOLM[3], K. ANDREASSEN[3], A. M. SEBASTIÃO[2,1], B. STÄDLER[3], S. H. VAZ[2,1]
[1]Inst. de Medicina Mol., Lisbon, Portugal; [2]Inst. de Farmacologia e Neurociências, Faculdade de Medicina da Univ. de Lisboa, Lisbon, Portugal; [3]Interdisciplinary Nanoscience Ctr. (iNANO), Aarhus Univ., Aarhus, Denmark

Abstract: Excitotoxicity is a common phenomenon in several neurological diseases, associated with an impaired clearance of synaptically-released glutamate by astrocytes, leading to overactivation of post-synaptic glutamate receptors. This starts an intracellular cascade of neurotoxic events, including exacerbated production of H_2O_2 and NH_4^+ toxicity. Several therapeutic approaches focus on limiting glutamate release or blocking post-synaptic glutamate

receptors. This type of permanent blockage interferes with physiological glutamate functions, generating side effects.
We report the assembly and characterization of microreactors equipped with platinum nanoparticles (Pt-NP) that counteract cellular excitotoxicity in a neuroblastoma cell line. Pt-NP-based microreactors were able to rescue cell viability when the cells were exposed to 100 µM H_2O_2 (N=3; $p<0.01$) and to 250 µM H_2O_2 (N=3-5; $p<0.0001$) . Furthermore, the microreactors were able to ameliorate cell viability when the cells were exposed to 2.5 mM NH_4^+ (N=3-5; $p<0.0001$) and to 5 mM NH_4^+ (N=3-5; $p<0.05$).
We also report the successful co-encapsulation of two enzymatic pathways with up to five enzymes into compartmentalized microreactors. Specifically, we confirmed the activity of an encapsulated enzymatic cycle that conjugates the actions of glutamate dehydrogenase and glutathione reductase, using $NADP^+$/NADPH as a common co-factor (N=3, $p<0.01$), as well as an encapsulated enzymatic cascade combining β-galactosidase, glucose oxidase, and catalase (N=3, $p<0.05$), representing a relevant advancement in encapsulated catalysis toward the assembly of therapeutic cell mimics, capable of degrading glutamate.
The activity of the microreactors in primary neuronal cultures, obtained from Sprague-Dawley rats (embryonic day 16), is now being explored. We found that microreactors containing Pt-NP are able to ameliorate cell survival when the cell culture is exposed to exogenous H_2O_2 or NH_4^+ (N=2).
Taken together, our work represents the first attempt to create a simple artificial astrocyte to counteract excitotoxicity and it is, to our knowledge, the first study that focuses on enzyme and Pt-NP-based cell mimics as a therapeutic approach in a neuronal setting.

Disclosures: A. Armada-Moreira: None. **E. Taipaleenmäki:** None. **M. Baekgaard-Laursen:** None. **P.S. Schattling:** None. **B. Thingholm:** None. **K. Andreassen:** None. **A.M. Sebastião:** None. **B. Städler:** None. **S.H. Vaz:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.04/III37

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: German Federal Ministry of Education and Research (01 EO 0901)
DFG CRC 870
DFG 478/3-1

Title: Semi-intact preparations of larval amphibians for studying oxygen consumption and energy metabolism in the brain

Authors: *S. OEZUGUR[1], L. KUNZ[2], H. STRAKA[3]
[1]Ludwig Maximilians Univ. (LMU), Planegg, Germany; [2]Div. of Neurobio., LMU Munich Biocenter, Martinsried, Germany; [3]Div. of Neurobio., LMU Munich - Biocenter Martinsried, Planegg, Germany

Abstract: Signal processing in the brain depends on the availability of energy for intrinsic neuronal firing and synaptic activity. The dependency of ATP generation by oxidative phosphorylation on the availability of oxygen makes the latter molecule a highly relevant marker for studying the interrelation between neuronal metabolism and computation. In order to bridge the gap between *in vivo* experiments in intact animals and *in vitro* slice recordings, a previously established semi-intact preparation of larval *Xenopus laevis* tadpoles with functional sensory organs (eyes and inner ears) and motor effectors was employed. Here, we describe the methodological approach for sustained recordings of neuronal activity in such preparations, while concurrently monitoring the oxygen level in the bath chamber and the brain during superfusion with Ringer solutions at various oxygen levels. Completely submerged amphibian preparations were fixed to the Sylgard floor of a central chamber that allowed continuous and stable extracellular recordings of a selected extraocular motor nerve. Oxygen levels, temperature, and pH were constantly monitored using electrochemical micro-sensors. The oxygen-sensitive electrodes were positioned in the bath chamber as well as in the open and accessible IVth ventricle of the hindbrain. The oxygen concentration could be fast and reversibly changed by aerating the Ringer solution with carbogen or nitrogen in a small separate container immediately upstream to the recording chamber. The use of carbogen necessitated HEPES- instead of bicarbonate-buffered frog Ringer to maintain a fixed pH of 7.4 at the different oxygen levels. The oxygen monitoring revealed that the oxygen level of 20% in the recording chamber at a distance from the semi-intact preparation was virtually depleted within the IVth ventricle. This indicates that the tissue and particularly the brain represents a considerable oxygen sink. Blocking all neuronal activity in the brain by bath application of 0.05% 3-aminobenzoic acid ethyl ester methanesulfonate (MS-222), as indicated by the absence of spontaneous spike discharge in the extraocular motor nerve, entailed a robust and reversible increase of the oxygen concentration from 0% to 5% in the IVth ventricle. This finding suggests that spontaneous spike activity in the brain consumes considerable amounts of oxygen. Thus, the employment of semi-intact preparations with the possibility to physiologically activate various reflex circuits and to easily apply different drugs represents an excellent experimental model for studying the correlation between oxygen level and neuronal computation.

Disclosures: S. Oezugur: None. **L. Kunz:** None. **H. Straka:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.05/III38

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant R01MH104261
ONR Grant N00014-12-1-0366
Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Consortium
NIDA Grant U01DA043098

Title: Transcript mapping of neuronal systems in the rat brainstem using a combination of HCR-FISH and iDISCO tissue clearing method

Authors: *V. KUMAR[1], D. M. KROLEWSKI[2], C. AYDIN[3], H. AKIL[2], S. J. WATSON, Jr.[2]
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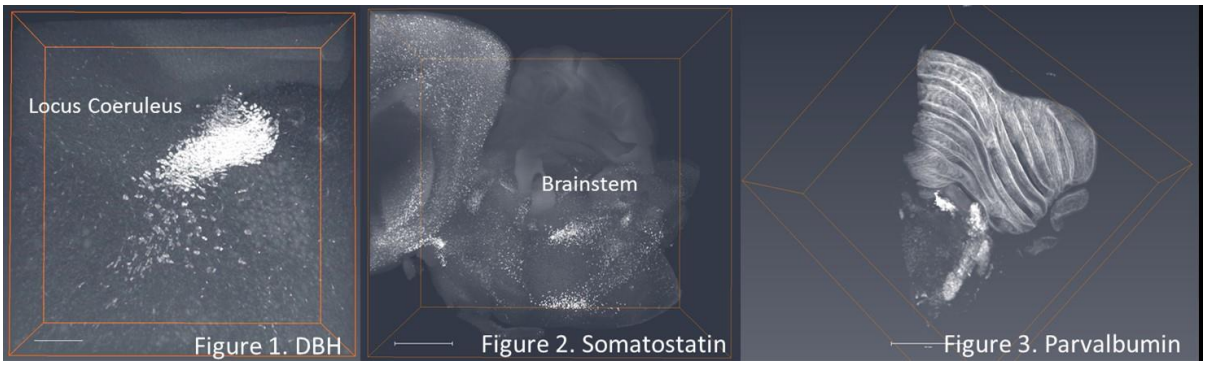
Abstract: Hybridization chain reaction (HCR) based fluorescent *in situ* hybridization (FISH) in iDISCO processed tissues, has potential to provide vital spatiotemporal information for molecular characterization and mapping of heterogeneous neuronal populations in the brain. HCR-FISH relies on binding of cDNA probes on target mRNAs to initiate chain reactions in which metastable fluorophore-labeled DNA hairpins self-assemble into tethered fluorescent amplification polymers. HCR method significantly improves sensitivity, efficiency, and amplifies the FISH signal. In our experience, iDISCO clearing method has shown the best compatibility for HCR-FISH with fresh frozen tissues, later has been preferentially used as the starting material for the radioactive/digoxigenin based *in situ* hybridization. We are using HCR-FISH and iDISCO together to map behaviorally relevant key transcripts in the brainstem region. A great deal of study has shown that noradrenergic (NE) and GABAergic system play a significant role in the pathophysiology of depression, however much of the underlying specific mechanisms induced by the stress, still need to be understood. A circuit level investigation of gene expression would help us better understand the neurobiological mechanisms underlying such disorders. To achieve an optimal transcript signal for this mapping study, we first successfully optimized the probe hybridization efficiency and permeability in the fresh frozen tissues processed with modified iDISCO protocol. In the next step, we chose a few of the predominant genes from the NE/GABAergic systems- dopamine-beta-hydroxylase (Fig.1), somatostatin (Fig.2) and parvalbumin (Fig.3) to test and validate the mapping efficiency of HCR-FISH/iDISCO combination. By using light sheet theta microscope, we anticipate to capture a detailed transcript map of NE and GABAergic systems in the brainstem. A possible implication would be to utilize this developed system in behaviorally relevant animal model and assess the qualitative/quantitative molecular adaptations in the neuronal circuits.



Disclosures: V. Kumar: None. **D.M. Krolewski:** None. **C. Aydin:** None. **H. Akil:** None. **S.J. Watson:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.06/III39

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: TEKES (the Finnish Funding Agency for Innovation) Human Spare Parts project
Finnish Cultural Foundation grant numbers 00140325 and 00150312
Academy of Finland grant number 286990
Academy of Finland Center of excellence grant 312409

Title: 3D *in vitro* human neuronal networks inside a hydrogel scaffold - Cell adhesion and maturation

Authors: *T. JOKI, L. YLÄ-OUTINEN[1], V. HARJU[1], J. KARVINEN[2], J. KOIVISTO[2], M. KELLOMÄKI[2], S. NARKILAHTI[1]
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Abstract: INTRODUCTION: Human pluripotent stem cell (hPSC) –derived neural cells are seen as a potential cell source for neural *in vitro* models [1]. Extracellular matrix (ECM) - mimicking biomaterials can be utilized in 3D tissue models as scaffold to replace native ECM. In neural field, hydrogels are prominent due their brain ECM mimicking physical properties [2]. In addition to physical support, the optimal biomaterial also offers attachment sites to cells.
In this study, composite hydrogel from hyaluronan (HA) and poly (vinyl alcohol) (PVA) with or without collagen was used as 3D scaffold for hPSC-derived neuronal cells. The aim of this work was to study neuronal cell adhesion on different materials.
METHODS: Human neural cells used in this study were derived from either human embryonic

stem cells or human induced pluripotent stem cells. Cells were maintained and cultured according to previously published protocols [3]. Hydrogels were crosslinked via hydrazone crosslinking using aldehyde-modified HA component and hydrazide-modified PVA component [4]. After two to four weeks of culturing period, the neuronal networks were analysed using qPCR and immunocytochemical analysis.
RESULTS & DISCUSSION: Hydrogel gelation via hydrazone crosslinking was successful with or without collagen as physical mixture. The hPSC-derived neuronal cells formed neuronal networks and had good viability in these hydrogels. Both HA and collagen are considered as supportive materials for neuronal cell cultures but they suffer from poor stability [2]. Based on the results one can say that in addition to remaining biologically active, the studied HA-PVA-collagen based composite hydrogels were relatively stable due to the PVA component.
CONCLUSIONS: Hydrazone crosslinked HA-PVA based hydrogel was found to be promising scaffold material for further *in vitro* neural studies. Especially combining natural polymers (HA and collagen) and synthetic polymers (PVA) in the scaffold was seen beneficial.
REFERENCES: [1] I. Kelava and M. A. Lancaster, Cell Stem Cell, vol. 18, no. 6, 736–748, (2016). [2] A. R. Murphy et al., Acta Biomater. 54, 1–20, (2017). [3] J. T. Koivisto et al., Biomed. Mater., 1–38, (2017). [4] J. Karvinen et al., React. Funct. Polym. 124, 29–39, (2018).

Disclosures: L. Ylä-Outinen: None. **V. Harju:** None. **J. Karvinen:** None. **J. Koivisto:** None. **M. Kellomäki:** None. **S. Narkilahti:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.07/III40

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: AMidex funding by Aix Marseille University

Title: A new polyplex-based approach to gene-edit post natal neuronal cells in rodent

Authors: *A. REPRESA[1], O. ZELPHATI[2], C. DI SCALA[1], M. TESSIER[1], C. SAPET[2], F. POULHES[2], F. SICARD[2], C. PELLEGRINO[1]
[1]INSERM, INMED, Marseille Cedex, France; [2]OZBiosciences, Marseille, France

Abstract: Modifying gene expression in the post natal brain is one of the most challenging task in the modern Neurosciences field, here we present a new polyplex-based approach that allow rapid, efficient and highly reproducible method to modify neuronal cells in the post natal rodent brain.
By using stereotaxic approach we were able to deliver DNA straight to the brain without triggering inflammatory processes. Furthermore we were able to play with the diffusion process

by modulating the injected volume . Finally targetting the neuronal specific potassium-chloride cotransporter 2, namely KCC2 using short hairpin RNA knocked down we were able to modify seizures suceptibility to convulsivant agent. This highlight first the large efficacy of our new design compound finally confirming the potency of this new method in modifying a large cell population.

Disclosures: A. Represa: None. **O. Zelphati:** A. Employment/Salary (full or part-time):; OZBiosciences. **C. Di Scala:** None. **M. Tessier:** None. **C. Sapet:** None. **F. Poulhes:** None. **F. Sicard:** None. **C. Pellegrino:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.08/III41

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: École polytechnique fédérale de Lausanne

Title: Protein semisynthesis provides access to tau disease-associated post-translational modifications (PTMs) and paves the way to deciphering the tau PTM code in health and diseased states

Authors: *M. HAJ-YAHYA, H. LASHUEL
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Abstract: The microtubule-associated protein Tau plays a central role in neurodegeneration and is a leading therapeutic target for the treatment of Alzheimer's disease (AD). Several lines of evidence suggest that post-translational modifications (PTMs) regulate the function(s) of Tau, including its subcellular localization, clearance, aggregation, toxicity, and pathology spreading. However, the lack of tools and methodologies that allow site-specific introduction of PTMs in Tau have limited our ability to dissect the role of PTMs in regulating Tau functions in health and disease. To facilitate deciphering the Tau PTM code, we have developed, for the first time, semisynthetic strategies that allow for the site-specific introduction of single or multiple physiological or disease-associated PTMs that occur within residues 246-441 of Tau, which includes the microtubule-binding domain (MTBD). As a proof of concept, we produced unmodified Tau and three Tau variants with single or multiple disease-associated PTMs that were not previously accessible as homogeneously modified proteins; AcK280, pY310, and pS396/pS404. We then focused on investigating the effect of acetylation at lysine280 (AcK280) on the structure, aggregation, and microtubule binding properties of Tau. Our results show that site-specific acetylation at K280 significantly enhances the aggregation rate of Tau and impairs microtubule assembly. Surprisingly, compared with unmodified Tau, which forms long and

flexible filaments, AcK280 Tau forms predominantly globular oligomers and short fibrils (< 200 nm) that exhibit a reduced propensity to assemble into long filaments. These findings are consistent with the increased aggregation propensity and pathogenicity of this mutant in animal models of AD and suggest that acetylation at this residue might enhance the seeding capacity or formation of toxic Tau species in vivo. Beyond acetylation and phosphorylation, the development of this semisynthetic strategy provides new opportunities to investigate other types of Tau PTMs and to study the cross-talk between PTMs that occurs within residues 246-441, which were previously inaccessible, thereby paving the way to deciphering the Tau PTM code in health and disease.

Disclosures: H. Lashuel: None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.10/III43

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH (R01NS087494)

Title: Model guided optimization of biosensors for neurotransmitters

Authors: *B. HUANG, M. CLAY, H. MONBOUQUETTE
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Abstract: Microprobes with an array of electroenzymatic sensing sites have emerged as useful tools for the monitoring of glutamate and other neurotransmitters *in vivo*; and implemented as such, they can be used to study many complex neurological diseases and disorders including Parkinson's disease and drug addiction. Electroenzymatic sensors work by transducing highly selective enzyme-catalyzed turnover of analyte into measurable electrical signals. Typically, oxidases are used that catalyze reactions resulting in the generation of H_2O_2, which can then be oxidized at an underlying electrode to give a current signal. However, these sensors must include a permselective film to block unwanted, electrooxidizable species (*e.g.*, ascorbic acid) other than H_2O_2 from reaching the electrode surface and generating a false current signal. The sensor therefore consists of a metal electrode upon which one or more permselective materials are deposited that is topped with a crosslinked enzyme layer. A detailed model has been constructed that describes diffusion and reaction of species in the sensor coatings, H_2O_2 electrooxidation, and current signal generation. Model simulations showed that sensor performance could be increased dramatically through optimal design modifications. Systematic experimental work guided by the model led to optimized glutamate sensors with a <5-μm-thick crosslinked glutamate oxidase layer and permselective films (polyphenylenediamine, polypyrrole and Nafion) reduced from ~6

μm to sub-micron in thickness. These design modifications led to a nearly 6-fold improvement in sensitivity to 290±14 nA/μM/cm^2 (n = 20) and a halving of the response time to <0.4 sec while maintaining excellent selectivity. A similar optimization process applied to choline sensors also led to excellent sensitivity 559±78 nA/μM/cm^2 (n = 14) and a response time of ~1 sec. These biosensor improvements are enabling more accurate tracking of chemical signaling in the brains of laboratory rodents engaged in reward-seeking behavior.

Disclosures: B. Huang: None. **M. Clay:** None. **H. Monbouquette:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.11/III44

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Standardizing tau amyloid seeding using sonication

Authors: *M. APOSTOL[1], G. NAUMANN[1], M. SCHULTZE[1], I. PANTELEEVA[2], J. KROONEN[2], R. SAXENA[3], J. BERTELSEN[3], G. BERGUET[3], J. TREANOR[1]
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Abstract: Sonication of amyloid fibers is conventionally used to create amyloid seeds that enable the investigation of the mechanisms that underlie amyloid formation and its propagation in cellular and animal models of disease. Sonicated fibers and the resulting amyloid seeds have a greater ability to seed amyloid formation from a pool of un-aggregated protein. The sonication process achieves this by breaking or shearing amyloid fibers into smaller pieces, thus opening up more ends for fiber elongation. However, standardizing input seeding material can be difficult. Conventional sonication with an immersed probe can produce variable results due to poor control of temperature and energy that is transferred to the amyloid sample. The Diagenode Bioruptor®, on the other hand, utilizes a sonication bath-based rotor in which tubes are rotated through an ultrasound field allowing for consistent exposure of energy. In addition, the combination of the Bioruptor's ultrasound and isothermal processing preserve protein integrity and maximize sample recovery. Here we show that unlike probe sonication, the Bioruptor allows better control of the sonication time and temperature enabling consistent energy to be passed into the amyloid sample leading to reproducible amyloid seeding that is equivalent to a probe-sonicated sample. Specifically, we have shown that Tau amyloid seeds can be produced consistently, thus allowing better control of their ability to seed amyloid formation as demonstrated by both a reproducible decrease in lag time as monitored by Thioflavin T, and in an increase in induction of intracellular Tau aggregation in a cellular model of seed propagation. We present field flow fractionation and electron microscopy data that analyzes the relationship between decreasing size of amyloid controlled by time of sonication in the Bioruptor and

potency of seeding. Standardization of amyloid seed size will be beneficial in the reproducibility of many aspects of research where multiple batches of input amyloid material are required, such as high-throughput screening and in animal models of amyloid propagation.

Disclosures: M. Apostol: A. Employment/Salary (full or part-time):; ADRx, Inc. **G. Naumann:** A. Employment/Salary (full or part-time):; ADRx, Inc. **M. Schultze:** A. Employment/Salary (full or part-time):; ADRx, Inc. **I. Panteleeva:** A. Employment/Salary (full or part-time):; Diagenode. **J. Kroonen:** A. Employment/Salary (full or part-time):; Diagenode. **R. Saxena:** A. Employment/Salary (full or part-time):; Diagenode. **J. Bertelsen:** A. Employment/Salary (full or part-time):; Diagenode. **G. Berguet:** A. Employment/Salary (full or part-time):; Diagenode. **J. Treanor:** A. Employment/Salary (full or part-time):; ADRx, Inc..

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.12/III45

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: R41NS102049 (NINDS/NIH, USA)
T32AA007456 (NIAAA/NIH, USA)

Title: Combined HPLC-electrochemical detection method for quantitation of monoamines and amino acids

Authors: M. J. CHURCHILL[1], *H. NEDELESCU[2], M. W. BUCZYNSKI[3], N. SUTO[4], S. AZUMA[5]
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Abstract: It is frequently necessary to quantify both amino acid and monoamine neurotransmitters in microdialysate, tissue, and other samples. The methods used to detect amino acids such as glutamate (Glu) and γ-aminobutyric acid (GABA), and monoamines such as dopamine (DA) and serotonin (5-HT) are traditionally quite different, requiring separate mobile phases, HPLC columns, and detector conditions for each group of analytes. Additionally, it is usually necessary to derivatize amino acids to make them more readily detectable by fluorescence or electrochemical detection. It is also possible to quantify both groups of analytes with a sufficiently sophisticated HPLC-mass spectrometry system; however, access to such systems for large numbers of samples is frequently unavailable to many neuroscientists.
We present conditions for using a single mobile phase, separation column, and a set of detection

conditions for both sets of analytes. This is accomplished by modulating the retention time of each set of analytes by the appropriate choice of derivatization agent. In this case, by reacting the monoamines with ortho-phthaldialdehyde (OPA) and sulfite to form isoindole sulfonate derivatives, and reacting the amino acids with OPA and a thiol to form alkylthio-isoindole derivatives. The resulting isoindole derivatives all have similar enough retention times on a C18 column to make them amenable to separation in a single isocratic reversed phase HPLC analysis of 20 minutes or less. Careful selection of the thiol reagent and the ratio of sulfite to thiol can be used to bias the sensitivity of the combined analysis towards either amino acids or monoamines. The combination of these derivatization reactions should allow for higher throughput of samples requiring analysis of both monoamine and amino acid neurotransmitters by eliminating the time used to switch between alternate HPLC configurations and equilibrate them.

Disclosures: M.J. Churchill: None. **H. Nedelescu:** None. **M.W. Buczynski:** None. **N. Suto:** None. **S. Azuma:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.13/III46

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: LDRD 16-ERD-035

Title: Fabrication and characterization of more robust and multiplexed biosensors using flexible polymer microelectrode arrays

Authors: *A. M. YORITA, A. IVANOVSKAYA, J. PEBBLES, D. HILKEN, J. ZHOU, A. M. BELLE
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Abstract: We have fabricated flexible microelectrode arrays with the goal of creating a multiplexed implantable biosensor. Amperometric electrochemical methods of neurotransmitter detection involve the reaction of electroactive species on the surface of a microelectrode held at a constant potential, with the resulting change in current correlating to the release of the neurotransmitter of interest. In the case of non-electroactive molecules, such as glutamate and glucose, an enzyme layer is necessary to generate an electroactive intermediate that can then oxidize on the electrode, thus indirectly detecting the presence of that neurotransmitter. To create a truly functional multimodal biosensor, it is necessary to increase the robustness of chemical sensors and ensure multiple sensor types work in close proximity with little cross-talk. Polyimide-based neural implantable devices, designed and fabricated at Lawrence Livermore National Laboratory, were created for the simultaneous detection of neurotransmitters and

electrical signaling. We studied methods to increase the robustness of our biosensors, which include optimized deposition methods to selectively immobilize the enzymes on sensing microelectrodes. Most current methods rely on manual deposition of a crosslinked protein solution onto the microelectrode surface. As this makes creating repeatable and reliable enzymatic layers difficult, electrochemical methods of immobilizing the enzymes onto microelectrodes were studied and optimized for sensitivity and selectivity. Soak tests mimicking components of the chemical environment of the brain were conducted to study the lifetime of these sensors in vitro. Our method also provides deposition selectivity between electrodes as close as 40 μm apart. By striving to increase the overall selectivity of these biosensors, chemical sensing on a multimodal level can be utilized to study changes in neurotransmitter release and their relation to electrophysiological signaling on a much longer timescale.
This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.

Disclosures: A.M. Yorita: None. **A. Ivanovskaya:** None. **J. Pebbles:** None. **D. Hilken:** None. **J. Zhou:** None. **A.M. Belle:** None.

Poster

253. Molecular, Biochemical, and Genetic Techniques: Biochemical Techniques

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 253.14/III47

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: UES AFRL
UTC AFRL

Title: Aspartic protease plays major role in neuropeptide y metabolism in human eccrine sweat: Implications for npy functionality in skin

Authors: *E. M. STERNBERG[1], J. R. RUNYON[2], M. JIA[2], G. TSAPRAILIS[2], P. SKEATH[2], J. A. STUART[2]
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Abstract: The ultimate objective of this study was to evaluate Neuropeptide Y (NPY) in human eccrine sweat as a means to assess human performance. To that end chemical characterisitcs of NPY in sweat were evaluated using ELISA and mass spectrometry. Sweat NPY concentrations from different body locations and NPY stability in sweat were investigated. Full length NPY was observed to undergo rapid aspartyl peptidolytic cleavage in human eccrine sweat. ELISA results confirmed the presence of cathepsin D, an aspartyl protease, in sweat at concentrations ranging from 2 – 7 ng/mL. Filtration of sweat effectively removed cathepsin D, but also NPY. Aspartyl

peptidase inhibitor Pepstatin A prevented ~60-80% degradation of NPY within 1 hour at body temperature, while other individual inhibitors such as aprotinin, bestatin, E-64, Leupeptin and AEBSF only provided very limited protection within the first 15 minutes. A combination of a DPPIV inhibitor and protease inhibitor cocktail fully stopped the hydrolysis of NPY. In the absence of protease inhibitors NPY was cleaved into NPY_{1-30} and NPY_{31-36} between Leu30-Ile31 as confirmed by mass spectrometry results. This metabolic pathway is the same as that found in human brain (central nervous system CNS) but is different from that found in human blood where NPY is mainly cleaved into NPY_{3-36} at the N-terminus. Because of the presence of similar NPY fragments in CNS we hypothesize that sweat NPY may better reflect nervous system processes than blood NPY measures. This would be of great interest to the large effort currently underway in medicine to develop non-invasive wearable devices to detect biomarkers without the need to draw blood. Sweat biomarkers will play a central role in such devices. The fact that NPY rapidly degrades in sweat also informs device development, which will need to take into account such rapid degradation in order to accurately measure this biomarker.

Disclosures: J.R. Runyon: None. **M. Jia:** None. **G. Tsaprailis:** None. **P. Skeath:** None. **J.A. Stuart:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.01/III48

Topic: I.07. Data Analysis and Statistics

Support: NIMH R44MH105091

Title: Improving 3D stereologic cell quantification with automated machine learning techniques

Authors: *W. D. PACK[1], N. ROUSSEL[1], A. D. LEDUC[1], B. S. EASTWOOD[1], C. SCHMITZ[2], S. J. TAPPAN[1], P. J. ANGSTMAN[1], J. R. GLASER[1]
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Abstract: Stereology is a rigorous and unbiased methodology for quantifying features of biological tissues such as the size, shape, distribution, and quantity of objects. Although it is the gold-standard for quantification, wide-spread adoption of stereological analysis has been hindered because it is labor-intensive even with modern software tools. In contrast, high-throughput automated cell detection methods are more widely used but fall victim to sampling bias and fail to account for differences in cell size and distribution within the region of interest. To address the need for accurate, unbiased, high-throughput cell quantification in a biological context, we have developed the first complete hardware and software system utilizing state-of-

the-art resonant scanning confocal microscope technology and automated stereological analysis software, FastCount. FastCount detects cell-like objects using computer vision segmentation techniques and modifies the segmentation using machine learning algorithms that identify cells, clusters, and fragments. During training, the classifier runs continuously to provide the user with the predicted detection rates of cells, clusters, and invalid objects. After the classifier has been applied to the collection of image sets, the population estimate is calculated that complies with the stereologic principle that each object has an equal opportunity to be counted once and only once within the region of interest. In the current study we validated automated stereology by performing a comparative analysis of the results from FastCount against ground truth data from manual stereology studies as well as against non-stereologic cell detection algorithms often used in cell counting studies. Total cell counts, false positive, false negative, true positive, and true negative detection rates were compared across these methods. Our results indicate that FastCount performed on par with manual stereology. We further demonstrate the impact of machine learning by applying the classifier created in a single training session to multiple animals in the experiment using batch processing. The utilization of machine learning algorithms in stereologic cell estimation methods also dramatically reduced the amount of user input and subjective judgments necessary for analyzing multiple image stacks resulting in substantial time savings compared to the manual stereology process. In summary, FastCount produces reproducible and unbiased results while increasing scientific throughput.

Disclosures: W.D. Pack: A. Employment/Salary (full or part-time):; MBF Bioscience. **N. Roussel:** A. Employment/Salary (full or part-time):; MBF Bioscience. **A.D. LeDuc:** A. Employment/Salary (full or part-time):; MBF Bioscience. **B.S. Eastwood:** A. Employment/Salary (full or part-time):; MBF Bioscience. **C. Schmitz:** None. **S.J. Tappan:** A. Employment/Salary (full or part-time):; MBF Bioscience. **P.J. Angstman:** A. Employment/Salary (full or part-time):; MBF Bioscience. **J.R. Glaser:** A. Employment/Salary (full or part-time):; MBF Bioscience.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.02/III49

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R01AG022381
NIH Grant R01MH107345

Title: Novel frequency-driven regional parcellations of abnormal white matter and application to hypertension during midlife

Authors: *A. CHEN[1], R. NOTESTINE[1,4], A. C. GAMST[2,4], L. WETHERELL[1], M. CARROLL[1], R. LIEU[1], L. K. MCEVOY[3], M. S. PANIZZON[1], L. T. EYLER[1], C. E. FRANZ[1], W. S. KREMEN[1,5], C. FENNEMA-NOTESTINE[1,3]
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Abstract: White matter disease is characterized by factors such as demyelination, inflammation and gliosis, and is associated with aging, hypertension (HTN), and impaired cognition. Several methods identify abnormal white matter (AWM) on structural MR images, and classification of global AWM into subtypes may improve specificity of clinical associations. Common delineations include periventricular relative to deep AWM based on distance from ventricles, or global lobar designations; these may be biased by varied levels of atrophy or may lack sensitivity. We investigated novel classifications based on the anatomical distribution of AWM over a middle-aged sample from the Vietnam Era Twin Study of Aging (VETSA; n=250). Subtypes were defined as higher frequency clusters in MNI space delineated by lower frequency valleys. This data-centric, frequency-driven approach may identify anatomical regions where different mechanisms are driving the observed abnormalities. We present two region-of-interest (ROI) parcellation models and explore relationships with HTN. Multi-channel (T1, T2, PD) segmentations including AWM were non-linearly warped to MNI space to construct an AWM population frequency atlas. We investigated parcellations by varying inputs to the Insight Segmentation and Registration Toolkit (ITK) watershed algorithm. Parcellations were reverse warped back to each subject's anatomical space, and each AWM voxel was assigned to an ROI. Our parcellation model selection struck a balance between simplicity and perceived anatomical relevance, resulting in 5-ROI and 14-ROI models. Both separated frontal, posterior, deep subcortical, anterior periventricular (APV), and temporal stem areas; the 14-ROI further subdivided frontal, posterior, and deep subcortical areas. We performed stepwise logistic regression to determine the best fit combination of ROIs to predict HTN. For 5-ROI, the best model fit included solely APV as a predictor of HTN ($p<0.005$). APV white matter, located in a poorly vascularized arterial border zone, is particularly vulnerable to reduced oxygenation. For 14-ROI, the best fit included only the inferior superior corona radiata (ISCR), lateral to the APV and supplied by the middle cerebral artery, as a predictor of HTN ($p<0.005$). The further subdivision of the deep subcortical area revealed a region which is a distinct predictor of HTN not apparent in the 5-ROI model. These findings may suggest an underlying anatomical distinction between the white matter vulnerability in these regions, supporting the potential for improved sensitivity with the use of frequency-driven parcellations.

Disclosures: A. Chen: None. **R. Notestine:** None. **A.C. Gamst:** None. **L. Wetherell:** None. **M. Carroll:** None. **R. Lieu:** None. **L.K. McEvoy:** None. **M.S. Panizzon:** None. **L.T. Eyler:** None. **C.E. Franz:** None. **W.S. Kremen:** None. **C. Fennema-Notestine:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.03/III50

Topic: I.07. Data Analysis and Statistics

Support: NIH grant R01NS102904

Title: High resolution diffusion magnetic resonance imaging based atlas of the C57BL/6J adult mouse brain: A tool for examining mouse brain structures

Authors: *T. AREFIN[1], W. SHAO[2,3], C. LEE[1], S. SHI[2], J. ZHANG[1]
[1]Dept. of Radiology, New York Univ. Sch. of Med., New York, NY; [2]Mem. Sloan Kettering Cancer Ctr., New York, NY; [3]Biochemistry, Cell and Mol. Biol. Allied Grad. Program, Weill Cornell Med. Col., New York, NY

Abstract: The widespread use of mouse models in the neuroscience research demands a standard space for mapping the structural and functional patterns during brain development as well as under various pathological conditions. Here we report an MRI-based high-resolution whole brain atlas, constructed from group-averaged C57BL/6J adult mouse brains with detailed labels for cortical and subcortical structures compatible with the Allen reference atlas (ARA). We further quantitatively examined the structural phenotypes of several mutant mouse models using this atlas. Both *in vivo* and *ex vivo* MR images were acquired from postnatal and adult mouse brains at an isotropic resolution of 100-125 μm. To transform the structural labels from ARA to our MRI data, firstly, MRI data were aligned to ARA using landmark-based rigid transformation, followed by intensity-based affine transformation and large deformation diffeomorphic metric mapping (LDDMM) (Fig. 1ai-aiii). Fine anatomical segmentations from ARA (Fig. 1bi) were then transferred into the MRI using regional LDDMM (Fig. 1bii) producing 17, 5, 33, and 44 sub-regions within the cortex, hippocampus, amygdala, and thalamus, respectively. The adult mouse brain atlas was further transferred to several postnatal stages (P21, P28, P42 and P60). This atlas will be a useful tool for MRI-based studies, such as, locating anatomical structures, investigating the macroscopic structural connectivity in mouse brain with high throughput, examining potential disrupted connections/volumetric changes in genetically modified mouse strains and compare different mutant strains in a common template. To demonstrate this point, we used the atlas (Fig. 1c-d) to quantitatively measure macroscopic morphological and structural connectivity changes in the cortex and hippocampus in two mouse models with disrupted neuronal migrations. In conclusion, our proposed atlas and database will be useful for gene/connectome study providing the requisite template for cross-examination of different mutant strains.

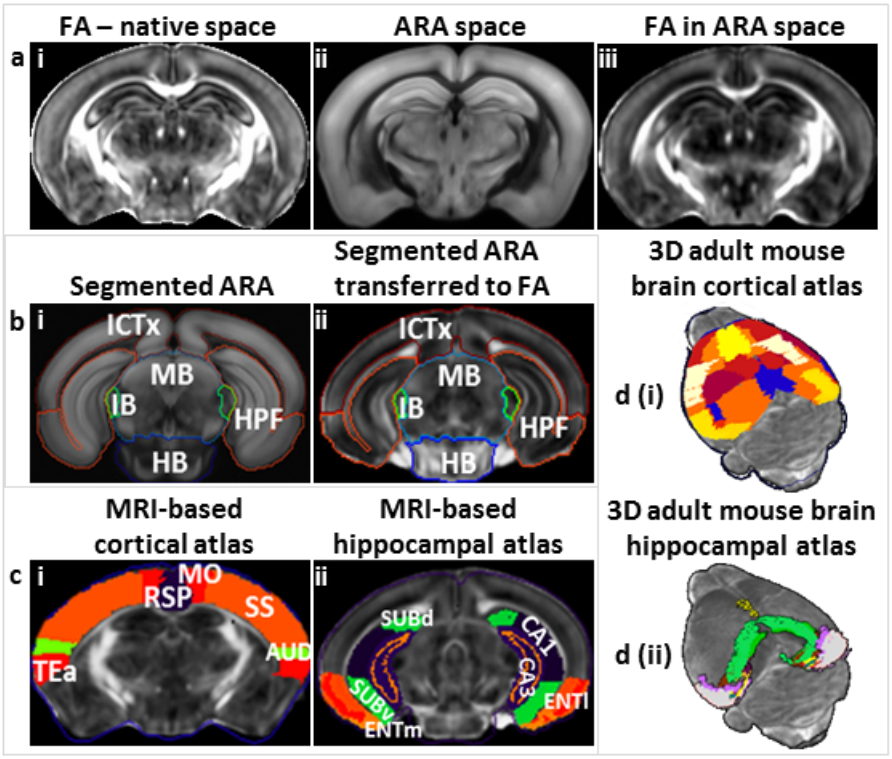

Fig 1: a) Co-registration of diffusion weighted MR image to the Allen Reference Atlas (ARA): (i) representative slice of mouse brain MR image (Fractional anisotropy - FA), (ii) example of mouse brain slice from ARA, (iii) co-registered MR image to the ARA. b) Transforming segmented ARA into the MR image: example of segmented ARA (Isorcortex - ICTx, Hippocampus - HPF, Striatum - STR, Interbrain - IB, Midbrain - MB, Hindbrain - HB and Cerebellum - CB), (ii) MR image after the transformation of segmented ARA. c) Example of MR-based mouse atlases: (i) cortical (Retrosplenial area – RSP, MO – Motor area, SS – Somatosensory area, AUD – Auditory area, Tea – Temporal Association Area) and (ii) hippocampal (Dorsal and Ventral Subiculum – SUBd & SUBv, Lateral and Medial Entorhinal Area – ENTl & ENTm). d) Three dimensional (3D) representation of adult mouse brain (i) cortical and (ii) hippocampal atlases

Disclosures: T. Arefin: None. **W. Shao:** None. **C. Lee:** None. **S. Shi:** None. **J. Zhang:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.04/III51

Topic: I.07. Data Analysis and Statistics

Support: Stanford Bio-X program
NIH grant EY02858

Title: Deep learning approach towards automated detection of dendritic spines

Authors: X. XIAO[1], *M. DJURISIC[2], A. HOOGI[3], R. W. SAPP[4], C. J. SHATZ[2], D. L. RUBIN[3]
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Abstract: Dendritic spines are neural structures housing excitatory postsynaptic machinery on pyramidal cells in mammalian cortex. These structures reflect novel experience both via changes in their density as well as their shape. Currently, most of the analysis of dendritic spines is via manual interrogation of fluorescent images; semi-automated methods developed by individual labs are also available, but these usually do not transfer well to different datasets. Therefore, a generalizable, fully automated, and unbiased, approach to describe dendritic spines under different experimental and health conditions is needed to match the rise in large imaging datasets generated across labs. Here, we present an automated and reproducible process for detecting dendritic spines using fully convolutional neural networks (FCN), a deep learning approach. Two-dimensional maximum-intensity projected images from de-convolved confocal microscopic images were used as input into FCNs. A set of different FCN architectures were tested for each image. To reduce false positives, detections from the networks were further pruned by extraction of dendritic shaft. However, our results turned out not to be strongly dependent on this post-processing step. Finally, the performance of the most successful FCN architecture was compared to the positions of dendritic spines annotated manually by two experts. The averaged distance between the predicted spines and manually annotated ones is 2.81 ± 2.63 pixels (0.082 ± 0.076 microns) and 2.87 ± 2.33 pixels (0.084 ± 0.068 microns), respectively, based on the two experts. Moreover, our automated FCN detection achieves F scores of 0.82 and 0.85 on two sets of annotations from experts, outperforming two other existing spine detection software systems, NeuronStudio and Neurolucida, with statistical significance (p-value &lt 0.02). This improvement seems at least in part to be attributable to the better detection of thin spines by FCNs: out of the total of 213 true positives based on Reader 1’s annotations, FCNs detect 31 more spines from the “thin” category than Neurolucida. To the best of our knowledge, this is the first instance of using deep learning methods towards automated dendritic spine analysis. We

hope to extend this approach to 3D volumes, and diversify training sets, in order to increase generalizability and robustness of detection and segmentation of datasets of different origin.

Disclosures: X. Xiao: None. **M. Djurisic:** None. **A. Hoogi:** None. **R.W. Sapp:** None. **C.J. Shatz:** None. **D.L. Rubin:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.05/III52

Topic: I.07. Data Analysis and Statistics

Support: AMED/MEXT JP17gm0610006
AMED/MEXT JP17dm0207049
AMED/MEXT JP17am0301025
WPI-IRCN
JSPS KAKENHI 25221004

Title: CUBIC-Cloud: A point-cloud-based computational framework to analyze, visualize and share data for whole brain profiling by tissue clearing

Authors: *T. MANO, H. R. UEDA
The Univ. of Tokyo, Tokyo, Japan

Abstract: Whole brain profiling empowered by tissue clearing methods has revolutionized the landscape of neuroscience by offering data-driven, hypothesis-free approaches to study the brain of rodents. The unexplored challenge in this field would be to design a framework to efficiently share data between research groups and promote collaboration, so that researchers can fully exploit the potential of whole brain data as collective and massive knowledge and catalyze new discoveries. Recently, we reported a single-cell-resolution whole brain atlas, named CUBIC-Atlas[1], where the whole brain is represented as a point cloud, i.e. an ensemble of cell coordinates with biological attributes. Because cell is the basic unit of living system, point cloud is a biologically natural and minimum representation of the whole tissue, as opposed to conventional raster representation. Built upon this novel approach, we have built CUBIC-Cloud, a computational framework to analyze, visualize and share whole brain data. CUBIC-Cloud is consisted of two modules, CloudMap and CloudEye. CloudMap is a library to map individual brains onto a common brain coordinate (e.g. CUBIC-Atlas) to perform quantitative comparison and analysis. CloudEye is a web-browser-based application that allows researchers to visualize tens of millions of cells and interact with them using devices with limited graphics capability (e.g. laptops). It can also be used to add annotations and publish the data for collaborators and research communities over the internet. Notably, the framework does not restrict itself to a

particular clearing method or imaging modality and thus can be used in a variety of experimental settings. The capability of CUBIC-Cloud will be demonstrated by (1) analyzing the brain-wide projection using viral tracers, (2) investigating neuronal activity change under perturbation and (3) profiling cellular distribution with cell-type specific markers. The CUBIC-Cloud framework is available as an open source, and the widespread adoption and use of this framework in the community will further accelerate the collaboration-based whole brain profiling and help understand the brain architecture at the single-cell-resolution.
Reference:1. Murakami et al. Nature Neuroscience 21, 625-637 (2018)

Disclosures: T. Mano: None. **H.R. Ueda:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.06/III53

Topic: I.07. Data Analysis and Statistics

Support: NIH DA042206

Title: A novel method for quantifying regional distribution of neural manipulations relative to a reference atlas

Authors: *A. G. GORDON[1], L. FENNELL[1], M. FANG[1], K. ZITTEL[1], M. MARINELLI[2]
[2]Neurosci., [1]Univ. of Texas at Austin, Austin, TX

Abstract: To identify brain regions that mediate specific functions, researchers often rely on manipulating the candidate brain regions. However, in order to attribute a function to a specific brain region one must accurately assess where the manipulation has occurred. A common method for determining the location of neural manipulations (e.g. viral tools, lesions) relies on a qualitative assessment of the location of the region of manipulation (ROM), relative to a reference atlas. Qualitative assessments may produce inconsistencies or inaccuracies that go unnoticed across experiments or labs, but that could have important effects on results and data interpretation. Criteria for ROM size and location vary across labs, which means that publications on a particular brain region may include meaningful variance in the amount of the intended brain region and collateral regions covered by the ROM. Even when atlas images are included in publications, quantifying differences of expression across samples or publications is not possible.
We have developed a method to quantify the distribution of ROMs relative to a reference atlas. The method is composed of three steps: 1) Creating a reference atlas, in which each brain region has a unique color-coded value (RBG value); the corresponding color code for each brain region is referenced in an Excel sheet; 2) Marking the ROM on the reference atlas for each subject and

brain section; 3) Analyzing the ROM with respect to the reference atlas, using a Matlab script that compares the number of pixels of the ROM with respect to those in the reference atlas. With this method we are able to quantify the proportion of each brain region that contains the ROM and the proportion of the ROM that is located in each brain region. Researchers can implement this method into their lab simply by mapping ROM onto our reference atlas, using any pixel-based imaging software. Our method still relies on proper imaging techniques and subjective mapping of ROMs from histological slices onto the color-coded reference atlas. However, our method eliminates the subjective qualitative assessment of the ROM and allows, instead, for an objective quantification.
This ability to quantify ROMs objectively has multiple uses; for example one can establish "hits or misses" based on an objective quantification; results can also be used to perform correlations between ROM distribution patterns and experimental outcomes. Furthermore, distribution values can be published to allow other labs to compare ROMs across publications and against their own data, permitting for more accuracy and experimental reproducibility.

Disclosures: A.G. Gordon: None. **L. Fennell:** None. **M. Fang:** None. **K. Zittel:** None. **M. Marinelli:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.07/III54

Topic: I.07. Data Analysis and Statistics

Title: Marker-less co-registration of brain MRI data to a subject's head via a mixed reality device

Authors: *C. LEUZE, G. YANG, J. A. MCNAB
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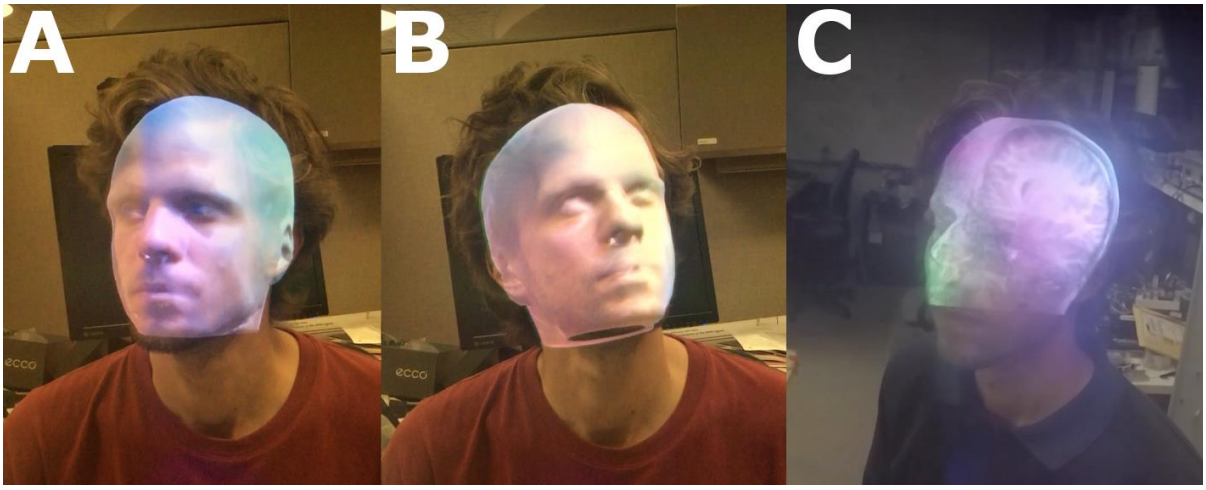
Abstract: Introduction: Many medical applications such as surgery or brain stimulation require the clinician to identify the internal location of a specific brain region. In this project we present a method to marker-less track a subject's head to overlay and update a holographic rendering of the subject's head in real time. This is done by tracking the face using a depth-sensing camera, which tracks facial features and sends location and rotation information to a see-through display to update a rendering of the head's MRI data. **Methods:** An Intel RealSense SR300 RGBD camera was attached to the Microsoft Hololens and connected via USB to an external laptop. We developed custom software that uses the Intel RealSense SDK to track the world coordinates of a subject's facial features and uses these coordinates to update the pose of a holographic head rendering in the Hololens display. To get the transformation from RealSense camera space to the virtual Hololens display space where the pose of the holographic head is rendered, we performed

a calibration according to [1], to find the transformation matrix from Realsense depth camera to mixed reality display. **Results & Conclusion:** Figure 1 shows surface renderings (A,B) and a volumetric rendering (C) of the head overlaid on the subject viewed through the Hololens. Head translation and rotation was detected reliably for all three axes. Head tracking accuracy depended on camera distance and head rotation with respect to the camera with higher accuracy of 2.2±1.9mm for a frontal face in 30cm distance from the camera distance up to 10.6mm±3.2mm for a face at 45^{o} in 60cm distance to the camera. Our method to project a hologram on a subject based on facial feature tracking will allow clinicians in the future a high flexibility and simple localization of internal organs by just looking at the patient and without the need for time-consuming calibration. [1] Garon et al. Real-time High Resolution 3D Data on the HoloLens, ISMAR 2016



Disclosures: C. Leuze: None. **G. Yang:** None. **J.A. McNab:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.08/DP15/III55

Topic: I.07. Data Analysis and Statistics

Support: SC CTSI Grant

Title: Quality control of MRI segmentation using virtual reality and crowdsourcing

Authors: *D. DUNCAN[1], A. JABERZADEH[2], T. ARD[1], D. PELLETIER[2], A. W. TOGA[1]
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Abstract: Objective: In our recent study to differentiate disease-specific regional atrophy between multiple sclerosis and Alzheimer's Disease subjects, we have processed more than 5,000 3T MRI brain scans with FreeSurfer 6.0 (FS), a software package that performs automatic segmentation. However, FS is imperfect, and to detect FS segmentation failures for gray matter, white matter, and subcortical regions, experts must review segmentations. We have provided a user-friendly, collaborative web service in which experts can remotely check available segmentations in the database to pass or fail them and leave comments. This tool can be used to cross-validate raters that participate in the quality control (QC) phase, and the final outcome is determined by a majority vote. To include all valuable collected MRI for our study, the failed brain scans must then be corrected manually, so we used the Virtual Brain Segmenter (VBS), a virtual reality (VR) tool, as an intuitive and efficient way to correct these failures.
Methods: VBS, using the HTC Vive, is used for QC of MRI segmentation. We use FS to perform automatic segmentation of the MRI, then users correct any errors made using VBS. We provide 4 scenarios for which we used VBS. In each case, a source image, a target image, and a corresponding failed segmented surface are overlaid. The user browses the image and removes voxels of the target volumes that do not belong to a specific region. When the user has finished editing the voxels, FS commands are used to regenerate correct surfaces.
Results: We have shown that VBS can be used successfully for pial surface edits, white matter surface edits, lesion corrections, and optic nerve removal. User experience feedback was collected when these four use cases were demonstrated as part of an exhibit booth during the 2018 American Academy of Neurology meeting to determine the advantages of our VR tool in these scenarios.
Conclusion: We demonstrate the strengths and weaknesses of VR and crowdsourcing as methods for QC of MRI segmentation. We show how these methods can help researchers to correct segmentation errors more efficiently and intuitively in VR as well as the features of this platform that enable crowdsourcing among expert and non-expert users to expedite the process further. A faster segmentation program saves valuable time and resources during imaging analysis, which may significantly expedite our research on disease-specific brain atrophy.

Disclosures: D. Duncan: None. **A. Jaberzadeh:** None. **T. Ard:** None. **D. Pelletier:** None. **A.W. Toga:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.09/III56

Topic: I.07. Data Analysis and Statistics

Support: NIMH DIRP

Title: A digital hierarchical atlas and anatomical template of the macaque brain

Authors: B. JUNG[1], C. SPONHEIM[3], J. SEIDLITZ[4,2], L. G. UNGERLEIDER[1], *A. MESSINGER[1]
[1]Lab. of Brain and Cognition, [2]Developmental Neurogenomics Unit, Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Univ. of Chicago, Chicago, IL; [4]Dept. of Psychiatry, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: We created a representative anatomical template of the monkey brain, called the *National Institute of Mental Health Macaque Template*, or NMT for short (Seidlitz et al., 2017). The NMT is a nonlinear average of the T1-weighted *in vivo* MRI scans of 31 adult rhesus macaque monkeys. The NMT and its tools provide a volume and surface for alignment of anatomical and functional imaging data for individual or group analysis. Several data sharing and analysis platforms are providing the NMT and/or NMT-aligned data (e.g., PRIME-DE, AFNI, NeuroVault).
Here we introduce updates to the NMT, including a novel Cortical Hierarchical Atlas of the Rhesus Macaque (CHARM-250). The revised NMT covers the whole-head and is symmetric. We reflected the left and right hemispheres of each subject before the iterative averaging process, effectively doubling our subject count to 62. We also provide rigid body registration parameters so the NMT's AC-PC alignment, with its origin at the anterior commissure, can be put in (Horsley-Clarke) stereotaxic alignment, with the origin midway along the interaural meatus. This coordinate frame is beneficial for planning stereotaxic surgeries.
The CHARM-250 is a 6-tiered hierarchical atlas that segments the cortical surface at various scales using a total of 250 regions. At the coarsest level, the cortex is divided into the four lobes. Cortical divisions at the finest level were largely based on warping the D99 digital atlas (Reveley et al., 2016) to the NMT. This map was manually edited to bridge discontinuities within an area, prevent areas from jumping across sulci, and fuse areas smaller than 13.5 mm^3 with a neighbor so they can be reliably warped to the anatomies of other monkeys. At successive levels of the hierarchy, areas were combined based on contiguity, cytoarchitectonic similarity, shared membership in a cortical area or larger region (e.g., lobule, sulcus, or surface), and common function. The CHARM-250 permits description of whole-brain data sets at varying levels of generality, delineates the constituent areas of larger regions, and facilitates comparisons of anatomical descriptors across species. Data from individual monkeys can be warped to the NMT for volumetric or surface-based CHARM-250 analysis. Alternatively, the NMT and CHARM-250 can be warped to an individual's *in vivo* anatomical scan. Because the NMT is a population average of *in vivo* scans, these warps of the NMT and its hierarchical atlas tend to faithfully conform to individual anatomies.

Disclosures: B. Jung: None. **C. Sponheim:** None. **J. Seidlitz:** None. **L.G. Ungerleider:** None. **A. Messinger:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.10/III57

Topic: I.07. Data Analysis and Statistics

Support: NIMH U24 MH114827
NIBIB P41 EB019936
NIDA U24 DA039832

Title: The NIF ontology: Brain parcels, cell types, and methods

Authors: *T. GILLESPIE[1], A. E. BANDROWSKI[2], J. S. GRETHE[2], M. E. MARTONE[3]
[1]Neurosci., UCSD, LA Jolla, CA; [3]Neurosci., [2]UCSD, La Jolla, CA

Abstract: The Neuroscience Information Framework Standard Ontology (NIFSTD, http://ontology.neuinfo.org) has been in use and maintained for over a decade. Here we present an update on content of the ontology, focusing on three areas: brain parcellation schemes, neuronal cell types, and techniques and methods used in neuroscience. These are three major ares of terminology where NIF has collaborated with multiple projects including the BRAIN Initiative Cell Census Network, the Human Brain Project, the Blue Brain Project, and Center for Reproducible Neuroimaging Computation. The parcellation of the brain into regions is both a fundamental organizaing principle in neuroscience and of great practical importance in experimental neuroscience. It is difficult to keep track of how many parcellation schemes exist and are in use because new schemes are continually developed as new methods are developed and new atlases are released. We present the framework used by NIFSTD to manage parcellation schemes and the conceptual model for mapping between them as well as a fundamental model delimiting the possible ways to name parts of the brain where those parts are practically meaningful. Identifying and classifying cell types in the brain is a continual challenge in neuroscience and there are now a number of initiatives working to do this systematically across the whole brain in multiple species. Terminology for naming neuron types based on the phenotypes that neurons show when they are interrogated experimentally forms the basis for creating a data driven ontology of types and models that can transcend the experimental conditions under which they are studied. We present the results of applying our phenotype based model for experimental neuron types to existing neuronal datasets and the preliminary results of mapping experimental neuron types to classical higher level types. As alluded to above, both brain parcellation, and cell typing are dependent on the methods and techniques used to divide the brain and populations of cells in the brain into parts and types. However, traditional individual approaches to both tend not to treat methodology explicitly. Accounting for methodology explicitly could help as we start to integrate information from multiple source. To

this end we have updated NIFSTD's modeling of methods, techniques, and protocols. We present NIFSTD's conceptual model for methods and techniques as well as their application to naming cell types and brain regions.

Disclosures: T. Gillespie: None. **A.E. Bandrowski:** None. **J.S. Grethe:** None. **M.E. Martone:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.11/III58

Topic: I.07. Data Analysis and Statistics

Support: NARSAD Independent Invetigator
DP5OD012109
R01MH108590
R01MH112189

Title: Bringing legacy neuroimaging data into the human connectome project's cifti analysis framework

Authors: *A. ANTICEVIC[1], J. JI[2], B. ADKINSON[3], S. N. SOTIROPOULOS[4], A. KRALJIC[5], E. DICKIE[6], A. VOINESKOS[6], T. S. COALSON[7], D. C. VAN ESSEN[8], M. F. GLASSER[9], G. REPOVS[5]
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Abstract: The Human Connectome Project's (HCP) minimal preprocessing pipelines (HCP-MPP) have yielded major improvements to cross-subject alignment by analyzing multi-modal neuroimaging data with methods that respect the sheet-like 2D cortical and 3D globular subcortical geometries of the human brain. However, the application of these state-of-the-art advances has been limited to neuroimaging data collected via HCP-Style hardware and acquisition protocols designed to map and remove sources of geometric distortions across image modalities and maximize spatio-temporal resolution. Tens of thousands of imaging datasets collected via 'legacy' approaches do not meet HCP-MPP standards to varying degrees. These 'legacy' datasets will benefit from adopting the surface-based framework that the HCP-MPP has pioneered via the Connectivity Informatics Technology Initiative (CIFTI), which enables improved cross-subject alignment while reducing deleterious effects of smoothing. In fact, recent

efforts offer a framework that brings surface-based analysis to legacy datasets using the ciftify tool, which builds on FreeSurfer's outputs (https://github.com/edickie/ciftify). Here we present the Legacy Minimal Preprocessing Pipelines (L-MPP) - a processing route that parallels the HCP-MPP workflow within the same codebase but supports a wider variety of raw data that do not meet HCP-MPP standards. L-MPP supports the following scenarios: i) It can use both T1w/T2w images or use only a single T1w image (though without producing cortical myelin maps); ii) It can run FreeSurfer 5.3-HCP or 6.0 (or the latest version), incorporating features for expert file optimization, manual editing of segmentation errors, and support for longitudinal analyses. iii) The L-MPP fMRI workflow supports datasets lacking fieldmaps by instead using an adaptation of FSL's TOPUP tool for non-linear distortion correction. iv) Finally, L-MPP provides support for 'legacy' diffusion imaging data not collected with phase-encoding reversals. Collectively, we show that L-MPP, leveraging the same codebase, can yield HCP-style advances for ‘legacy’ imaging data. This offers CIFTI support for datasets previously incompatible with the HCP-MPP analytic framework. Importantly, the L-MPP extension of the core HCP-MPP functionality is intended to work in parallel with ciftify, which builds on FreeSurfer's outputs. The L-MPP workflow thus provides rapid and robust integration of legacy datasets into a CIFTI 2D/3D format, which stands to appreciably improve multi-modal neuroimaging results for many existing datasets.

Disclosures: **A. Anticevic:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BlackThorn Therapeutics. F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics. **J. Ji:** None. **B. Adkinson:** None. **S.N. Sotiropoulos:** None. **A. Kraljic:** None. **E. Dickie:** None. **A. Voineskos:** None. **T.S. Coalson:** None. **D.C. Van Essen:** None. **M.F. Glasser:** None. **G. Repovs:** F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.12/III59

Topic: I.07. Data Analysis and Statistics

Title: SpineTracker: An open-source, broadly adaptable plugin for fully automated imaging and stimulation of dendritic spines

Authors: *M. S. SMIRNOV, R. YASUDA
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Abstract: Synaptic plasticity, the cellular basis for learning and memory, is mediated by a complex biochemical network of signaling proteins compartmentalized in dendritic spines. The ability to screen a high number of molecular targets for their effect on dendritic spine structural

plasticity will require a high-throughput imaging system capable of stimulating and monitoring hundreds of dendritic spines in various conditions. As microscope systems capable of advanced, high-resolution imaging of molecular targets often rely on highly specialized and customized software controllers, they tend to lack automation capabilities. We have built a standalone Python tool which can be easily interfaced with various two-photon imaging programs, allowing users to specify an imaging/photostimulation timeline and track positions for 3D drift. Notably, our plugin includes a pre-trained, end-to-end, deep machine learning system based on the YOLOv2 architecture, allowing for the identification of dendritic spines with essentially no time lag. Therefore, once experimental parameters are set, users need only to click a single button to collect time-lapse imaging and photostimulation results from multiple dendritic spines within a single field of view.

Disclosures: M.S. Smirnov: None. **R. Yasuda:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.13/III60

Topic: I.07. Data Analysis and Statistics

Support: ARRS Grant J7-8275 (PI: Repovš)
ARRS Grant J7-6829 (PI: Repovš)
ARRS Grant J7-5553 (PI: Repovš)
ARRS Grant P3-0338 (PI: Podnar)
NIH-DP5OD012109 (PI: Anticevic)
NIH-R01MH108590 (PI: Anticevic)
NARSAD Independent Investigator Grant (PI: Anticevic)

Title: MNAP: Multimodal neuroimaging analysis platform for flexible, extensible and rapid analytic throughput

Authors: *G. REPOVS[1], A. ANTICEVIC[3], L. JIE JI[3], J. MURRAY[3], B. ADKINSON[3], C. SCHLEIFER[3], Z. TAMAYO[3], M. FLYNN[3], A. KOLOBARIC[3], Y. T. CHO[3], A. KRALJIC[2], N. PURG[2], A. SLANA OZIMIC[2]
[2]Dept. of Psychology, [1]Univ. of Ljubljana, Ljubljana, Slovenia; [3]Dept. of Psychiatry, Yale Univ., New Haven, CT

Abstract: A major challenge for human neuroimaging is flexible, robust and rapid deployment of state-of-the-art methods. The Multimodal Neuroimaging Analysis Platform (MNAP) provides a software ecosystem that collectively supports an extensible framework for data organization, preprocessing, quality assurance, and analyses across neuroimaging modalities. The MNAP suite

is flexible and extensible by adding functions developed around its component interconnected modules: i) MNAP 'Connector' module developed to wrap various tools and functions throughout the MNAP suite. ii) MNAP 'neuroimaging utilities' [NIUtilities] module for parallelizable processing and analyses. NIUtilities processing manager supports both local and high-performance computing job management, and integrates tools from freely-available analysis packages in an efficient unified preprocessing workflow. iii) MNAP 'Matlab' module provides signal processing and statistical general linear modeling (GLM) functions for preprocessing and analyses that are invoked throughout the MNAP suite but can be used as stand-alone tools. iv) MNAP provides modified version of the Human Connectome Processing (HCP) minimal processing pipelines optimized for both 'legacy' single-band and multi-band data. v) MNAP 'Library' module provides support files, libraries, and data templates (e.g. atlases) used across the suite. Collectively, MNAP enables rapid and efficient handling of neuroimaging data across multiple workflows: from importing of DICOMs, preprocessing, advanced GLM task-based analyses, functional and structural connectivity analyses, statistical testing and visualization. MNAP tools are built around a flexible architecture that facilitates massive parallelization across multiple cores of a single machine or across multiple nodes on a high-performance cluster or in the cloud. This in turn enables rapid throughput of large-scale datasets. Collectively, we introduce the MNAP ecosystem [https://bitbucket.org/hidradev/mnaptools/], which is purpose-built for flexible, extensible and rapid analytic throughput.

Disclosures: G. Repovs: F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics. **A. Anticevic:** F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics. **L. Jie Ji:** None. **J. Murray:** F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics. **B. Adkinson:** None. **C. Schleifer:** None. **Z. Tamayo:** None. **M. Flynn:** None. **A. Kolobaric:** None. **Y.T. Cho:** None. **A. Kraljic:** None. **N. Purg:** None. **A. Slana Ozimic:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.14/III61

Topic: I.07. Data Analysis and Statistics

Support: NIMH Grant R44MH108053
NIMH Grant R44MH105091

Title: Automated characterization of the anatomic distribution of CRF positive cells in male and female mouse brain

Authors: *N. J. O'CONNOR[1], B. S. EASTWOOD[1], S. GERFEN[1], S. J. TAPPAN[1], P. J. ANGSTMAN[1], T. KAWAMURA[2], J. R. GLASER[1], H. J. KARTEN[3], P. P. SANNA[2]

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Abstract: Corticotropin releasing factor (CRF) is a peptide hormone centrally involved in stress response and stress mediated addiction mechanisms in the brain. The differences in brain-wide distribution of CRF between male and female mouse brain is not well characterized. Here we present NeuroInfo, an automated system for mapping brain image volumes and CRF-positive cellular populations to a standardized reference space. This technology reconstructs a whole brain image from serial sections, detects cells in the 3D image, aligns the image to a reference atlas, and then partitions cell populations using the anatomic boundaries in the reference space. Automatically mapping cell populations to a standardized atlas allows researchers to objectively accumulate and compare results without the need for extensive expertise in neuroanatomy.
This automated mapping system registers brain volumes and the detected cell coordinates to the Allen Institute for Brain Science's Common Coordinate Framework (CCF). Following registration, anatomic delineations from the CCF are imposed on the cell counts to partition them into a list of counts within each anatomy.
We analyzed CRF-positive cell populations in three female and male brains. Sections from the brains were automatically extracted, aligned, and compiled into full resolution 3D whole-brain images. Automatic cell detection was performed on the images, and images and counts were then automatically registered to the CCF using nonlinear transform optimization. Normalized differences between female and male brain regions were calculated and top 5^{th} percentile of regional differences plotted.
For validation, manual tracings and counts were compared in one brain for multiple regions. The accuracy of the automated registration was assessed by: 1) manually tracing hippocampal and amygdalar regions and comparing the areas and perimeters of delineations, and 2) calculating the distances between the centroids of manually and automatically delineated regions. In these brain regions, manual and automatic cell counts were compared to establish false negative and positive error rates.
Here we present an application of technology that automatically maps cellular populations in reconstructed whole brain images to brain structures in a common reference space. This technology provides repeatable, objective measures that can be compared across experiments and laboratories. This automation also creates the possibility of increasing the efficiency of experimental workflows. Further work will increase the number of animals to establish the sensitivity of detecting differences in brain regions between male and female cohorts.

Disclosures: **N.J. O'Connor:** A. Employment/Salary (full or part-time):; full-time. **B.S. Eastwood:** A. Employment/Salary (full or part-time):; full-time. **S. Gerfen:** A. Employment/Salary (full or part-time):; full-time. **S.J. Tappan:** A. Employment/Salary (full or part-time):; full-time. **P.J. Angstman:** A. Employment/Salary (full or part-time):; full-time. **T. Kawamura:** None. **J.R. Glaser:** A. Employment/Salary (full or part-time):; full-time. **H.J. Karten:** None. **P.P. Sanna:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.15/III62

Topic: I.07. Data Analysis and Statistics

Support: The work was performed within the framework of the Basic Research Program at the National Research University Higher School of Economics (HSE)
The work was supported within the framework of a subsidy by the Russian Academic Excellence Project '5-100'

Title: CoordsFinder - software tool for systematic search for brain coordinates of interest for area-based meta-analyses

Authors: *P. NOVIKOV[1], M. ARSALIDOU[2,3]
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Abstract: Neuroimaging studies are accumulating fast. A significant number of these studies use functional magnetic resonance imaging (fMRI) and report stereotactic brain coordinates. In the last 15 years meta-analytic software tools have been developed to identify over-arching data agreement across studies (e.g., http://www.brainmap.org/). Meta-analytic studies help establish statistical concordance and quantitatively summarize large amounts of evidence. To date there are 944 papers on fMRI meta-analyses, as indexed by Web of Science (WOS; 28/04/18). Before analyzing coordinates researchers have to compile, systematically review relevant literature and extract stereotaxic coordinates. One process of pooling information from the articles requires manual search of the articles and manual extraction the relevant data, such as coordinates (i.e., foci), contrasts (i.e., experiments) and types of analyses (whole-brain or region of interest). Another available approach is offered by software with pre-extracted information, such as Sleuth (http://brainmap.org/sleuth/), Neurosynth (http://neurosynth.org/) and other open-source programs. Critically, these methods do not have up to date datasets covering only a limited number of studies (e.g., 11406 papers in the Neurosynth and 3294 papers in the Sleuth 2.4 at the 28/04/2018), whereas, a WOS search for the keyword ("fMRI") yields 61976 papers.
To improve the quality of the manual search for area-based meta-analyses and increase the speed of the identification of the foci of interest, we developed CoordsFinder - standalone graphical interface software for addressing the challenge of processing multiple fMRI articles reporting data in coordinate space. The software is written using WPF (C# and XAML), based on .NET Framework 4.5.2, and it supports Microsoft Windows 7 operating system or higher. The CoordsFinder estimates the foci uploaded in the software manually and searches for it inside the

specified folder, which contains the pdf files of the papers, as this is the most common file format for articles. Foci coordinates can be found both in tables and in a plain text of the articles. The foci file uploaded could contain MNI or TAL space coordinates, and the software can indicate each type. In the current version, CoordsFinder can explore only files stored at the user's computer, and process 274 papers per minute for a typical computer. Practically this software provides a solution for automatically extracting coordinates from multiple articles for effectively organizing and further analyzing data already available in the literature.

Disclosures: P. Novikov: None. **M. Arsalidou:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.16/III63

Topic: I.07. Data Analysis and Statistics

Support: Friebe Foundation

Title: Cloud-based relational database for managing large amounts of multimodal animal data

Authors: *M. ASWENDT, N. PALLAST, F. WIETERS, M. NILL, G. R. FINK
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Abstract: Objectives
Data management becomes prone to user-errors when working with extensive multimodal and longitudinal datasets. Although outlined in the Good Laboratory Practice guidelines of the WHO, most labs store their data not in a standardized way and lack way behind clinical standards. In order to be prepared for big data initiatives in neuroscience and to improve standardization of data management, we have developed a cost-effective and user-friendly cloud-based relational database.
Methods
We are using tools provided by commercial software (Ninox Software GmbH, Berlin, Germany). The database accepts in vivo and ex vivo mouse data: type of surgery (stroke, fiber/virus implantation), behavioral test (cylinder, rotating beam, grid walk), MRI, electrophysiology, and histology. Each mouse is identified by an experiment-specific ID which relates to an experimental project, sub-group, mouse cage and mouse number. The raw data is stored on a central fileserver and linked in the database. Entries are logged by timestamp and user. The software is operating system independent and accessible via a web interface or an app - also simultaneously by many users.
Results
Our approach is different to existing data management tools such as REDCap and electronic

laboratory notebooks (ELN). We provide a framework for efficient multi-user data entries. Here, the data is entered and organized in a relational way. A mouse and all related experiments are linked to each other. The database is indexed and enables filtering and a free text search, e.g., it is possible to list all T2-weighted MRI scans obtained during a specified period. We adapted a print function for animal permission-relevant data such as the time under anesthesia and details of surgery. Several automated procedures are included, which for example calculate the current animal age in weeks and several measures of the behavioral tests. There are different levels of user rights, which allow to blind users for the experimental group (e.g. sham vs. treatment) and lock access to experimental data.

Conclusions

Our relational database design for multimodal mouse data improves data accessibility, search efficiency, validity, and reporting. The database is especially useful for labs collecting longitudinal in vivo data and subsequent ex vivo measurements. There are only minimal programming skills necessary and the template can be easily adapted to other labs, collaborative work and other experimental conditions.

Disclosures: M. Aswendt: None. **N. Pallast:** None. **F. Wieters:** None. **M. Nill:** None. **G.R. Fink:** None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.17/III64

Topic: I.07. Data Analysis and Statistics

Support: American Heart Association, Scientist Development Grant (16SDG27130006)

Title: Map Manager: Software to annotate and analyze image volume time-series

Authors: *R. H. CUDMORE
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Abstract: The increasing availability of confocal, two-photon, and light sheet microscopes coupled with rapid developments in fluorescent reporters have made 3D imaging and analysis a central component of modern neuroscience research. The ease of acquiring 3D images from living neural tissue is creating progressively larger datasets, prompting the need for image analysis software that is both rapid and accurate. A major bottleneck in the analysis of 3D image data is its segmentation into discrete 3D annotations which is especially problematic for time-series data where corresponding annotations need to be linked between time-points. Here, we present Map Manager, powerful and easy to use software written in Igor Pro that is optimized for the annotation, analysis, and curation of 3D image time-series data. Map Manager semi-

automatically links corresponding annotations between time-points without the need to pre-process image volumes with alignment. Once a database of annotations is created, Map Manager provides a rich set of curation tools including searching, plotting, and report generation. A key benefit of Map Manager is that large datasets can be managed while focusing on the quality-control of individual annotations in the context of their raw 3D image data. Built in time-series analysis includes tracking the addition, subtraction, and trajectories of annotations. In addition to the analysis of 3D point annotations, Map Manager has an extended set of features for neuronal spine dynamics and intensity analysis. To extend the analysis of datasets created in Map Manager, we provide a Matlab toolbox which allows experiment-specific customized analysis to be easily implemented.

Disclosures: R.H. Cudmore: None.

Poster

254. Software Tools Connectivity Analysis Macro/Micro Structure

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 254.18/III65

Topic: I.07. Data Analysis and Statistics

Support: German Research Foundation (FOR 1847)

Title: ARCADE: A modular multithreaded stimulus presentation software for the real-time control of stimuli, actions and reward during behavioral experiments

Authors: *J. R. DOWDALL, J. T. SCHMIEDT, M. STEPHAN, P. FRIES
Ernst Strüngmann Inst., Frankfurt Am Main, Germany

Abstract: Behavioral experiments with non-human primates are typically controlled by computer software that presents stimuli and responds to subject actions. The ability to present and control stimuli precisely, both temporally and spatially, requires hardware (i.e., audio and graphics cards) and access to that hardware through a programmable interface (referred to as an Application Programming Interface or API). Both the hardware and interfaces are in constant development, thus for any software to remain compatible it must be actively maintained. To mitigate the work involved, we developed ARCADE (Application for Real-time Control of Actions and stimulus Display in behavioral Experiments), a freely-available modular stimulus presentation software, which simplifies software development and maintenance through compartmentalization. An additional advantage of modularization is that it lends itself well to modern CPU/GPU architectures designed for multitasking, such that modules can run independently with dedicated tasks. ARCADE is a suite of modules, written in C++ and MATLAB, running in parallel on Microsoft Windows using standard Windows libraries for inter-process communication. ARCADE simultaneously displays precisely timed visual stimuli

(using the DirectX API) while tracking eye movements, controlling digital input/output, and providing online behavioral monitoring to the user via a MATLAB graphical interface. With the DirectX API and dynamically-compiled pixel shaders (referred to as fragment shaders in OpenGL), ARCADE provides users with a powerful tool for stimulus design and control. DirectX pixel shaders are small programs, written in the C-like High Level Shader Language (HLSL), which execute a user-defined routine for each pixel. The implementation of pixel shaders in ARCADE allows users to design and control stimuli, static or animated, with a user-defined pixel shader function accepting a finite number of user-defined input parameters including pixel position and frame count. Experimental design in ARCADE has been simplified while maintaining flexibility through a state-machine design pattern in which the "states" are realized as parts of a trial (i.e., fixation, stimuli on, response, etc.). A user only needs to write one MATLAB script that defines the "states" (parts of a trial), the actions associated with those states (i.e., stimuli on/off), and the next state, which can be determined by subject behavior or state variables such as time elapsed. In summary, ARCADE is a modular state-based experimental stimulus presentation software providing online behavioral control with flexibility and simplicity for the present and future.

Disclosures: J.R. Dowdall: None. **J.T. Schmiedt:** None. **M. Stephan:** None. **P. Fries:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.01/III66

Topic: I.04. Physiological Methods

Support: NIH Grant R01MH075957

Title: Structural insights into anion conduction of natural and designed anion channelrhodopsins

Authors: *Y. KIM[1], H. E. KATO[1], J. M. PAGGI[1], C. RAMAKRISHNAN[1], L. E. FENNO[1], K. E. EVANS[1], K. INOUE[2], S. ITO[2], H. KANDORI[2], B. K. KOBILKA[1], K. DEISSEROTH[1]
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Abstract: Within the broad family of light-gated ion channels, anion selectivity was initially created by crystal structure guided re-design of natural cation-conducting channelrhodopsins (CCRs); anion selectivity was subsequently found to have naturally evolved in certain cryptophyte algae. Both designed and natural anion-conducting channelrhodopsins (dACRs and nACRs) have since been applied as optogenetic tools (enabling selective inhibition of targeted-cell activity during behavior in many vertebrate and invertebrate animals), but each also exhibits performance limitations, underscoring key tradeoffs in channel structure/function relationships. For example, befitting their provenance from CCRs that achieved versatile applicability in part

through engineered gating properties spanning ~6 orders-of-magnitude from several milliseconds to tens of minutes), dACRs offer a much wider range of kinetics relevant to neuroscience than do nACRs; on the other hand, nACRs exhibit larger photocurrents (despite high anion selectivity). Therefore, molecular and structural insight, jointly into both dACRs and nACRs, will be critical not only to understand the fundamental mechanisms of light-gated anion-channel function, but also to enable creation of next-generation optogenetic tools. Here we report the first high-resolution crystal structures of an nACR (the most widely used variant GtACR1, at 2.9 Å), and a dACR (multiple structures of iC++ at pH 8.5 and 6.5, at 2.9 Å and 3.2 Å resolution respectively). The resulting series of structural, spectroscopic, electrophysiological, and computational analyses provided unexpected insights into ACR pH-dependence, substrate recognition, channel gating, and ion-selectivity. Finally, synthesis of insights from the structures of both iC++ and GtACR1 enabled design, verification, and practical application of the first ACR integrating all the
key functional features of large photocurrent magnitude and 20-fold faster kinetics alongside exclusive anion selectivity.

Disclosures: Y. Kim: None. **H.E. Kato:** None. **J.M. Paggi:** None. **C. Ramakrishnan:** None. **L.E. Fenno:** None. **K.E. Evans:** None. **K. Inoue:** None. **S. Ito:** None. **H. Kandori:** None. **B.K. Kobilka:** None. **K. Deisseroth:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.02/III67

Topic: I.04. Physiological Methods

Support: DARPA Neuro-FAST

Title: Igniting an artificial percept with cellular-resolution optical stimulation

Authors: *J. H. MARSHEL, S. QUIRIN, T. A. MACHADO, Y. KIM, C. RAJA, A. CHIBUKHCHYAN, C. RAMAKRISHNAN, M. INOUE, S. GANGULI, K. DEISSEROTH
Stanford Univ., Stanford, CA

Abstract: Microstimulation of few neurons can drive sensations and remarkably specific experiences in humans. Activating functionally-tagged populations in animals can modulate perceptual decisions and elicit specific behaviors. Conversely, much neural activity is likely outside awareness suggesting that circuit phenomena exist for selecting and amplifying specific pathways to drive distinct behaviors. Here, we study these phenomena using ensemble-level all optical read/write approaches. Mice are trained to discriminate grating orientations to high performance (d’ > 2). Functional ensembles are identified with volumetric two-photon calcium

imaging (GCaMP6m) of superficial layers through layer 5 of primary visual cortex (≥0.7 x 0.7 x 0.4 mm^3). Ensembles (mean 41.5±13.5 neurons, n = 8 in 4 mice) specifically responding to visual targets (lick; Go) or visual distractors (no lick; No Go) are selected for two-photon, holographic-based ensemble optogenetic stimulation with cellular resolution, using a novel, red-shifted excitatory opsin (MO20; ~1ms simultaneous stimulation of all cells using a custom multiple spatial light modulator system, MultiSLM[1]). Mice discriminate artificial ensemble stimulation without a visual stimulus present (d' > 2). We investigate the same ensembles and surrounding populations every day across weeks (mean 54±5 days, n = 4 mice). Varying the number of neurons, cortical layer and timing of stimulation within ensembles we find that mice can discriminate activity in small numbers of neurons (min = 2 per ensemble in layer 5; min = 8 in layer 2/3) especially when stimulated simultaneously, mapping the neural activity threshold for behavioral performance. Follow on activity patterns in non-stimulated neurons largely match between visual-only and optogenetic-only trials, indicated by high performance of a linear discriminant analysis (LDA) classifier trained on visual-only trials and tested on optogenetic-only trials. The same classifier yields poor performance when random populations are stimulated—consistent with observed deficits in behavioral performance. Furthermore, stimulation of sub-ensembles of neurons leads to specific recruitment of held-out neurons within the full ensemble ($p<0.0001$ vs orthogonal populations, n = 4 mice). These results, and future studies building on these approaches, provide a mechanistic view of the critical point at which artificial activity integrates into the native circuit to drive broader networks and the perception and behavior of the animal.

[1]Marshel et al. Wide field-of-view three dimensional all-optical neurophysiology with millisecond-resolution *in vivo*. Presented at SfN 2017.

Disclosures: J.H. Marshel: None. **S. Quirin:** None. **T.A. Machado:** None. **Y. Kim:** None. **C. Raja:** None. **A. Chibukhchyan:** None. **C. Ramakrishnan:** None. **M. Inoue:** None. **S. Ganguli:** None. **K. Deisseroth:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.03/III68

Topic: I.04. Physiological Methods

Support: NIH Grant 5 F32 MH 110144-2

Title: Cell-type specific reward dynamics of medial habenula neurons

Authors: *E. L. SYLWESTRAK[1], S. VESUNA[1], A. CROW[1], C. RAMAKRISHNAN[1], K. DEISSEROTH[2]

[1]Bioengineering, Stanford Univ., Stanford, CA; [2]Bioengin & Psych, Stanford Univ. Dept. of Psychology, Stanford, CA

Abstract: The processing of appetitive and aversive stimuli is essential to guide motivated behavior and is represented in many structures across the mammalian brain. The habenular complex is comprised of a transcriptionally diverse group of cells in the dorsal thalamus, divided into two anatomically distinct regions. The medial subdivision receives input from the limbic system, sends projections to the midbrain, and has been shown to play a role in behaviors related to processing of aversive and appetitive stimuli, including stress, nicotine withdrawal, and voluntary exercise. This region is smaller and less studied than its lateral counterpart, but it displays a strong degree of transcriptional heterogeneity, with cells expressing a wide variety of neuromodulatory receptors, neurotransmitters, and neuropeptides. Using multiplexed in situ hybridization we characterize the overlap of neuromodulatory cell type markers in habenular neurons. In transgenic animals, viral projection mapping and tissue clearing reveal that TH-, ChAT- and Substance P- expressing neurons show cell type-specific termination zones in the midbrain. Using Cre-mediated viral delivery in subpopulations of medial habenula neurons and fiber-based calcium recording during an operant conditioning task, we find that these three transcriptionally-defined cell types exhibit distinct reward dynamics: TH-expressing neurons respond to reward-predictive cues (%dF/F = -3.6, s.d. = 1.2, p =0.02, n= 5 animals), ChAT neurons are not significantly modulated by reward (%dF/F = -.65, s.d. = 0.44, n = 7 animals), and Substance P-expressing neurons show strong transient activation during reward omissions (%dF/F = 21.0 , s.d. = 13.9, p = 0.01 , n=4 animals), but persistent activity during delivered rewards (%dF/F = 7.1, s.d. = 5.5, p <0.01 , n= 5 animals). Moreover, changes to reward contingencies and cue-reward associations trigger rapid adaptive changes in habenular activity. These data suggest that medial habenula neurons encode multiple aspects of reward responses and could serve as a mechanism to modulate motivated behavior in different emotional states.

Disclosures: E.L. Sylwestrak: None. **S. Vesuna:** None. **A. Crow:** None. **C. Ramakrishnan:** None. **K. Deisseroth:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.04/JJJ1

Topic: I.04. Physiological Methods

Support: NDDK Grant K01DK114165
HHWF F-1052
NIMH Grant R01MH075957
NIMH Grant R01MH086373

DARPA NeuroFAST W911NF-14-2-0013

Title: Activity-based projection mapping to identify cortical representations of internal states

Authors: *B. HSUEH[1,2], L. YE[2,5], M. GOUBRAN[3], C. RAMAKRISHNAN[2], J. H. JENNINGS[2], M. RAFFIEE[2], D. TANG[2], A.-C. WANG[2], M. M. ZEINEH[3], K. DEISSEROTH[4]
[2]Bioengineering, [3]Radiology, [4]Bioengineering & Psychiatry, [1]Stanford Univ., Palo Alto, CA; [5]Neurosciences, Scripps Res. Inst., La Jolla, CA

Abstract: How cortical ensembles encode internal homeostatic states and coordinate with other structures throughout the brain to drive adaptive behavior remains a fundamental question in neurobiology. To achieve access to such cortical populations, we developed an expanded viral toolkit for permanent genetic labeling of activity-defined neuronal populations both for unbiased, whole-brain labeling, and for targeted, projection-specific labeling. In conjunction with a computational framework enabling automated quantification of cortical projections in atlas-registered, cleared whole mouse brains, we performed a brain-wide screen for projections activated by hunger, and found increased activation of a projection from posterior insular cortex to the amygdala. Optogenetic stimulation of this projection was sufficient to increase food consumption in otherwise sated animals (two-way ANOVA, $p = 0.042$, $n = 7$ mice per group) without affecting water consumption, and elicit aversion of a neutral environment (paired t-test, $p = 0.044$, $n = 7$ mice), while optogenetic inhibition suppressed consumption in fasted animals (two-way ANOVA, $p = 0.011$, $n = 6$ mice per group). These findings demonstrate the utility of this new viral approach for activity-dependent input mapping, and support the role of posterior insula in top-down coordination of responses to perturbed homeostatic states.

Disclosures: B. Hsueh: None. **L. Ye:** None. **M. Goubran:** None. **C. Ramakrishnan:** None. **J.H. Jennings:** None. **M. Raffiee:** None. **D. Tang:** None. **A. Wang:** None. **M.M. Zeineh:** None. **K. Deisseroth:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.05/JJJ2

Topic: I.04. Physiological Methods

Support: MLB: Helen Hay Whitney Foundation (HHMI)
MLB: NARSAD Young Investigator's Award (BBRF)
MLB: NIMH K99 (NIH)
ASA: Helen Hay Whitney Foundation
ASA: NARSAD Young Investigator's Award (BBRF)
KD: HHMI

KD: NIMH

Title: Divergent population states across the hypothalamus during homeostatic threats

Authors: *M. LOVETT-BARRON[1], R. CHEN[1], S. BRADBURY[2], A. S. ANDALMAN[1], K. DEISSEROTH[1,3]
[1]Bioengineering, Stanford Univ., Palo Alto, CA; [2]Biol., Stanford Univ., Stanford, CA; [3]HHMI, Stanford Univ., Stanford, CA

Abstract: Animals living in changing environments encounter a variety of threats to homeostasis. Such threats can evoke behavioral and endocrine states believed to be implemented by the hypothalamus, which promote strategies to restore homeostasis and maintain health and survival. However, population dynamics across the hypothalamus, the specific cell types implementing these dynamics, and their effects on the rest of the brain are not well characterized. To study the mechanisms underlying behavioral responses to homeostatic threats, we used cellular-resolution activity imaging in behaving larval zebrafish, which allow for comprehensive functional characterization of neurons across the hypothalamus. Under head-fixed conditions, we found that larval zebrafish executed swimming responses to acute homeostatic threats (increases in salinity, acidity, or temperature). We performed brain-wide volumetric 2-photon calcium imaging during this behavior, and registered the resulting functional maps to a common brain atlas (Z-Brain Atlas; Randlett et al., *Nat. Meth.*, 2015). Similar to previous reports in zebrafish and other species, we found movement-correlated cell types throughout the brain, with more cells localized to posterior parts of the brain such as the dorsal hindbrain. We also found neurons with sustained and transient stimulus responses throughout the brain, including many in the hypothalamus. Few hypothalamic cells showed common excitatory responses to multiple threat stimuli, and neurons correlated with stimulus-induced motor actions were negatively correlated with one another (heat vs salinity, r = -0.37; heat vs acidity, r = -0.24; salinity vs acidity, r = -0.32; $P<1x10^{-9}$). When compared across different types of threats, we observed that hypothalamic populations entered distinct network states upon stimulus onset, and recovered following stimulus offset. We further characterized the molecular identity of these functional cell types using an extension of MultiMAP (Lovett-Barron et al., *Cell*, 2017): we imaged the hypothalamus during behavior, then processed fish for triple fluorescent in situ hybridization, followed by cellular-resolution volume registration to align the activity of each cell with expression of neuropeptide genes. We found multiple peptidergic cell types correlated with the sensory and motor aspects of responses to homeostatic threats, including clusters of *AVP*+, *OXT*+, *VIP*+, *SST*+, and *NPY*+ neurons in the preoptic area. These findings reveal that different homeostatic threats evoke unique hypothalamic network states that encompass the transformation from threat sensation to action.

Disclosures: M. Lovett-Barron: None. **R. Chen:** None. **S. Bradbury:** None. **A.S. Andalman:** None. **K. Deisseroth:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.06/JJJ3

Topic: I.04. Physiological Methods

Support: NIMH (R01MH099647)
NIDA (P50DA042012)
DARPA NeuroFAST program W911NF-14-2-0013
NOMIS Foundation
Fresenius Foundation
Wiegers Family Fund
James Grosfeld Foundation

Title: Three-dimensional intact-tissue mapping of single-cell transcriptional states by *in situ* sequencing

Authors: *X. WANG[1], W. E. ALLEN[1], M. A. WRIGHT[1,2], E. L. SYLWESTRAK[1], G. P. NOLAN[3], F.-A. BAVA[3], K. DEISSEROTH[1,2,4]
[1]Dept. of Bioengineering, [2]Dept. of Psychiatry and Behavioral Sci., [3]Dept. of Microbiology and Immunol., Stanford Univ., Stanford, CA; [4]Howard Hughes Med. Inst., Stanford, CA

Abstract: The mammalian brain consists of an intricate tapestry of cell types, with diversity crucial for function that arises from both differential gene expression and circuit-specific anatomy. Yet, retrieving high-content gene-expression information while retaining 3D positional anatomy at cellular resolution has been difficult, limiting integrative understanding of brain structure and function. Here we introduce and apply a technology for 3D intact-tissue RNA sequencing in brains and other organs, termed STARmap (Spatially-resolved Transcript Amplicon Readout Mapping), which integrates a novel sequencing-by-ligation process, highly-specific signal amplification, and new hydrogel-tissue chemistry. The initial instantiation of STARmap enabled cellular-resolution expression mapping via sequencing of 1,020 genes in all cells within mouse visual cortex slices. Applying quantitative single-cell STARmap, we identified diverse anatomically- and molecularly-resolved cell types within cortical layers (including interneuron and glial subtypes) and quantified expression of activity-regulated genes as a function of visual stimulation, spatial position, and molecularly-defined cell typology. In extending this approach to levels of throughput orders-of-magnitude larger than previously accessed even in 2D (>30,000 cells in cubic millimeter-scale volumes), we discovered a gradient-distribution of excitatory neuron subtypes contrasting with 3D clustering patterns of inhibitory neurons.

Disclosures: X. Wang: None. **W.E. Allen:** None. **M.A. Wright:** None. **E.L. Sylwestrak:** None. **G.P. Nolan:** None. **F. Bava:** None. **K. Deisseroth:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.07/JJJ4

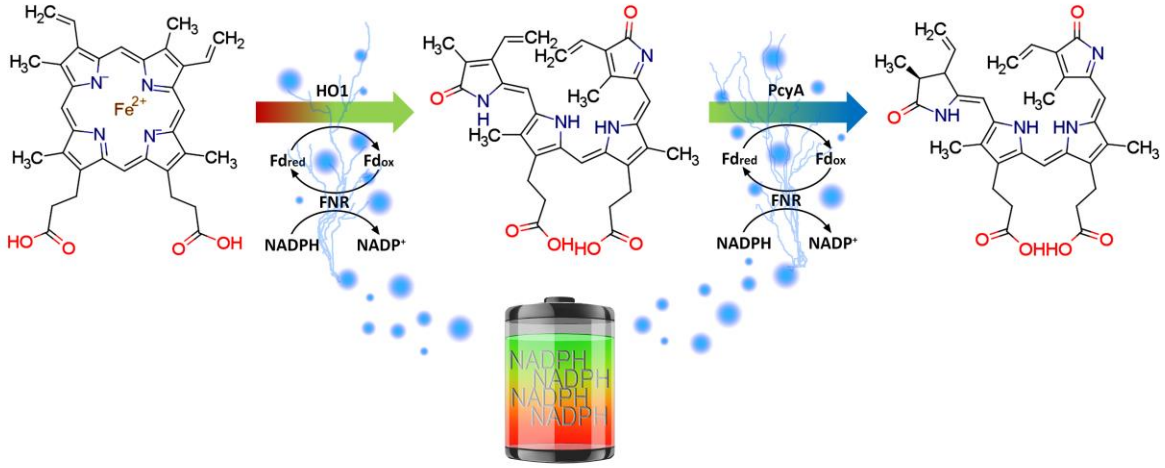
Topic: I.04. Physiological Methods

Support: Kavli Institute for Brain and Mind at UC San Diego and the Salk Institute
National Science Foundation through the NSF Center for Science of Information under Grant CCF-0939370
NIH Grant NS060847
UCSD School of Medicine Microscopy Core Grant P30 NS047101
Training in Multiscale Analysis of Biological Structure and Function, Training Grant: NIH grant T32 EB009380
UCSD Cellular and Molecular Genetics Training Program through an institutional grant from the National Institute of General Medicine (T32 GM007240)
AAUW (American Association of University Women) 2015 International Fellowship

Title: Genetically encoded PhyB optogenetic tools in animal cells

Authors: *P. KYRIAKAKIS, M. CATANHO, V. J. HU, T. P. COLEMAN
UCSD, San Diego, CA

Abstract: Tools providing high spatial and temporal resolution to control biological activity are indispensable for the study of neurological processes. Using structured illumination with PhyB optogenetics has the ability to control biological activity down to the subcellular level, making it a powerful tool to study neuronal networks. However, until recently, the requirement of an exogenous chromophore, phycocyanobilin (PCB), for light sensitivity has limited the use of the most well characterized and versatile red-light modulated systems. Our recent report demonstrated how to overcome this barrier, leading to the genetic encoding of the PCB production in animal cells. Using these findings, we optimized the PCB production system and combined it with a tissue penetrating red/far-red sensing PhyB optogenetic gene switch in animal cells. We further characterized this system in several mammalian cell lines using red and far-red light. The PhyB-PIF3 light-switchable gene system remains active for several hours upon a one-minute red-light pulse and requires very small amounts of light for maximal activation. To facilitate the use of optogenetics, we designed a low-cost computer-controlled illumination system that attaches to most surfaces, including in cell culture incubators. We further extended the PhyB optogenetic toolbox to control several biological activities, including the control of endogenous genes, gene editing and as a tool for mapping neural connections.



Disclosures: P. Kyriakakis: None. **M. Catanho:** None. **V.J. Hu:** None. **T.P. Coleman:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.08/JJJ5

Topic: I.04. Physiological Methods

Support: Malcolm Feist Weiler Research Seed fund

Title: Optimization of optogenetic induced seizure activity in primary neurons of the hippocampus

Authors: *B. J. BARKER[1], H. SUN[2]
[1]Louisiana State Univ. Hlth. Sci. Ctr., Shreveport, LA; [2]Louisiana State Univ. Hlth. Sci. Ctr. Shreveport, Shreveport, LA

Abstract: Optogenetic stimulation is a promising method for inducing seizures in rodents. Traditional temporal lobe seizure models, such as electrical stimulation and local drug injections, tend to be unpredictable.
Wild-type mice were injected with AAV to achieve hippocampal channelrhodopsin (ChR2) expression. Glutaminergic neurons were targeted using a CaMKIIA promoter. After approximately three weeks, a custom, single-channel optic fiber-electrode (optrode) assembly was surgically implanted into the hippocampus for stimulation and EEG recording. Injection and optrode implantation use stereotactic surgical techniques to ensure accurate placement. Optogenetic stimulation trials with 473 nm laser with simultaneous EEG recording were performed to determine and refine optimal experimental parameters, including stimulation

duration, pulse frequency, duty ratio, and optical intensity. Seizure occurrence and duration was determined using EEG and behavioral data. Optrode placement and ChR2 expression in the hippocampus was confirmed with immunohistochemistry. Two control experiments were used. ChR2-expressing mice were stimulated with 589 nm laser, and blank-AAV mice were stimulated with 473 nm laser.
Six ChR2 expressing animals were each subjected to multiple sessions of laser stimulation. To produce the desired frequency of seizure events, the optimal experimental parameters were determined to be: a stimulation duration of 30 seconds, 10 Hz pulse frequency, 0.05 duty ratio, and terminal optical intensity of 5-6 mW. Stimulation periods and subsequent rest periods had a total time of two minutes. The optimal parameters resulted in an average frequency of 5.273 generalized seizures per hour, and average seizure duration of 29.759 seconds (s=13.453). Seizure frequency decreased when the stimulation duration was reduced to 15 and 10 seconds, resulting 2.667 and 1.0 generalized seizures per hour, respectively. There was no significant difference in average seizure duration between the stimulation duration groups (p=0.559). No consecutive seizure events were produced. On the contrary, a seizure event is always followed by a significantly depressed EEG response to the next stimulation. Identical stimulation parameters using a 589 nm laser produced no changes of EEG signals.
We successfully produced generalized seizures in wild-type mice using laser stimulation of the hippocampus with CHR2 expression.

Disclosures: B.J. Barker: None. **H. Sun:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.09/JJJ6

Topic: I.04. Physiological Methods

Support: Wilhelm Leibniz Gemeinschaft Grant SAW-2014-DPZ-1

Title: Histological evaluation of optogenetic tools in rhesus monkey fronto-parietal-temporal network

Authors: *M. G. FORTUNA[1], J. HÜER[2], H. GUO[3], L. T. SCHILLER[4], J. GRUBER[4], H. SCHERBERGER[5], J. F. STAIGER[6], S. TREUE[3], A. M. GAIL[3]
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Abstract: Optogenetics in non-human primates is challenged by limited set of genetic tools, large tissue volumes, and not well understood long-term effects of opsin over-expression. To investigate the impact of frontal lobe on parietal and temporal areas with optogenetics in rhesus monkeys (Macaca mulatta), we evaluated the protocol for viral vector injections which would result in large volume transduction and strong opsin expression in long-range axonal projections. We tested the local expression spread, axonal projections to target areas, and neuronal specificity for the frontal eye field (FEF) and dorsal and ventral premotor cortex (PMd and PMv) with two different opsins. One monkey was injected with an AAV2/5 virus carrying hChR2(H134R)-eYFP and eNpHR3.0-mCherry constructs, both under the CaMKIIα promoter. The NpHR virus was injected into FEF with a single penetration - 7 µl distributed evenly by seven 1 µl deposits over 6 mm in depth. ChR2 was injected into the PMv with 3 penetrations at 1.5 mm triangular distance - 9 µl distributed by nine 1 µl deposits over 2 mm cortical depths. After 10 weeks, immunohistological analyses of 50 µm thick coronal sections were performed. Both constructs led to a robust transgene expression, restricted to cortical neurons, with no signs of inflammation, pathology or tissue damage. Consistent with the CaMKIIα promoter, expression predominantly occurred in pyramidal neurons. While ChR2-eYFP was almost entirely expressed on the cell membrane, NpHR-mCherry also accumulated in intracellular vesicular compartments. Both proteins displayed strong dendritic and axonal expression, including axonal projections terminating in layer 5/6 in respective target areas in the parietal and temporal lobe. Neurons were infected throughout the depth of cortical layers, fairly homogeneous across the volume, with the highest expression observed within 1 mm radius of each injection site. However, we also observed sparse transduced cell bodies many millimeters away from the injection site, only attributable to retrograde transport of the virus. To confirm these observations, three additional animals were injected with similar approaches. Histological examination is pending. Electrophysiological recordings from two of the animals confirm effective light-sensitivity of long-range axonal projections. In conclusion, the histological analysis indicates that the used viruses and injection protocol are well suited for efficient and large-scale transduction of frontal areas in the rhesus monkey, and axonal expression of the opsins allows for projection-specific light-induced (in-) activation in the temporal/parietal target areas.

Disclosures: M.G. Fortuna: None. **J. Hüer:** None. **H. Guo:** None. **L.T. Schiller:** None. **J. Gruber:** None. **H. Scherberger:** None. **J.F. Staiger:** None. **S. Treue:** None. **A.M. Gail:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.10/JJJ7

Topic: I.04. Physiological Methods

Support: NIH-NEI BRAIN Initiative Grant 1R21EY027620

Title: Structure-guided design and *in vivo* characterization of photoselectable channelrhodopsins

Authors: *S. G. KING[1], R. DOMINGUEZ[4], A. ISHCHENKO[2], A. SADYBEKOV[2], E. CHANG-SING[3], A. M. ZBELA[4], I. V. KATRITCH[2], V. CHEREZOV[2], J. Y. LIN[5], S. A. HIRES[3]
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Abstract: Ensembles of neurons related to particular functions in the cortex are spatially distributed and genetically heterogeneous, leaving few exploitable attributes to allow flexible, specific control of their activity with existing technologies. To address this challenge, we are developing a photoselectable variant of the red-activatable channelrhodopsin (ReaChR), which we term PReaChR. We identified three mutations (H174R, D196A, and R308N) in the ReaChR backbone that confer a desired tri-state stability: closed and unavailable, closed and primed, and stably open. In HEK293 cells, PReaChR candidates can open from a primed state by 1 second illumination with red-orange light (590 nm; typically 30 pA for the double mutant, typically 40 pA with faster kinetics for the triple mutant). Currents were stable for > 30 seconds. Opening was dependent on the prior illumination of the channel. Illumination with ultraviolet light (405 nm) closed the channel and allowed subsequent opening with 590nm. Illumination with 470nm closed the channel and prevented opening by 590nm illumination until further illumination with 405nm. When the double mutant was expressed in barrel cortex, light was unable to reliably evoke action potentials in most expressing neurons. However, light did evoke local field potentials. Addition of a Kv2.1 soma-targeting sequence dramatically improved channel surface expression. We present new results with soma-targeted versions of these PReaChR candidates in awake, behaving mice.

Disclosures: S.G. King: None. **R. Dominguez:** None. **A. Ishchenko:** None. **A. Sadybekov:** None. **E. Chang-Sing:** None. **A.M. Zbela:** None. **I.V. Katritch:** None. **V. Cherezov:** None. **J.Y. Lin:** None. **S.A. Hires:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.11/JJJ8

Topic: I.04. Physiological Methods

Title: Photostable live cell imaging culture media that protects neurons and glial cells from light-induced cellular damage

Authors: N. ASBROCK, *V. T. CHU
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Abstract: Fluorescent detection of targets in live cultured cells, including fluorescence microscopy, optogenetics, and fluorescence activated cell sorting (FACS) often require prolonged exposure to high levels of blue light. The wide use of green fluorescent protein (GFP) as a fluorescent protein tag in live cell imaging requires blue light (470 nm) excitation. Also, recently discovered optogenetic actuators often depend on light in the blue range of the visible spectrum for their photoactivation. Cell culture media and supplements often contain components that are converted to toxic free radicals by exposure to light of certain wavelengths and can lead to marked disruption of cellular metabolism and significant increases in cytotoxicity. We have developed a new suite of cell culture media and supplements in which distinct photo-toxic components have been removed or replaced. These media maintain exceptional support for cell function and viability in both neuronal and glial cell types during prolonged exposure of cells to blue light. Furthermore, the levels of auto-fluorescence and photobleaching is dramatically reduced in the media, thereby significantly improving the quality of data that can be obtained using fluorescent live cell imaging.

Disclosures: N. Asbrock: A. Employment/Salary (full or part-time):; MilliporeSigma. **V.T. Chu:** A. Employment/Salary (full or part-time):; MilliporeSigma.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.12/JJJ9

Topic: I.04. Physiological Methods

Support: R01 MH111520
R01 NS08171

Title: A photoswitchable GPCR-based opsin for synaptic inhibition

Authors: *B. A. COPITS[1], A. M. VASQUEZ[4], A. M. GOMEZ[2], K. E. PARKER[2], P. O'NEILL[3], X. MESHIK[3], C. STANDER[2], N. GAUTAM[3], R. K. SUNAHARA[4], R. W. GEREAU[1], M. R. BRUCHAS[2]
[1]Pain Center, Dept of Anesthesiol., [2]Anesthesiol. and Neurosci., [3]Anesthesiol., Washington Univ. Sch. of Med., Saint Louis, MO; [4]Pharmacol., Univ. of California San Diego, San Diego, CA

Abstract: The implementation of optogenetic tools to manipulate the activity of specific cell types in the nervous system has accelerated our understanding of the neural circuits underlying complex behavior. The most commonly used opsins are light-gated ion channels or pumps to control activity on millisecond timescales. While optogenetic activation can be precisely tuned across a wide range of firing frequencies, inhibition has proven to be much more problematic.

The most commonly used inhibitory opsins are chloride or proton pumps, which require constant illumination, which can result in tissue damage. Additionally, biophysical constraints due to altered ion gradients can result in paradoxical excitation, rather than inhibition of activity. The development of opto-GPCR chimeras grants spatial and temporal control to control distinct intracellular signaling cascades. Unlike the binary on/off control of activity when using optogenetic ion channels or pumps, modulating endogenous activity patterns may more accurately reflect circuit dynamics. However, these rhodopsin-based approaches possess several limitations, including high photosensitivity and irreversible activation.
Here we have identified a novel photoswitchable GPCR-based opsin that engages endogenous inhibitory signaling cascades to silence synaptic transmission. This UV/blue/green light-sensitive opsin couples to G-proteins to reversibly inhibit neuronal voltage-gated calcium channel function, with similar efficacy to endogenous $GABA_BRs$. Long-term optical inhibition can be achieved with pulsed light, does not desensitize, and most importantly, inhibition is rapidly reversed by illumination with amber or red light. This opsin can also be stimulated by 2-photon excitation, permitting subcellular activation of G-protein subunits, and may allow for precise patterns of inhibition deep within tissues. We are currently testing the ability of this opsin to suppress genetically-defined circuits *in vivo*. Finally, we have adapted this GPCR-based opsin to serve as a novel scaffold for next-generation opto-XR chimeras with photoswitchable control of Gs-, Gq-, and Gi-coupled signaling cascades.

Disclosures: B.A. Copits: None. **A.M. Vasquez:** None. **A.M. Gomez:** None. **K.E. Parker:** None. **P. O'Neill:** None. **X. Meshik:** None. **C. Stander:** None. **N. Gautam:** None. **R.K. Sunahara:** None. **R.W. Gereau:** None. **M.R. Bruchas:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.13/JJJ10

Topic: I.04. Physiological Methods

Title: Simultaneous multiwell optogenetic stimulation and microelectrode array recording for evaluating functional network electrophysiology *in vitro*

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

Abstract: Microelectrode arrays (MEAs) monitor and manipulate cultured cell activity *in vitro*, providing insight into neuronal network interactions to inform “disease-in-a-dish” models, stem cell characterization, toxicology screening, and drug safety and development. Multiwell MEA systems, such as the Maestro, enable high-throughput assessment of functional endpoints at

greatly reduced time and cost. While network activity may be monitored under spontaneous conditions, stimulation of neural activity allows evaluation of evoked activity measures, reduces well-to-well variability, reduces assay duration by increasing activity levels, and enables application-specific protocols to assess network connectivity. Optogenetics integrates fast, light-activated channels (opsins) that allow targeted, precise manipulation of cellular activity, providing advantages such as targeting specific cell types, activity suppression, minimal stimulus artifact, and uniform stimulus delivery across a culture. Here, we demonstrate the application of the Lumos, a commercial multiwell optical stimulation system, to characterize the use of opsins for in vitro neurophysiology assays. ChR2, Chronos, and Chrimson were evaluated at multiple light intensities across four wavelengths (470nm, 530nm, 612nm, 655nm) to assess spectral separation in the neural response to single and paired pulse stimulations. As expected, ChR2 exhibited a greater evoked response for 470nm light pulses than other wavelengths, whereas Chronos was slightly green-shifted, with consistent evoked response for 470nm and 530nm wavelengths. Chrimson had the broadest activity across wavelengths, but the peak response occurred for 612nm wavelength. The paired stimulation quantified aspects of network inhibition, by comparing the response to a second stimulus relative to the first at varying inter-stimulus intervals. Measures of evoked neural response for single and paired pulse stimulation were used to quantify changes in activity induced by pharmacological manipulation. Phenytoin and picrotoxin produced significant decrease and increase, respectively, in the evoked response for single pulses and the excitability for paired pulse stimulation. These findings demonstrate the potential of optically-integrated multiwell MEA systems to improve assessment of neuropharmacological effects.

Disclosures: H.B. Hayes: A. Employment/Salary (full or part-time):; Axion BioSystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems. **A.M. Nicolini:** A. Employment/Salary (full or part-time):; Axion BioSystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems. **C.A. Arrowood:** A. Employment/Salary (full or part-time):; Axion BioSystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems. **I.P. Clements:** A. Employment/Salary (full or part-time):; Axion BioSystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems. **D.C. Millard:** A. Employment/Salary (full or part-time):; Axion BioSystems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axion BioSystems.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.14/JJJ11

Topic: I.04. Physiological Methods

Support: Wellcome Trust
BBSRC
ERC

Title: Dynamic closed-loop all-optical manipulation of neural circuits *in vivo*

Authors: *Z. ZHANG[1,2], L. E. RUSSELL[1], A. M. PACKER[1], O. M. GAULD[1], P. DZIALECKA[1], M. HAUSSER[1]
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Abstract: The ability to simultaneously read out and control neuronal activity using an "all-optical" combination of imaging and photostimulation now allows interventions to be targeted to individual neurons based on their functional signature. However, this targeting has hitherto been performed only on neurons whose functional signatures have been characterized using offline analysis, typically by averaging activity across multiple trials. Since the activity of individual neurons can vary from moment to moment and from trial to trial, it is essential to be able to target photostimulation guided by online readout of activity. To address this challenge, we have recently developed an online feedback strategy to close the loop between optical readout and stimulation, and use it to demonstrate different classes of activity-guided circuit manipulations at cellular resolution *in vivo*. We integrated hardware and software tools to enable rapid online analysis of population activity acquired from two-photon calcium imaging, that is then used to tailor photostimulation patterns. We show how this closed-loop system can be used to control user-specified neurons in the circuit: clamping spike rates at different levels, boosting weak sensory-evoked responses, and activating network ensembles gated by detected activity. We also demonstrate that repeated optical 'yoking together' of neighboring neurons can be used to induce long-term changes in network dynamics. To improve our online readout of activity patterns, we have incorporated the open-source package 'OnACID' [1],[2], which includes motion correction, neuronal source extraction, activity denoising and deconvolution in real time. Integrating this framework into our closed-loop system further extends the flexibility of our control strategy, in particular as it allows neurons to be identified and tracked directly from raw data streams. We show that neurons can be automatically recruited into the photostimulation ensemble as they are progressively detected online. This closed-loop all-optical system thus enables powerful new types of experiments, such as correcting erroneous network trajectories recorded from animals

performing decision-making tasks, guiding subsequent interrogation during the online mapping of functional connectivity, and preventing the propagation of cortical seizures. [1] Giovannucci, A., Friedrich, J., Kaufman, M., Churchland, A., Chklovskii, D., Paninski, L., & Pnevmatikakis, E. A. (2017). OnACID: Online Analysis of Calcium Imaging Data in Real Time. In Advances in Neural Information Processing Systems (pp. 2378-2388) [2]
https://github.com/flatironinstitute/CaImAn

Disclosures: Z. Zhang: None. **L.E. Russell:** None. **A.M. Packer:** None. **O.M. Gauld:** None. **P. Dzialecka:** None. **M. Hausser:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.15/JJJ12

Topic: I.04. Physiological Methods

Title: Re-engineering a luminopsin tool to study the *Caenorhabditis elegans* nervous system

Authors: *N. H. ELDER, R. EL BEJJANI
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Abstract: The nematode *Caenorhabditis elegans* and its well characterized nervous system have provided an ideal model system in which to study neurobiology. Due to the organism's rapid generation time and tractable genetics, numerous forward genetic screens have utilized *C. elegans* to identify a range of pathways and genes involved in processes such as synaptic transmission and axon regeneration. The ease of generating transgenes in these naturally translucent worms has also made them an ideal system in which to develop and use optogenetic tools, including channelrhodopsins. However, due to ChR's need for an external light source and a photo-labile retinal co-factor, it is not easily applied to large screens of *C. elegans*. Luminopsins (LMOs) are dual opto- and chemical genetic tools that have the potential to be utilized in *C. elegans* screens to investigate a range of processes, such as neural development, regeneration, and plasticity. LMOs consist of a channelrhodopsin (ChR) tagged with an N-terminus *Gaussia* luciferase (GLuc) and a C-terminus fluorescent protein. LMO proteins retain ChR's functional response to an external light source but can also open when GLuc metabolizes coelenterazine (CTZ) to produce blue light. The GLuc-produced light in turn provides the nearby channelrhodopsin with the energy required to open the ion channel and depolarize a neural cell membrane. Chemical activation of LMO allows for non-invasive neural stimulation that can be scaled to large genetic screens in *C. elegans*. Additionally, titrated CTZ concentration would allow for interrogation of effects of neural firing over a range of excitation strengths, including subthreshold stimulation levels. LMOs can also be applied to study if there are differential effects of rapid light-induced neuron firing and chronic chemically-induced firing on processes

such as axon regeneration and synaptic plasticity. Here, we present an adapted LMO that expresses in the *C. elegans* nervous system and preliminary work to validate LMO function.

Disclosures: N.H. Elder: None. **R. El Bejjani:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.16/JJJ13

Topic: I.04. Physiological Methods

Support: Schaefer Research Scholars Program of Columbia University to A.M.
MIUR PRIN 494 2015, (2015795S5W) to A.M.
European Research Council (ERC) 2015 Advanced Grant 495 n.695078 noMAGIC to A.M. and G.T.
DFG priority program SPP1926 to G.T.
Fondazione Istituto Italiano di Tecnologia to R.T. , A.L. , A.J.B.
AIRAlzh Onlus-COOP italian fellowship to S.P.

Title: A light-gated K^+ channel for sustained neuronal inhibition in freely moving animals

Authors: *R. TONINI[1], L. ALBERIO[3], A. LOCARNO[1], A. SAPONARO[3], E. ROMANO[3], V. BERCIER[5], S. ALBADRI[5], F. DEL BENE[5], F. SIMEONI[3], S. MOLERI[3], M. BELTRAME[3], S. PELUCCHI[4,6], E. MARCELLO[4], M. DI LUCA[4], G. ROMANI[3], K. KUKOVETZ[7], A. J. BOENDER[1], A. CONTESTABILE[2], S. LUO[8], A. MOUTAL[8], Y. JI[8], R. KHANNA[8], H. M. COLECRAFT[9], G. THIEL[7], A. MORONI[3,9,10]
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Abstract: Currently available inhibitory optogenetic tools provide short and transient silencing of neurons but fail to provide long-lasting inhibition because of the requirement for high light intensities or ion gradients. Here, we present an optimized blue light-sensitive synthetic K^+ channel, BLINK2, which expresses well in neurons across three species. The channel is activated by illumination with low doses of blue light and remains active over (tens) of minutes in the dark. This activation causes long periods of inhibition in neuronal firing in mouse neurons in *ex*

vivo recordings and impairs motor neuron response in zebrafish *in vivo*. As a proof-of-concept for potential applications we show that, in a free moving rat model for neuropathic pain, activation of a small number of BLINK2 channels caused a remarkable long lasting (> 30 min) reduction in pain sensation.

Disclosures: R. Tonini: None. **L. Alberio:** None. **A. Locarno:** None. **A. Saponaro:** None. **E. Romano:** None. **V. Bercier:** None. **S. Albadri:** None. **F. Del Bene:** None. **F. Simeoni:** None. **S. Moleri:** None. **M. Beltrame:** None. **S. Pelucchi:** None. **E. Marcello:** None. **M. Di Luca:** None. **G. Romani:** None. **K. Kukovetz:** None. **A.J. Boender:** None. **A. Contestabile:** None. **S. Luo:** None. **A. Moutal:** None. **Y. Ji:** None. **R. Khanna:** None. **H.M. Colecraft:** None. **G. Thiel:** None. **A. Moroni:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.17/JJJ14

Topic: I.04. Physiological Methods

Title: Circuit mapping of nucleus accumbens connections to the lateral hypothalamus

Authors: J. YEOH[1], C. MITCHELL[1], C. D. ADAMS[1], J. S. BAINS[2], G. P. MCNALLY[3], B. A. GRAHAM[1], *C. V. DAYAS[4]
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Abstract: The cell bodies of orexin-expressing neurons are located exclusively within the hypothalamus and project widely throughout the brain to influence a range of motivated behaviors including effort based reward-seeking behavior. Orexin neurons receive inputs from cortical, striatal and amygdaloid regions, but how these inputs trigger orexin neurons remains unclear. In light of recent work showing that the activation of the nucleus accumbens shell (NACsh) to the lateral hypothalamus (LH) pathway reduces reward-seeking behavior, we were interested in how inputs from the striatum influence orexin neuron activity. To examine how NACsh terminals might influence orexin neuron activity, we used a genetic, electrophysiological and optogenetic approach. Our first angle involved injections of an AAV5-hSyn-ChR2-YFP into the NACsh of orexin-GFP mice. After a 4-week incubation period, hypothalamic brain slices were prepared for either immunohistochemistry or targeted electrophysiological recordings of orexin neurons. An examination of LH tissue revealed YFP terminals from NACsh that were in close proximity to orexin neurons. Interestingly, 473nm photostimulation identified projections from NACsh to LH orexin neurons that were either mono or polysynaptic based on their sensitivity to TTX. We then classified these monosynaptic or polysynaptic inputs as either

GABAergic or glutamatergic based on sensitivity to glutamate antagonist CNQX or the GABA-A receptor antagonist picrotoxin. 65% of light evoked projections to orexin neurons (17 cells, yield/animal = 5, n=7 mice) were both TTX and CNQX sensitive, and therefore considered polysynaptic glutamatergic. Of the remaining 35% (9 cells) that were sensitive to picrotoxin, and therefore termed GABAergic, 27% (7 cells) were TTX sensitive (polysynaptic), while only 8% (2 cells) were TTX insensitive (monosynaptic). In a separate approach we crossed *Vgat-Cre* mice with orexin-GFP mice to create a double transgenic mouse line. Mice then received injections of AAV2/5-CAG-FLEX-ChR2-tdtomato into the NACsh. These studies revealed a similar percentage of NACsh◊orexin cell connections that were sensitive to both TTX and CNQX (30%, 3 out of 10 cells, 2 mice). Together our findings suggest that the NACsh can influence the activity of orexin neurons through both mono and polysynaptic connections and likely involve modulation of local interneuron populations.

Disclosures: J. Yeoh: None. **C. Mitchell:** None. **C.D. Adams:** None. **J.S. Bains:** None. **G.P. McNally:** None. **B.A. Graham:** None. **C.V. Dayas:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.18/JJJ15

Topic: I.04. Physiological Methods

Support: Simons Foundation of the Simons Center for the Social Brain at MIT

Title: Magnetochemical technique for remote manipulation of neurons

Authors: *S. RAO[1], R. CHEN[1], A. LAROCCA[1], M. CHRISTIANSEN[1], A. SENKO[1], C. SHI[1], P.-H. CHIANG[1], P. ANIKEEVA[2]
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Abstract: For the rodent models, whose behavior is sensitive to the implanted foreign objects, investigation of the underlying neural circuits via invasive optogenetic and electrical neuromodulation devices poses a challenge. Remote deep brain stimulation with alternatiing magnetic field has been demonstrated to realize well-defined neural excitation. Here we developed a minimally invasive neuromodulation tool for magnetothermal deep brain interrogation of neural populations in freely moving rodents. This approach enabled temporally and spatially precise chemical manipulation of neural activity by local release of designer drugs in response to remote exposure to alternating magnetic fields. We achieved the implant-free convenience of magnetothermal neuromodulation together with the precision of chemoreceptors, and thus enabled spatial and temporal modulation for behavioral investigation. We anticipate that the magnetochemical tools will facilitate investigation of neural circuits during behavioral

experiments and enable neuromodulation studies in rodent models incompatible with permanently implanted hardware.

Disclosures: S. Rao: None. **R. Chen:** None. **A. LaRocca:** None. **M. Christiansen:** None. **A. Senko:** None. **C. Shi:** None. **P. Chiang:** None. **P. Anikeeva:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.19/JJJ16

Topic: I.04. Physiological Methods

Support: NIH grant EB009041
NIH grant AG038961

Title: Non-invasive optogenetic excitation using focused-ultrasound-mediated delivery of virus-encoded Chrimson and transcranial red-light exposure

Authors: *A. POULIOPOULOS, N. KWON, S. HUSSAINI, E. KONOFAGOU
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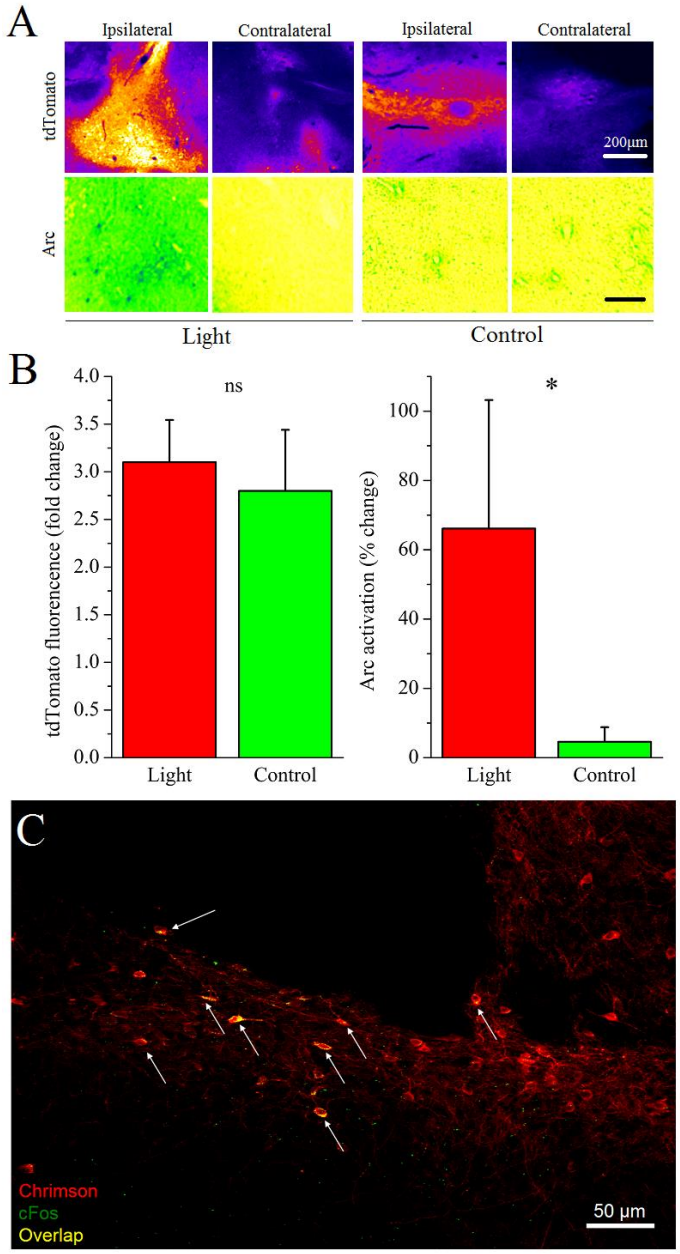
Abstract: In conventional optogenetics, channelrhodopsin (ChR) is encoded by an adeno-associated virus (AAV) delivered via direct injection into the brain and activated via blue-light illumination through implanted optical fibers. However, these invasive procedures are sources of morbidity and damage to the surrounding tissues and alter physiological brain responses. Here, we aimed at fully non-invasive optogenetic excitation using focused-ultrasound(FUS)-mediated viral delivery of the red-shifted ChR variant Chrimson and transcranial red light exposure. AAV encoding tdTomato-labelled Chrimson (peak absorption wavelength ~ 600 nm) was delivered into the brain of wild-type mice through FUS exposure in the presence of systemically circulating microbubbles. To remotely trigger neuronal activity, we transcranially illuminated the mouse brains using an LED source (635nm, beam size: 4 mm) 2 weeks after viral delivery. Mice were then sacrificed and their brains were imaged with fluorescence microscopy to confirm the presence of Chrimson and neuronal activation inferred by Arc and cFos expression. AAV was primarily delivered in the treated hemisphere (fig. A). Similar AAV delivery was achieved in both illuminated and control mice. Arc staining showed that neuronal activation occurred at areas of AAV expression, suggesting that light-sensitive channels were activated due to red light exposure. Arc activation was on average 66 ± 37 % higher on the ipsilateral side compared to the contralateral side in illuminated brains (fig. B). In contrast, the difference in Arc activation in non-illuminated mice was 4.57 ± 4.25 %. Although viral delivery was equivalent between illuminated and control mice ($p > 0.05$), Arc activation was significantly higher ($p < 0.05$) in mice exposed to red light. Finally, cFos upregulation overlapped with Chrimson-expressing

neurons, suggesting light-mediated neuronal activation (figure C). Our initial findings indicate that neuronal activity can be triggered remotely *in vivo* using a combination of ultrasound and light exposure through the intact skull.



Disclosures: A. Pouliopoulos: None. **N. Kwon:** None. **S. Hussaini:** None. **E. Konofagou:** None.

Poster

255. Physiological Methods: Optogenetics II

Location: SDCC Halls B-H

Time: Sunday, November 4, 2018, 1:00 PM - 5:00 PM

Program #/Poster #: 255.20/JJJ17

Topic: I.04. Physiological Methods

Title: Neural control of various aggressive behaviors in mice

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Abstract: Aggression is an evolutionarily conserved response to conspecifics, and an essential means to survive for animals from insects to human beings, yet the circuit mechanism is not well understood. Here, we identify a circuit mechanism from the basal forebrain to the midbrain to execute various aggression in different social contexts in which mice usually will not have aggressive behaviors. In addition, we uncover that the aggression executive role of the basal forebrain or the basal forebrain-midbrain circuit are controlled by the hypothalamus. Furthermore, we provide evidence to indicate that the sexual difference of aggression induced by the activation of hypothalamus to basal forebrain pathway was determined by the weaker strength of the projection and fewer basal forebrain neurons activated in female mice. Taken together, our study defines a disynaptic hypothalamus-basal forebrain-midbrain circuit through which aggression is generated, and the findings provide novel mechanistic insight into the aggression processing. Dysregulation of this ‘aggression circuit’ possibly contributes to pathological aggressions seen in humans.

Disclosures: Z. Zhu: None. **Q. Ma:** None. **H. Yang:** None. **Y. Yu:** None. **S. Duan:** None.